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ORTHOMOLECULAR PSYCHIATRY

TREATMENT OF SCHIZOPHRENIA

edited by
DAVID HAWKINS and LINUS PAULING



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ORTHOMOLECULAR PSYCHIATRY

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TREATMENT OF SCHIZOPHRENIA

EDITED BY

DAVID HAWKINS and LINUS PAULING

THE NORTH NASSAU MENTAL HEALTH CENTER
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Preface

In the article *Insanity* in the ninth edition of the Encyclopaedia Britannica (1881) insanity is defined as a chronic disease of the brain inducing chronic disordered mental symptoms. The author of the article (J. Batty Tuke, M.D., Lecturer on Insanity, School of Medicine, Edinburgh) then stated that this definition

> possesses the great practical advantage of keeping before the student the primary fact that insanity is the result of disease of the brain, that it is not a mere immaterial disorder of the intellect. In the earliest epochs of medicine the corporeal character of insanity was generally admitted, and it was not until the superstitious ignorance of the Middle Ages had obliterated the scientific, though by no means always accurate, deductions of the early writers that any theory of its purely psychical character arose. At the present day it is unnecessary to combat such a theory, as it is universally accepted that the brain is the organ through which mental phenomena are manifested, and therefore that it is impossible to conceive of the existence of an insane mind in a healthy brain.

By 1929, when the fourteenth edition of the Encyclopaedia Britannica was published, the situation had changed, largely because of the development of psychoanalysis by Sigmund Freud. The earlier definition of insanity was deleted, and replaced by discussions from two points of view: the point of view of the materialistic school

> that though in many states of insanity no observable structural changes are found, they exist all the same, only they are such that our imperfect methods cannot detect them, and in time they will be discovered . . .

and the point of view of the psychogenic school,

> that though mental disease may arise secondarily to physical disorder, the symptoms are psychological reverberations of that disorder and the body of an individual must be regarded as environmental to the ego. . . . The many structural changes which are found in certain forms of insanity should be reviewed as probably secondary to a perverted mentality.

Psychoanalysis has failed, and psychiatry is now rapidly returning to the scientific approach, the recognition of the corporeal character of mental disease, with manifestations determined to some extent by environmental stress and past experience. Supportive psychotherapy has great value—an example is the explanation to the schizophrenic patient and his family that his disturbed behavior and thinking are the result of an imbalance in the molecular composition of his body, and that this imbalance can be corrected (Hawkins, Chapter 29 of this volume). The recognition of the effectiveness of phenothiazines and other drugs (and the ineffectiveness of psychoanalysis) has accelerated the reacceptance of the concept that mental disease is disease of the brain, and that the brain itself needs to be treated, by changing its molecular composition.

The relation of vitamins to mental disease became evident as soon as vitamins were discovered. One manifestation of pellagra is psychosis. Pellagra is a vitamin-deficiency disease, and the psychosis is cured (averted) by the provision of an adequate intake of the vitamin (niacin). It is estimated that in the first decades of this century 10 percent of the persons in psychiatric hospitals were pellagrins (Kety, 1970). The discovery in 1937 that niacin is the pellagra-preventing vitamin soon led to its trial in controlling mental disease in patients not suffering from pellagra. Cleckley et al. (1939) and Sydenstricker and Cleckley (1941) reported some success in treating 48 subjects with acute mental illness of one sort or another by use of moderately large doses of niacin (300 to 1,500 mg per day, as compared with the pellagra-preventing intake of about 12 mg per day).

In 1943 Kaufman described the deterioration in mental and physical health of 150 patients with a disease to which he gave the name aniacinamidosis, and in 1949 he published a larger book on this subject, with discussion of 455 patients. Measurements of impairment of joint mobility and increase in blood sedimentation rate gave objective information about the progress of the disease. He found that most of the patients improved greatly on a regime of 1 to 5 g of niacinamide per day, in divided doses (6 to 16 per day), continuing for as long as nine years (Kaufman, 1955). He observed no untoward reactions from niacinamide in several thousand patient-years of continuous use. His recommended intake of niacinamide for treatment of restricted mobility of joints and other manifestations of aniacinamidosis is 4 or 5 g per day. Many of his patients showed striking improvement in mental health as well as physical health on this regime.

The effective introduction of megavitamin therapy for schizophrenia came in the period from 1952 on through the work of Hoffer and Osmond, as described in several chapters of this book. After making some studies on a few patients with encouraging results, they carried out several double-blind and blind comparisons of niacin, niacinamide, and a placebo. A study with 171 subjects (73 receiving 3 g of niacin per day for all or part of the period of study, 98 receiving a placebo) gave a statistically significant difference in the number transferred to the mental hospital and a difference in the number of suicides (0 and 4, respectively) with borderline statistical significance (Hoffer et al., 1957). Another study with 82 subjects (43 receiving 3 g of niacin per day and 39 receiving a placebo) gave a difference with high statistical significance in the number classified as improved or unimproved (Hoffer, 1962).

It is evident from the published accounts of these studies that amounts larger than 3 g per day of niacin or niacinamide are needed for a pronounced therapeutic effect for many schizophrenic patients. Hoffer and Osmond had in fact observed that daily amounts of niacin or niacinamide larger than 6 g seemed to be required by some patients, and also that many patients benefited from receiving 3 to 6 g per day of ascorbic acid. Other vitamins, especially pyridoxine in amounts 600 mg to 1,500 mg per day, have been found to be beneficial. In addition, many schizophrenics, probably more than 80 percent, suffer from hypoglycemia, which needs to be corrected, as described in some chapters in this book. The orthomolecular treatment of schizophrenia includes more than the routine administration of 3 g of niacin or niacinamide per day.

The importance of good nutrition to good health cannot be denied. There is much evidence to support the thesis that for most people the optimum daily intake of ascorbic acid is far larger than the usually recommended daily allowance (Pauling, 1970); 3 to 6 g per day, the amount customary in megavitamin treatment of schizophrenia, may well be only the average optimum for most human beings. Little effort has been expended in the study of the amounts of vitamins required for optimum health. The decision by most psychiatrists who do not accept the principles of orthomolecular psychiatry to restrict the intake of vitamins by their patients to certain arbitrary levels, without checking the possible benefit for the patient of an increased intake, cannot be justified.

Part of the resistance to megavitamin therapy is based on the idea that an increased intake of a vitamin should be subjected to as thorough testing as a new synthetic drug. This is nonsense; the vitamins are substances to which the human body has long been accustomed, and the toxicities of the water-soluble vitamins are known to be low and the side effects few. Another part of the resistance is the result of a misunderstanding of the meaning of statistical significance. Investigations described as attempts to replicate Hoffer and Osmond's results are reported to have failed to show a statistically significant difference between the subjects receiving niacin or niacinamide and those receiving a placebo. This conclusion is then incorrectly interpreted as meaning

that the investigations have shown niacin or niacinamide to have no greater value than a placebo.

For example, Hoffer had reported that mentally ill children receiving niacinamide and ascorbic acid benefited more than those receiving a placebo. Greenbaum (1970) then reported that he was unable to confirm the claimed value of niacinamide in his double-blind study of 17 children receiving niacinamide (1000 mg per day per 50 lb. body weight) and 24 children receiving a placebo (also 16 receiving niacinamide and a tranquilizer). The principal criterion was the increase during the six months of the study in the score on a clinical scale of observable behavior categories. Greenbaum reported that "there was no significant difference attributable to niacinamide." This statement is seriously misleading. The average improvement in the score was in fact 4.0 units for the niacinamide group and 2.6 units for the placebo group. The difference between 4.0 and 2.6 is reported as not statistically significant. But we see that Greenbaum found 54 percent greater improvement in the niacinamide group than in the placebo group. From Greenbaum's result we can say that it is more likely that niacinamide has an effect (54 percent greater than the placebo) than that it has no effect, but it is not 20 times more likely ($P < 0.05$, accepted as statistically significant).

The statistical significance is determined by the design of the investigation. If Greenbaum had got the same result (54 percent more improvement for the niacinamide group than for the placebo group) with a larger number of subjects the null hypothesis of equal effect of niacinamide (in the dosage used) and placebo could have been rejected with statistical significance ($P < 0.05$).

Ban (1971) states that "The hypothesis, based on these findings [by Hoffer], that nicotinamide therapy is useful in childhood schizophrenia was not verified by Greenbaum in a carefully designed—placebo controlled—study." I consider this statement to be wrong. Greenbaum found 54 percent more improvement in the niacinamide group than the placebo group. Surely 54 percent more improvement is useful. The amount of improvement, 54 percent, is unreliable, but that is what he found.

I have discussed this matter in some detail because much of the objection to the use of orthomolecular methods in psychiatry is based upon similar misrepresentations of the reported studies.

Another investigation that is quoted as having provided evidence against the hypothesis that niacin or niacinamide has value in the treatment of schizophrenia was published by Ananth et al. in 1970, with the title "Nicotinic acid in the prevention and treatment of artificially induced exacerbation of psychopathology in schizophrenics." It is known that a substance, such as the amino acid methionine, whose molecules can donate methyl groups to other molecules has the property of exacerbating the mental illness of schizophrenics when it is ingested, and it has been suggested that the effectiveness of niacin and niacinamide in controlling schizophrenia results from the action of their molecules as methyl acceptors—that is, they remove methyl groups

from some methylated compounds in the body that may be causing the mental illness. In the investigation by Ananth et al. schizophrenia patients were given daily doses of methionine. Some of the patients also were given niacinamide. All of the patients showed a pronounced exacerbation of their mental illness. The result has been interpreted as showing that niacinamide does not neutralize the methyl-donating effect of methionine in exacerbating schizophrenia by virtue of its function as a methyl acceptor. This conclusion is, however, not justified, because there was a serious flaw in the design of the experiment. The patients were given 20 g of methionine per day. Over 16 g of niacinamide per day would be required to accept the methyl groups donated by 20 g of methionine, but the patients were given only 3 g. It could have been predicted that the experiment would fail.

There is thoroughly convincing evidence that the methods of orthomolecular psychiatry discussed in this book have great value. Some aspects of the scientific basis of these methods are presented in the earlier chapters. Some of the chapters are of most interest to biochemists. Most of the chapters can, I believe, be read with understanding and profit by physicians and by laymen who have some acquaintance with the terminology of chemistry and other sciences. Despite the progress that has been made in controlling it, mental illness is still the cause of a tremendous amount of suffering. The work of Hoffer, Osmond, Hawkins, and others has shown that the methods of orthomolecular psychiatry can be used to decrease the amount of this suffering. I join my co-editor, Dr. David Hawkins, and the other contributors to this book in expressing the hope that it will be found useful not only by scientists and physicians but also by those who suffer from schizophrenia and by their families.

I thank Dr. Gustav Albrecht for his help.

August 1972 *Linus Pauling*

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Introduction

In this volume we have presented a new concept in psychiatry. Starting from theoretical premises we have gone on to their experimental verification and demonstration in the laboratory. We then describe the further development of these concepts in clinical research and their practical application in diagnosis and treatment. Finally, we include a description of a functioning model system in which the clinical application of these principles is extended to the delivery of health-care services to the community.

The authors have integrated their work to such an extent that the chapters are logically interconnected and the material is progressively interrelated. The degree of correlation of the material is notable in that all of the contributors worked independently of each other in different institutions and locations. The need for even better communication in this developing new field has resulted in the formation of the Academy of Orthomolecular Psychiatry, of which many of the authors in this book are founding members.

Much of the biochemical data in schizophrenia research have appeared to be contradictory, confused, and disorganized. When viewed from a new frame of reference, however, many of these apparent contradictions become clarified both theoretically and clinically.

A useful concept with which to approach a great mass of data is that of the radar screen. Each piece of information results in one dot appearing on the screen, and a recognizable profile emerges only as the resultant of a great many dots. The frame

of reference that we have tried to develop in this book acts as the screen of the radar set; it is our hope that a very useful profile will be formed in the mind of the reader as the data are presented.

The material has been organized into four sections. Section I is devoted to theoretical concepts, laboratory investigations, and background material. Because many psychiatrists do not belong to the American Association for the Advancement of Science, two fundamental papers are reprinted from *Science* with the permission of the Association: "Orthomolecular Psychiatry" by Pauling, and "The Genetics of Schizophrenia" by Heston. Another important concept, that of schizophrenia as a perceptual disorder, is presented in a basic paper by Ruth Kirk. The biochemical papers then present hypotheses of the mechanics of the genetic perceptual defect and possible means of correction. The theoretical concepts develop a view of the illness as a genetically based perceptual disorder in which the perceptual defect operates by means of biochemical mechanisms that can be influenced experimentally.

On an abstract level, the numerical frequencies of a specific variable in a given biologic population will result in a statistical probability curve with extremes of the population at each end. Ordinary diet obviously cannot fulfil the excessive requirements of the persons at the ends of the curve, who are atypical, and whose needs for a particular substance are also atypical. If the substance is an essential one, these individuals will become ill under ordinary nutrition, with the clinical type of illness different for deficiency in different essential substances.

We are concerned with those atypical persons classified as schizophrenic and the substances that they require for optimum functioning.

Section II is devoted to means of detection of the clinical and biochemical variables in the schizophrenic patient that are associated with being ill, and are such that knowledge about them suggests methods of correction. The extent of the perceptual nature of the illness and the clinical importance of the perceptual orientation to schizophrenia are stressed by various authors, who discuss several biochemical disorders of clinical importance.

Section III is concerned with means of correction and the ways to assess the clinical response when a biochemical abnormality in schizophrenia has been therapeutically corrected.

Section IV forms a composite whole and was written for the practicing clinician. Statistics, tables, and graphs have been avoided except in the few instances where they were necessary to demonstrate material visually. Lengthy descriptions of methodology are also omitted.

The short description of existing treatment systems in the last chapter may seem oversimplified to the American reader, but clinicians in a number of foreign countries are not familiar with the great variety of alternate systems and institutions available in the United States.

The busy clinician who is interested only in the practical aspects of the

orthomolecular approach, and who has enough theoretical background to provide a rationale, can turn at once to Section IV, and then go back to the previous sections for greater details of specific subjects.

The Appendix, which describes the work of Schizophrenics Anonymous, was written by two of its founders in the New York area. Although this organization has been growing and developing rapidly, this marks the first time it has been discussed in any book.

In the final analysis, science is a creative art. Data by and of themselves are meaningless; meaning results only from interpretation. Correlation of data with the scientist's personal experience results in a progressively comprehensive synthesis; the concept of orthomolecular psychiatry provides a new conceptual framework from which to interpret a great mass of data. The editors hope that this viewpoint will result in new insights and correlations in the mind of the reader, with resulting benefit for many suffering patients.

ACKNOWLEDGMENTS

The chapters "Orthomolecular Psychiatry" and "The Genetics of Schizophrenic and Schizoid Disease" are reprinted from *Science*. Both articles are included here by permission of the American Association for the Advancement of Science.

The chapter on "Perceptual Defect and Role Handicap: A Theory of the Etiology of Schizophrenia" is reprinted with permission of the *British Journal of Psychiatry*.

"The Use of Parenteral Vitamins in the Treatment of Schizophrenia" first appeared in *Schizophrenia* and is reprinted with permission of the American Schizophrenia Association.

Excerpts from Chapter 30, Section IV, were presented at the Pauling Award Luncheon of the American Schizophrenia Association on April 2, 1971, at the Biltmore Hotel in New York City.

I am personally indebted to the late William G. Wilson for the basic inspiration which ultimately resulted in this book, and to his assistant, Helen Wynn, not only for her continued interest but for her editing of the final section. I want to thank Estelle Loomis Goldenberg for the extensive work involved in the preparation of the manuscript, and Mollie Starr Shriftman for her considerable help. Lastly, I want to acknowledge the invaluable assistance of my wife, Margaret, for her help with the manuscript and bibliographies and her encouragement during the years in which the book was being compiled.

July 1972 *David Hawkins*

SECTION I

THEORETICAL AND EXPERIMENTAL BACKGROUND

1

Orthomolecular Psychiatry

LINUS PAULING

INTRODUCTION

The methods principally used now for treating patients with mental disease are psychotherapy (psychoanalysis and related efforts to provide insight and to decrease environmental stress), chemotherapy (mainly with the use of powerful synthetic drugs, such as chlorpromazine, or powerful natural products from plants, such as reserpine), and convulsive or shock therapy (electroconvulsive therapy, insulin coma therapy, pentylenetetrazol shock therapy). I have reached the conclusion, through arguments summarized in the following paragraphs, that another general method of treatment, which may be called orthomolecular therapy, may be found to be of great value, and may turn out to be the best method of treatment for many patients.

Orthomolecular psychiatric therapy is the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum

(*Reprinted with permission from* Science, *19 April 1968, vol. 160, pp. 265–271.* *Copyright © 1968 by the American Association for the Advancement of Science.*)

concentrations of substances normally present in the human body.[1] An example is the treatment of phenylketonuric children by use of a diet containing a smaller than normal amount of the amino acid phenylalanine. Phenylketonuria (Følling, 1934) results from a genetic defect that leads to a decreased amount or effectiveness of the enzyme catalyzing the oxidation of phenylalanine to tyrosine. The patients on a normal diet have in their tissues abnormally high concentrations of phenylalanine and some of its reaction products, which, possibly in conjunction with the decreased concentration of tyrosine, cause the mental and physical manifestations of the disease (mental deficiency, severe eczema, and others). A decrease in the amount of phenylalanine ingested results in an approximation to the normal or optimum concentrations and to the alleviation of the manifestations of the disease, both mental and physical.

The functioning of the brain is dependent on its composition and structure; that is, on the molecular environment of the mind. The presence in the brain of molecules of N,N-diethyl-D-lysergamide, mescaline, or some other schizophrenogenic substance is associated with profound psychic effects (see, for example, Woolley, 1962). Cherkin has recently pointed out (1967) that in 1799 Humphry Davy described similar subjective reactions to the inhalation of nitrous oxide. The phenomenon of general anesthesia also illustrates the dependence of the mind (consciousness, ephemeral memory) on its molecular environment (Pauling, 1961; Miller, 1961).

The proper functioning of the mind is known to require the presence in the brain of molecules of many different substances. For example, mental disease, usually associated with physical disease, results from a low concentration in the brain of any one of the following vitamins: thiamine (B_1), nicotinic acid or nicotinamide (B_3), pyridoxine (B_6), cyanocobalamin (B_{12}), biotin (H), ascorbic acid (C), and folic acid. There is evidence that mental function and behavior are also affected by changes in the concentration in the brain of any of a number of other substances that are normally present, such as L(+)-glutamic acid, uric acid, and γ-aminobutyric acid.[2]

OPTIMUM MOLECULAR CONCENTRATIONS

Several arguments may be advanced in support of the thesis that the optimum molecular concentrations of substances normally present in the body may be different from the concentrations provided by the diet and the gene-controlled synthetic

[1] I might have described this therapy as the provision of the optimum molecular composition of the brain. The brain provides the molecular environment of the mind. I use the word mind as a convenient synonym for the functioning of the brain. The word orthomolecular may be criticized as a Greek-Latin hybrid. I have not, however, found any other word that expresses as well the idea of the right molecules in the right amounts.

[2] The literature is so extensive that I refrain from giving references here.

mechanisms, and, for essential nutrilites (vitamins, essential amino acids, essential fatty acids) different from the minimum daily amounts required for life or the "recommended" (average) daily amounts suggested for good health. Some of these arguments are presented in the following paragraphs.

EVOLUTION AND NATURAL SELECTION

The process of evolution does not necessarily result in the normal provision of optimum molecular concentrations. Let us use ascorbic acid as an example. Of the mammals that have been studied in this respect, the only species that have lost the power to synthesize ascorbic acid and that accordingly require it in the diet are man, other Primates (rhesus monkey, Formosan long-tail monkey, and ring-tail or brown capuchin monkey), the guinea pig, and an Indian fruit-eating bat (*Pteropus medius*).[3] Presumably the loss of the gene or genes controlling the synthesis of the enzyme or enzymes involved in the conversion of glucose to ascorbic acid occurred some 20 million years ago in the common ancestor of man and other Primates, and occurred independently for the guinea pig and for one species of bat and one bird, in each case in an environment such that ascorbic acid was provided by the food. For a mutation rate of 1/20,000 per gene generation and for even a very small advantage for the mutant (0.01 percent more progeny) the mutant would replace the earlier genotype within about 1 million years. The advantage to the mutant of being rid of the ascorbic-acid-synthesis machinery (decrease in cell size and energy requirement, liberation of machinery for other purposes) might well be large, perhaps as much as 1 percent; a disadvantage nearly as large (less by 0.01 percent) resulting from a less than optimum supply of dietary ascorbic acid would not prevent the replacement of the earlier species by the mutant. Hence, even if the amount of the vitamin provided by the diet available at the time of the mutation were less than the optimum amount, the mutant might still be able to replace its predecessor. Moreover, it is possible that the environment has changed during the last 20 million years in such a way as to provide a decreased amount of the vitamin. Even a serious disadvantage of the changed environment would not lead to a mutation restoring the synthetic mechanism within a period of a few million years, because of the small probability of such mutations, far smaller than of those resulting in loss of function.

Moreover, the process of natural selection may be expected later on to lead to the survival of a species or strain that synthesizes somewhat less than the optimum amount of an autotrophic vital substance rather than of the species or strain that synthesizes the optimum amount. To synthesize the optimum amount requires

[3] For references, see Stone (1965). The only other vertebrates known to require exogenous ascorbic acid are the red-vented bulbul, *Pycnonotus cafer*, and related passeriform birds.

about twice as much biological machinery as to synthesize half the optimum amount. As suggested in Figure 1-1, the evolutionary disadvantage of synthesizing a less than

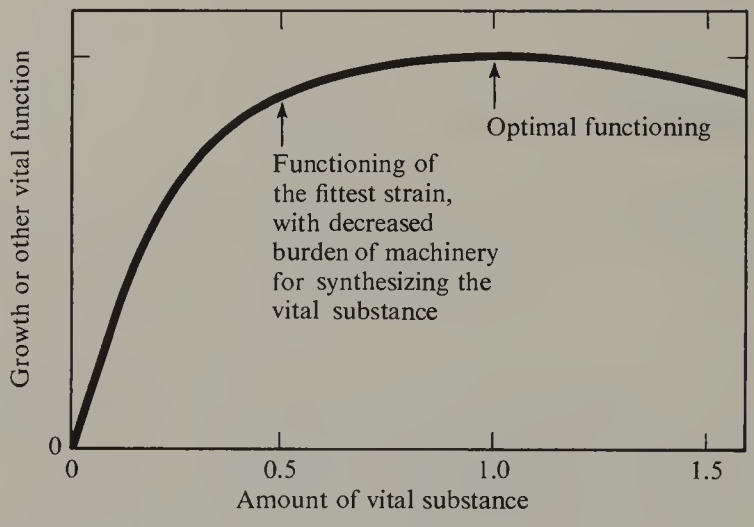


FIGURE 1-1.
Diagrammatic representation of growth rate or other vital property of an organism as function of the concentration of vital substance in the organism, showing the concentration at which the differential advantage of an increased amount of vital substance is just balanced by the differential disadvantage resulting from an increased amount of machinery for synthesis, and the concentration that gives optimum functioning without consideration of the burden of the machinery for synthesis.

optimum amount of the vital substance may be small, and may be outweighed by the advantage of requiring a smaller amount of biological machinery. Evidence from the study of microorganisms is discussed in the following paragraphs.

EVIDENCE FROM MICROBIOLOGICAL GENETICS

Many mutant microorganisms are known to require, as a supplement to the medium in which they are grown, a substance that is synthesized by the corresponding wild-type organism (the normal strain). An example is the pyridoxine-requiring mutant of *Neurospora sitophila* reported by G. W. Beadle and E. L. Tatum in their first *Neurospora* paper, published in 1941.

Several species of *Neurospora* that have been extensively studied are known to be able to grow satisfactorily on synthetic media containing inorganic salts, an inorganic source of nitrogen, such as ammonium nitrate, a suitable source of carbon, such as sucrose, and the vitamin biotin. All other substances required by the organism

are synthesized by it. Beadle and Tatum found that exposure to x-radiation produces mutant strains such that one substance must be added to the minimum medium in order to permit the growth at a rate approximating that of the normal strain. Their pyridoxine-requiring mutant was found to grow on the standard medium at a rate only 9 percent of that of the normal strain. When pyridoxine (vitamin B_6) is added to the medium, the rate of growth of this strain at first increases nearly linearly with the concentration of the added pyridoxine and then increases less rapidly, as shown in Figure 1-2.[4] The growth rate of the normal strain without added pyridoxine is equal to that of the mutant with about 10 micrograms of the growth substance per liter in the medium. At a concentration about four times this value (40 micrograms per liter) the growth rate of the mutant strain reaches a value 7 percent greater than that of the normal strain without added pyridoxine.

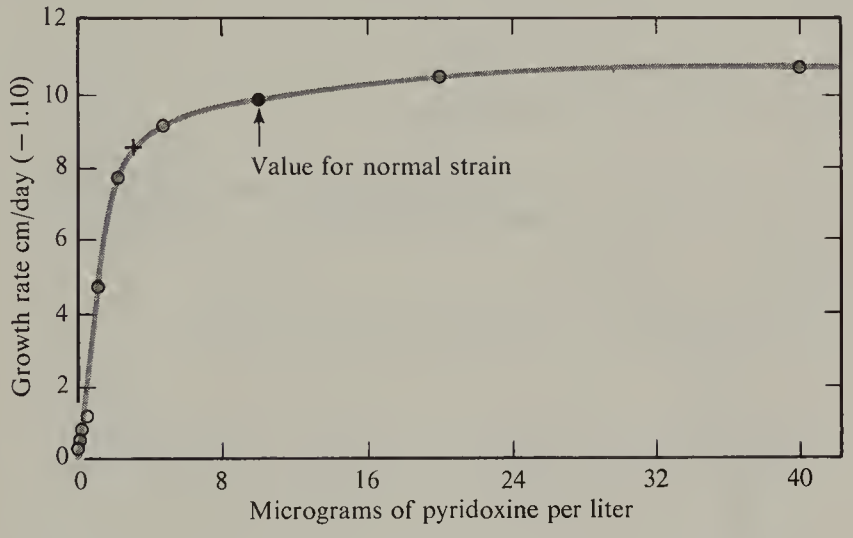


FIGURE 1-2.
The observed rate of growth of a pyridoxine-requiring *Neurospora* mutant (Beadle and Tatum, 1941), as function of the concentration of pyridoxine in the medium.

The point of maximum curvature of the curve in Figure 1-2, at about 3.2 micrograms of pyridoxine per liter (indicated by a cross), may be reasonably considered to mark the division between the region of vitamin deficiency (to the left) and the region of normal vitamin supply (to the right), such as might permit the mutant to compete with the wild type, which has the growth rate represented by the filled circle in Figure 1-2. The point marked by the cross might well correspond to an "adequate" or "recommended" amount of the vitamin, in that the growth rate of the mutant is only

[4] The points in Figure 1-2 represent my measurement of the slopes of the growth curves shown in Figure 1 of Beadle and Tatum (1941). They agree closely with the points of their Figure 2, except for one point, that for 1.2 μg/liter, which may have been misplotted.

12 percent less than that of the wild strain, and that the amount of the vitamin would have to be increased threefold to make up this 12 percent.[5]

As shown in Figure 1-2, quadrupling the concentration of pyridoxine that gives the mutant a growth rate equal to that of the wild type causes a further increase in growth rate by nearly 10 percent. The growth rates of the mutant and the wild type at very large concentrations of the vitamin have not been measured, so far as I know, and the optimum concentration is not known. From the work of Beadle and Tatum (1941) the optimum concentration may be taken to be greater than 40 micrograms per liter; that is, more than ten times the "adequate" concentration for the mutant and more than four times the concentration equivalent to the synthesizing capability of the wild type. The growth rate of the mutant at the optimum concentration is more than 22 percent greater than that at the "adequate" concentration and more than 9 percent greater than that of the normal strain.

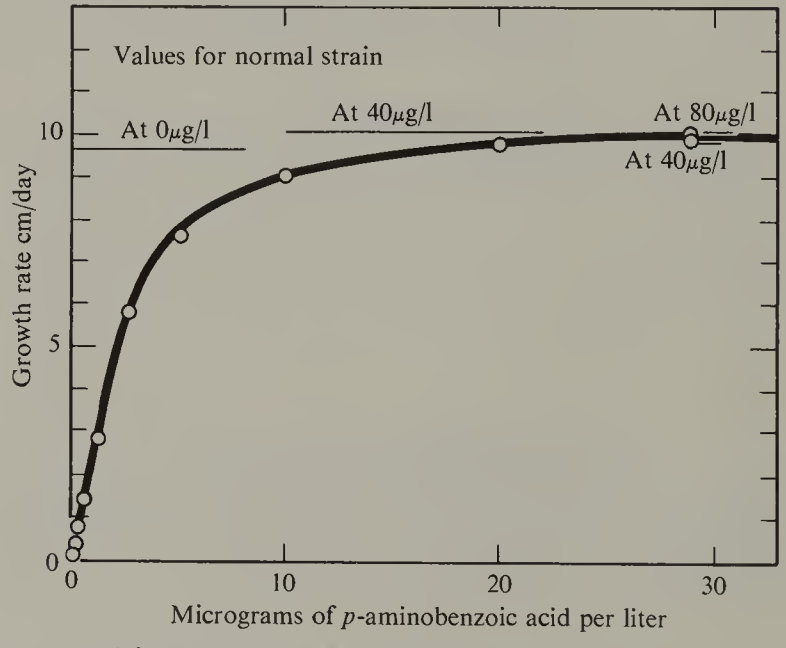


FIGURE 1-3.
The observed rate of growth of a *p*-aminobenzoic-acid-requiring *Neurospora* mutant (Tatum and Beadle, 1942), as function of concentration of the growth substance in the medium.

Similar results have been reported for other mutants of *Neurospora*. The values found by Tatum and Beadle (1942) for a *p*-aminobenzoic-acid-requiring mutant of *Neurospora crassa* as a function of the concentration of *p*-aminobenzoic acid added to the standard medium are shown in Figure 1-3. The growth-rate curve is similar in

[5] The reported growth rate for the normal strain in a medium with 40 μg of added pyridoxine per liter is 3 percent greater than that for the basic medium, as shown by the slopes of the lines in Figure 1 of Beadle and Tatum (1941).

shape to that for the pyridoxine-requiring mutant. The value of the growth rate for the normal strain of *Neurospora crassa* with no added *p*-aminobenzoic acid is equal to that for the mutant at a concentration of added *p*-aminobenzoic acid of about 15 micrograms per liter. A value about 4 percent greater is found for the normal strain at 40 micrograms per liter and for the mutant strain at 80 micrograms per liter, as indicated in Figure 1-3.

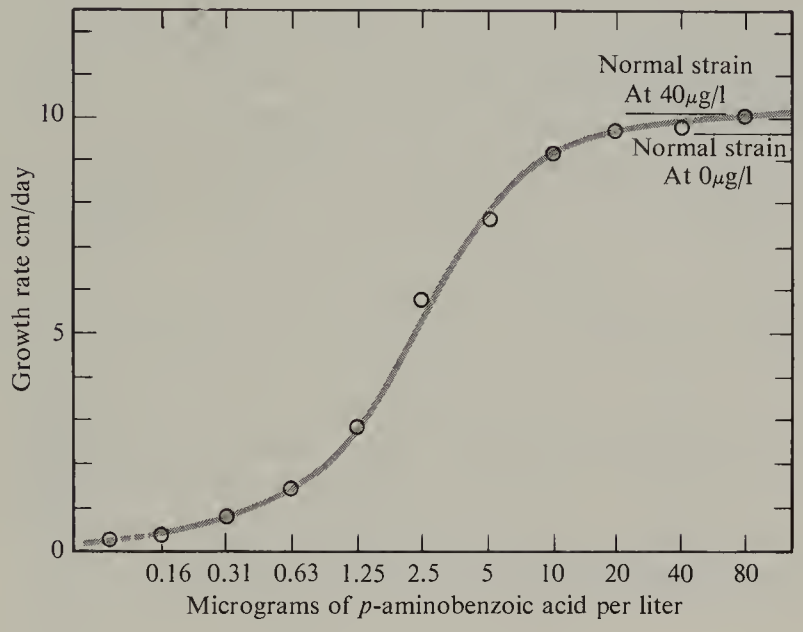


FIGURE 1-4.
Observed rate of growth of a *p*-aminobenzoic-acid-requiring *Neurospora* mutant as function of the logarithm of the concentration of *p*-aminobenzoic acid.

It is customary to plot values of the growth rate against the logarithm of the concentration of the growth substance, as shown in Figure 1-4. The amount of increase accompanying a doubling in the concentration of the growth substance is a maximum at 1.25 to 2.5 micrograms per liter, and decreases thereafter to about half the value for each successive doubling.

From these two examples we see that there may be a significant increase in rate of growth of the normal strain through addition of some of the growth substance that it synthesizes to the medium in which it is grown; that is, that the amount of the growth substance that is synthesized by the normal strain is not the optimum amount, but is somewhat less, leading to a rate of growth approximately 7 percent less than the maximum in the case of pyridoxine (with the normal strain of *Neurospora sitophila*) and 4 percent less for *p*-aminobenzoic acid (with the normal strain of *Neurospora crassa*). Many other examples are known of microorganisms that grow more

abundantly in a medium containing vitamins, amino acids, or other substances that they are able to synthesize than on a minimum medium.

Evidence supporting the above arguments has been presented recently by Zamenhof and Eichhorn (1967) in a paper entitled "Study of microbial evolution through loss of biosynthetic functions: Establishment of 'defective' mutants." These authors carried out experiments involving competitive growth in a chemostat of an auxotrophic mutant (a mutant requiring a nutrilite) and a prototrophic parent in a medium of constant composition containing the nutrilite. They found that the "defective" mutant has a selective advantage over the prototrophic parental strain under these conditions. For example, an indole-requiring mutant of *Bacillus subtilis* was found to show a strong selective advantage over the prototrophic back-mutant when the two were grown together in a medium containing tryptophan: the relative number of cells of the latter decreased 10^6-fold in 54 generations. They also found that greater advantage to the auxotroph accompanies a greater number of biosynthetic steps that have been dispensed with (earlier block in a series of reactions), with the final metabolite available. They point out that a mutant with a gene deletion would be at a distinct selective advantage over a point mutant, in that not only the synthesis of the metabolite, but also that of the structural gene, the messenger RNA, and perhaps the inactive enzyme itself would be dispensed with, and that accordingly the mutant with a deletion would replace the point mutant in competition. They mention evidence that some of the "defective" strains occurring in nature have lost one or more of their structural genes by deletions, rather than by point mutations.

MOLECULAR CONCENTRATIONS AND RATE OF REACTION

Most of the chemical reactions that take place in living organisms are catalyzed by enzymes. The mechanisms of enzyme-catalyzed reactions in general involve (1) the formation of a complex between the enzyme and a substrate molecule, and (2) the decomposition of this complex to form the enzyme and the products of the reaction. The rate-determining step is usually the decomposition of the complex to form the products or, more precisely, the transition through an intermediate state of the complex, characterized by activation energy less than for the uncatalyzed reaction, to a complex of the enzyme and the products of reaction, with a rapid dissociation. Under conditions such that the concentration of the complex corresponds to equilibrium with the enzyme and the substrate, the rate of the reaction is given by the following equation (the Michaelis–Menten equation; Michaelis and Menten, 1913):

$$R = \frac{d[S]}{dt} = \frac{kE[S]}{[S] + (1/K)}. \tag{1}$$

In this equation $[S]$ is the concentration of the substrate, E is the total concentration of enzyme (present both as free enzyme and enzyme complex), K is the equilibrium constant for formation of the enzyme complex ES, and k is the reaction-rate constant for decomposition of the complex to form the enzyme and reaction products. This equation corresponds to the case in which there are no enzyme inhibitors present.

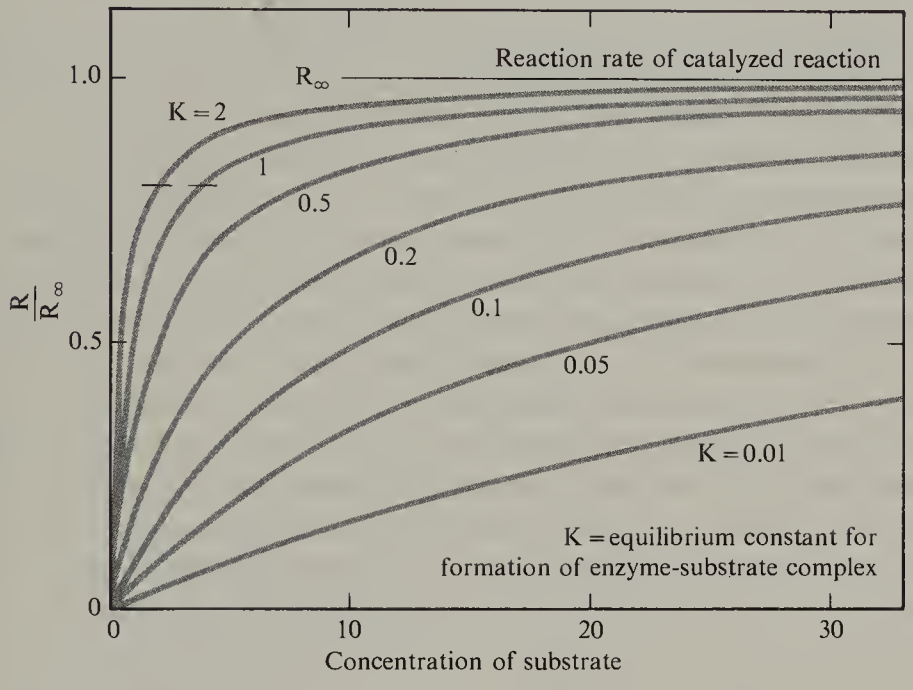


FIGURE 1-5.
Curves showing calculated reaction rate R/R_∞ of catalyzed reaction as function of the concentration of the substrate, for different values of the equilibrium constant K for formation of the enzyme-substrate complex.

Values of the reaction rate calculated from this equation for different values of K are shown in Figure 1-5. The curves are similar in shape to those of Figures 1-2 and 1-3. At concentrations much smaller than K^{-1} the reaction rate is proportional to the concentration of substrate. At larger concentrations, as the amount of enzyme complex becomes comparable to the amount of free enzyme, the reaction rate changes from the linear dependence. At substrate concentration equal to K^{-1} the slope of the curve is one-quarter of the initial slope, and the value is one-half of the value corresponding to saturation of the enzyme by the substrate.

The similarity of the curves of Figures 1-2 and 1-3 to appropriate curves in Figure 1-5 suggests that the growth substance may be involved in an enzyme-catalyzed reaction in which it serves as the substrate. The normal strain of the organism manufactures an amount of the substrate such as to permit the reaction to take place at what

may be considered a normal rate, 90 or 95 percent of the maximum rate, which corresponds to saturation of the enzyme. As described above, the gain in reaction rate associated with the manufacture of a larger amount of the substrate, with a corresponding advantage to the organism, might be balanced by the disadvantage to the organism associated with the upkeep of the larger amount of machinery required to manufacture the increased amount of substrate. An increase in rate of this reaction could also be achieved by an increase in the amount of the enzyme synthesized by the organism. Here, again, the advantage to the organism resulting from this increase may be overcome by the disadvantage associated with the increase in the amount of machinery required for the increased synthesis. During the process of evolution there has presumably been selection of genes determining the concentrations of the enzymes catalyzing successive reactions such as to achieve an approximation to the optimum reaction rate with the smallest amount of disadvantage to the organism.

The rate of an enzyme-catalyzed reaction is approximately proportional to the concentration of the reactant, until concentrations that largely saturate the enzyme are reached. The saturating concentration is larger for a defective enzyme with decreased combining power for the substrate than for the normal enzyme. For such a defective enzyme the catalyzed reaction could be made to take place at or near its normal rate by an increase in the substrate concentration, as indicated in Figure 1-5. The short horizontal lines intersecting the curves indicate what may be called the "normal" reaction rate, 80 percent of the maximum. For $K = 2$ the "normal" rate is achieved at substrate concentration $[S] = 2$. At this substrate concentration the reaction rate is only 29 percent of the maximum and 35 percent of "normal" for a mutated enzyme with $K = 0.2$; it could be raised to the "normal" value by a tenfold increase in the substrate concentration, to $[S] = 20$. Similarly, the still greater disadvantage of low reaction rate for a mutated enzyme with K only 0.01 could be overcome by a 200-fold increase in substrate concentration, to $[S] = 400$. This mechanism of action of gene mutation is only one of several that lead to disadvantageous manifestations that could be overcome by an increase, perhaps a great increase, in the concentration of a vital substance in the body. These considerations obviously suggest a rationale for megavitamin therapy.

MOLECULAR CONCENTRATIONS AND MENTAL DISEASE

The functioning of the brain and nervous tissue is more sensitively dependent on the rate of chemical reactions than the functioning of other organs and tissues. I believe that mental disease is for the most part caused by abnormal reaction rates, as determined by genetic constitution and diet, and by abnormal molecular concentrations of essential substances. The operation of chance in the selection for the child of half of

the complement of genes of the father and mother leads to bad as well as to good genotypes, and the selection of foods (and drugs) in a world that is undergoing rapid scientific and technological change may often be far from the best. Significant improvement in the mental health of many persons might be achieved by the provision of the optimum molecular concentrations of substances normally present in the human body. Among these substances, the essential nutrilites may be the most worthy of extensive research and more thorough clinical trial than they have yet received. One important example of an essential nutrilite that is required for mental health is vitamin B_{12}, cyanocobalamin. A deficiency of this vitamin, whatever its cause (pernicious anemia; infestation with the fish tapeworm *Diphyllobothrium*, whose high requirement for the vitamin results in deprivation for the host; excessive bacterial flora, also with a high vitamin requirement, as may develop in intestinal blind loops), leads to mental illness, often even more pronounced than the physical consequences. The mental illness associated with pernicious anemia (a genetic defect leading to deficiency of the intrinsic factor [a mucoprotein] in the gastric juice and the consequent decreased transport of cyanocobalamin into the blood) often is observed for several years in patients with this disease before any of the physical manifestations of the disease appear (Smith, 1950). A pathologically low concentration of cyanocobalamin in the serum of the blood has been reported to occur for a much larger fraction of patients with mental illness than for the general population. Edwin et al. (1965) determined the amount of B_{12} in the serum of every patient over 30 years old admitted to a mental hospital in Norway during a period of 1 year. Of the 396 patients, 5.8 percent (23) had a pathologically low concentration, less than 101 picograms per milliliter, and the concentration in 9.6 percent (38) was subnormal (101 to 150 picograms per milliliter). The normal concentration is 150 to 1300 picograms per milliliter. The incidence of pathologically low and subnormal levels of B_{12} in the serums of these patients, 15.4 percent, is far greater than that in the general population, about 0.5 percent (estimated from the reported frequency of pernicious anemia in the area, 9.3 per 100,000 persons per year). Other investigators[6] have also reported a higher incidence of low B_{12} concentrations in the serums of mental patients than in the population as a whole, and have suggested that B_{12} deficiency, whatever its origin, may lead to mental illness.

Nicotinic acid (niacin), when its use was introduced, cured hundreds of thousands of pellagra patients of their psychoses, as well as of the physical manifestations of their disease. For this purpose only small doses are required; the recommended daily allowance (National Research Council) is 12 milligrams per day (for a 70-kilogram male). In 1939 Cleckley et al. reported the successful treatment of 19 patients, and

[6] Hansen et al. (1966) report serum B_{12} concentration below 150 pg/ml in 13 of 1,000 consecutive patients admitted to a Copenhagen psychiatric clinic. Henderson et al. (1966) report that 9 of 1,012 unselected psychiatric patients in a region in Scotland were found to have B_{12} deficiency, in addition to 5 pernicious anemia patients in the group.

in 1941 Sydenstricker and Cleckley[7] reported similarly successful treatment of 29 patients with severe psychiatric symptoms by use of moderately large doses of nicotinic acid (0.3 to 1.5 grams per day). None of these patients had physical symptoms of pellagra or any other avitaminosis. More recently many other investigators have reported on the use of nicotinic acid and nicotinamide for the treatment of mental disease. Outstanding among them are Hoffer and Osmond, who since 1952 have advocated and used nicotinic acid in large doses, in addition to the conventional therapy, for the treatment of schizophrenia (Hoffer et al., 1957; Hoffer, 1962, 1966; Osmond and Hoffer, 1962; Hoffer and Osmond, 1964). The dosage recommended by Hoffer is 3 to 18 grams per day, as determined by the response of the patient, of either nicotinic acid or nicotinamide, together with 3 grams per day of ascorbic acid. Nicotinic acid and nicotinamide are nontoxic (the lethal dose, 50 percent effective [LD_{50}], is not known for humans, but probably it is over 200 grams; the LD_{50} for rats is 7.0 grams per kilogram for nicotinic acid and 1.7 grams per kilogram for nicotinamide), and their side effects, even in continued massive doses, seem not to be commonly serious. Among the advantages of nicotinic acid, summarized by Osmond and Hoffer (1962), are the following: it is safe, cheap, and easy to administer, and it is a well-known substance that can be taken for years on end, if necessary, with only small probability of incidence of unfavorable side effects.

Another vitamin that has been used to some extent in the treatment of mental disease is ascorbic acid, vitamin C. A sometimes-recommended daily intake of ascorbic acid is 75 milligrams for healthy adults. Some investigators have estimated that the optimum intake is much larger (Kyhos et al., 1945), perhaps 3 to 15 grams per day, according to Stone (1966, 1967). Williams and Deason (1967) have emphasized the variability of individual members of a species of animals; they have reported their observation of a 20-fold range of required intake of ascorbic acid by guinea pigs, and have suggested that human beings, who are less homogeneous, have a larger range.

Mental symptoms (depression) accompany the physical symptoms of vitamin-C deficiency disease (scurvy). In 1957, Akerfeldt reported that the serum of schizophrenics had been found to have greater power of oxidizing N,N-dimethyl-*p*-phenylenediamine than that of other persons. Several investigators then reported that this difference is due to a smaller concentration of ascorbic acid in the serum of schizophrenics than of other persons. This difference has been attributed to the poor diet and increased tendency to chronic infectious disease of the patients (Benjamin, 1958; Kety, 1959), and has also been interpreted as showing an increased rate of metabolism of ascorbic acid by the patients (Hoffer and Osmond, 1960; Briggs, 1962). It is my opinion, from the study of the literature, that many schizophrenics have an increased metabolism of ascorbic acid, presumably genetic in origin, and that the

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[7] References are given in this paper to some earlier work on nicotinic acid therapy.

ingestion of massive amounts of ascorbic acid has some value in treating mental disease.

Other vitamins (thiamine, pyridoxine, folic acid) and other substances (zinc ion, magnesium ion, uric acid, tryptophan, L(+)-glutamic acid, and others) influence the functioning of the brain. I shall review work on L(+)-glutamic acid as a further example. L(+)-Glutamic acid is an amino acid that is present at rather high concentration in brain and nerve tissue and plays an essential role in the functioning of these tissues (Weil-Malherbe, 1936). It is normally ingested (in protein) in amounts of 5 to 10 grams per day. It is not toxic; large doses may cause increased motor activity and nausea. In 1943 Price et al. reported favorable results for glutamic acid therapy of convulsive disorders (benefit to one out of three or four patients with petit mal epilepsy; Waelsch, 1948). Zimmerman and Ross (1944) then reported an increase in maze-running learning ability of white rats given extra amounts of glutamic acid. Zimmerman and many other investigators then studied the effects of glutamic acid on the intelligence and behavior of persons with different degrees and kinds of mental retardation. L(+)-Glutamic acid is apparently more effective than its sodium or potassium salts. The effective dosage is usually between 10 and 20 grams per day (given in three doses with meals), and is adjusted to the patient as the amount somewhat less than that required to cause hyperactivity. Several investigators[8] have reported an improvement in personality and increase in intelligence (by 5 to 20 I.Q. points) for many patients with mild or moderate mental deficiency.

LOCALIZED CEREBRAL DEFICIENCY DISEASES

The observation that the psychosis associated with pernicious anemia may manifest itself in a patient for several years before the other manifestations of this disease become noticeable has a reasonable explanation: the functioning of the brain and nervous tissue is probably more sensitively dependent on molecular composition than is that of other organs and tissues. The observed high incidence of cyanocobalamin deficiency in patients admitted to a mental hospital, mentioned above, suggests that mental disease may rather often be the result of this deficiency, and further suggests that other deficiencies in vital substances may be wholly or partly responsible for many cases of mental illness.

The foregoing arguments suggest the possibility that under certain circumstances a deficiency disease may be localized in the human body in such a way that only some of the manifestations usually associated with the disease are present. Let us consider, for example, a vitamin or other vital substance that is normally metabolized by the

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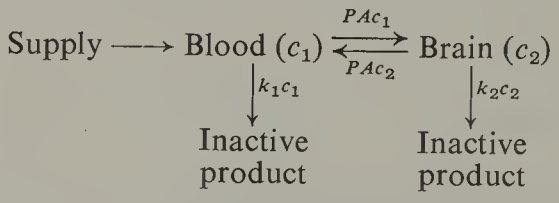
[8] A recent survey of the role of glutamic acid in cognitive behaviors has been published by Vogel et al. (1966). Many references to earlier work are given in this paper.

catalytic action of an enzyme normally present in the tissues and organs of the body. In a person of unusual genotype there might be an especially great concentration of this enzyme in one body organ, with essentially the normal amount in other organs. Through the action of this enzyme in especially great concentration the steady-state concentration of the vital substance in that organ might be decreased to a level much lower than that required for normal function. Under these circumstances there would be present a deficiency disease restricted to that organ.

An especially important case is that of the brain. We may, as a rough model of the human body, consider two reservoirs of fluid, the blood and lymph, with volume V_1, and cerebrospinal fluid, the extracellular fluid of the brain and spinal column, with volume V_2. We assume that a vital substance is destroyed in each of these reservoirs at a characteristic rate, corresponding to the rate constants k_1 and k_2, that it diffuses across the blood-brain barrier at a rate determined by the product of the permeability and area of the barrier and the difference $c_2 - c_1$ of the concentrations in the two reservoirs, and that it is introduced from the gastrointestinal tract into the first reservoir at a constant rate. The steady-state concentrations are then in the ratio

$$c_1/c_2 = 1 + (k_2V_2/PA)$$

where PA is the product of permeability and the area of the blood-brain barrier. The steady state corresponds to the following system:



From this equation it is seen, as shown also in Figure 1-6, that for small values of k_2V_2/PA the difference in steady-state concentrations in the cerebrospinal fluid and the blood is small, but that through either decrease in permeability of the barrier or increase in the metabolic rate constant k_2 the steady-state concentration in the brain becomes much less than that in the blood.

This simple argument leads us to the possibility of a localized cerebral avitaminosis or other localized cerebral deficiency disease. There is the possibility that some human beings have a sort of cerebral scurvy, without any of the other manifestations, or a sort of cerebral pellagra, or cerebral pernicious anemia. It was pointed out by Zuckerkandl and Pauling (1962) that every vitamin, every essential amino acid, every other essential nutrilite represents a molecular disease (Pauling et al., 1949) which our distant ancestors learned to control, when it began to afflict them, by selecting a therapeutic diet, and which has continued to be kept under control in this way. The localized deficiency diseases described above are also molecular diseases, compound molecular diseases, involving not only the original lesion, the loss of the ability to

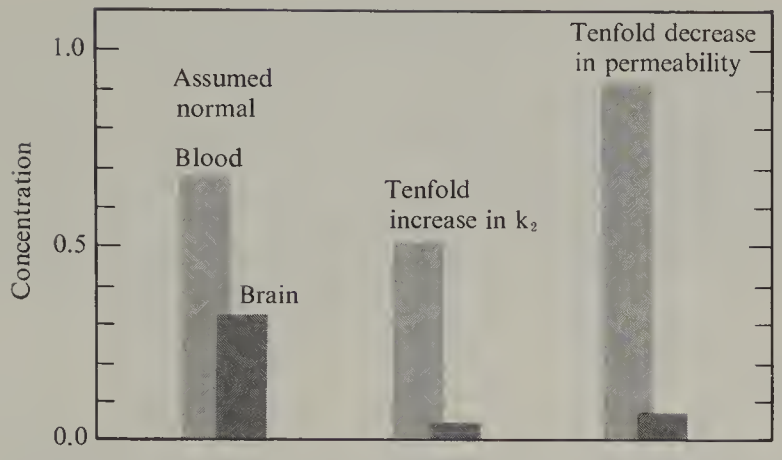


FIGURE 1-6.
Values of the concentration of a vital substance in the blood and in the cerebrospinal fluid for three different assumed sets of values of blood-brain barrier permeability and rate of destruction in the cerebrospinal fluid.

synthesize the vital substance, but also another lesion, one that causes a decreased rate of transfer across a membrane, such as the blood-brain barrier,[9] to the affected organ, or an increased rate of destruction of the vital substance in the organ, or some other perturbing reaction.

It has been suggested by Huxley et al. (1964), partially on the basis of the observations of Böök (1953, 1958) and Slater (1958) on the incidence of schizophrenia in relatives of schizophrenics, that schizophrenia is caused by a dominant gene with incomplete penetrance. They suggested that the penetrance, about 25 percent, may in some cases be determined by other genes and in some cases by the environment. I suggest that the other genes may, in most cases, be those that regulate the metabolism of vital substances, such as ascorbic acid, nicotinic acid or nicotinamide, pyridoxine, cyanocobalamin, and other substances mentioned above. The reported success in treating schizophrenia and other mental illnesses by use of massive doses of some of these vitamins may be the result of successful treatment of a localized cerebral deficiency disease involving the vital substances, leading to a decreased penetrance of the gene for schizophrenia. There is a possibility that the so-called gene for schizophrenia is itself a gene affecting the metabolism of one or another of these vital substances, or even of several vital substances, causing a multiple cerebral deficiency.

I suggest that the orthomolecular treatment of mental disease, to be successful, should involve the thorough study of and attention to the individual, such as is

[9] It has been suggested by Melander and Martens (1958, 1959) and by Hoffer and Osmond (1966) that the effects of taraxein (Heath et al., 1958) may result from changing the permeability of the blood-brain barrier.

customary in psychotherapy but less customary in conventional chemotherapy. In the course of time it should be possible to develop a method of diagnosis (measurement of concentrations of vital substances) that could be used as the basis for determining the optimum molecular concentrations of vital substances for the individual patient and for indicating the appropriate therapeutic measures to be taken. My coworkers and I are carrying on some experimental studies suggested by the foregoing considerations, and hope to be able before long to communicate some of our results.

SUMMARY

The functioning of the brain is affected by the molecular concentrations of many substances that are normally present in the brain. The optimum concentrations of these substances for a person may differ greatly from the concentrations provided by his normal diet and genetic machinery. Biochemical and genetic arguments support the idea that orthomolecular therapy, the provision for the individual person of the optimum concentrations of important normal constituents of the brain, may be the preferred treatment for many mentally ill patients. Mental symptoms of avitaminosis sometimes are observed long before any physical symptoms appear. It is likely that the brain is more sensitive to changes in concentration of vital substances than are other organs and tissues. Moreover, there is the possibility that for some persons the cerebrospinal concentration of a vital substance may be grossly low at the same time that the concentration in the blood and lymph is essentially normal. A physiological abnormality such as decreased permeability of the blood-brain barrier for the vital substance, or increased rate of metabolism of the substance in the brain, may lead to a cerebral deficiency and to a mental disease. Diseases of this sort may be called localized cerebral deficiency diseases. It is suggested that the genes responsible for abnormalities (deficiencies) in the concentration of vital substances in the brain may be responsible for increased penetrance of the postulated gene for schizophrenia, and that the so-called gene for schizophrenia may itself be a gene that leads to a localized cerebral deficiency in one or more vital substances.

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2

Results of a Loading Test of Ascorbic Acid, Niacinamide, and Pyridoxine in Schizophrenic Subjects and Controls

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INTRODUCTION

During the past fifteen years many studies of ascorbic acid in relation to schizophrenia have been published.[1] Our attention was brought to this field by the report by VanderKamp (1966) that a much larger intake of ascorbic acid is needed by hospitalized chronic schizophrenics than by other persons to reach a standard concentration of the acid in their urine (later verified by Herjanic and Herjanic, 1967). After making a preliminary quantitative study of the urinary excretion of ascorbic acid, we conducted a loading test (determination of the amount of ascorbic acid eliminated in the urine during the 6-hour period following oral ingestion of a sample) with schizophrenic subjects in University Hospital of San Diego County and in Mesa Vista Hospital (a private hospital in San Diego, California), in each case with a parallel control group of normal subjects. The technique of administering the vitamin was then improved somewhat, and the program was broadened to include two other

[1] See Chapter 14 for a summary of these studies.

TABLE 2-1.
Nature of the Vitamin Loading Tests

County, ascorbic acid:
46 County patients (23F, 23M), 14 controls (7F, 7M) from UCSD and County staff; vitamin in orange juice:*

County, niacinamide:
26 County patients, 20 controls from UCSD and County staff; vitamin in gelatin capsule, with one glass of water.

Mesa Vista, ascorbic acid:
16 Mesa Vista patients, 16 controls from Mesa Vista staff; vitamin in orange juice (after breakfast); vitamin administered on eight consecutive days, urine collected on first and eighth days (five patients failed to complete the experiment).

Patton-1, ascorbic acid, niacinamide, pyridoxine:
35 Patton patients† (18F, 17M), 15 controls‡ from UCSD staff; vitamins in gelatin capsules, with one can of Nutrament§ (instead of breakfast), two glasses of water.

Patton-2, ascorbic acid:
28 Patton patients (13F, 15M), of whom 18 (8F, 10M) had been used also in Patton-1; vitamins same as Patton-1, two months after Patton-1; analysis performed for ascorbic acid only.

Patton-(1 + 2), ascorbic acid:
44 Patton patients (22F, 22M); a combination of Patton-1 and Patton-2 where values for patients present in both Patton-1 and Patton-2 (8F, 10M) were averaged.

Stanford, ascorbic acid, niacinamide, pyridoxine:
44 controls (6F, 38M) from Stanford staff; vitamins in gelatin capsules, with one can of Nutrament (instead of breakfast), two glasses of water.

* All vitamins administered orally.
† One ascorbic acid sample and three niacinamide samples were lost during analysis.
‡ Only 13 controls were used for niacinamide and 11 controls for pyridoxine.
§ Nutrament breakfast drink is a registered brand name.

vitamins, niacinamide and pyridoxine, that had been reported to be of benefit to some schizophrenic patients. This program was then carried out with a group of schizophrenics in Patton State Hospital, Patton, California, with a control group there and a larger control group of normal subjects at Stanford University (Table 2-1).

In all our studies the schizophrenic groups consisted of persons who had been diagnosed as such by two physicians. We attempted no differential diagnosis.

THE LOADING TESTS

The vitamins were given orally to each patient in a dosage proportional to the two-thirds power of the body weight, with the constant such that a 200-pound subject received 0.01 mole of ascorbic acid and, if the other vitamins were being studied, 0.01 mole of niacinamide and 0.005 mole of pyridoxine. (An exception was the Stanford study, in which for convenience each subject received the 200-pound dose of each

vitamin: 1.76 g of ascorbic acid, 1.22 g of niacinamide, and 1.03 g of pyridoxine hydrochloride.) Complete samples of urine were taken during the 2-hour period preceding the oral dose of vitamins and for each of three 2-hour periods following. The samples were immediately frozen in solid carbon dioxide (after addition of 1 ml of 1 N hydrochloric acid solution—see section on experimental methods) and taken to the laboratory for later analysis by the methods described in the section on experimental methods. No interesting results were obtained from the first samples (before the oral dose), and the analytical values for this period are not given in this paper. Of the three later 2-hour samples, the values for a subject were usually proportional, with the fraction of the dose appearing in the urine during the second period usually about twice that in either the first or third period. To simplify the discussion, the sum of the three values (the fraction of the dose appearing in the urine during the period of 6 hours following the oral administration of the dose) is discussed in this report. No significantly different conclusions were reached by consideration of the results of analysis of the separate 2-hour specimens.

THE TESTS WITH ASCORBIC ACID

The fractions of the oral dose of ascorbic acid present in the urine of the subjects during the next 6 hours are shown in Figure 2-1. The mean values for the five control groups are consistently higher than those for the five schizophrenic groups (the sixth, Mesa Vista 8th day, is discussed below).

Because the experimental techniques changed somewhat in the course of the work, the most reliable comparisons are those between each schizophrenic group and its control group, which was studied at the same time and by the same methods. Application of the Wilcoxon series test (described, for example, by Sokal and Rohlf, 1969) showed that in each case the null hypothesis that the schizophrenic group and the control group are randomly selected groups from a uniform population is rejected with statistical significance. The level of confidence ($1 - P$, one-tailed) with which the null hypothesis is rejected has the following values:

County	99.99%
Mesa Vista	99.6%
Patton–1	99.993%
Patton–2	99.97%
Patton–(1 + 2)	99.996%

We have formulated another method for statistical evaluation of the results. Examination of the distribution of the points for normal subjects in the earlier studies (County, Mesa Vista, Patton) showed that they were not distributed in accordance with a distribution function approximating the error function in either the fraction

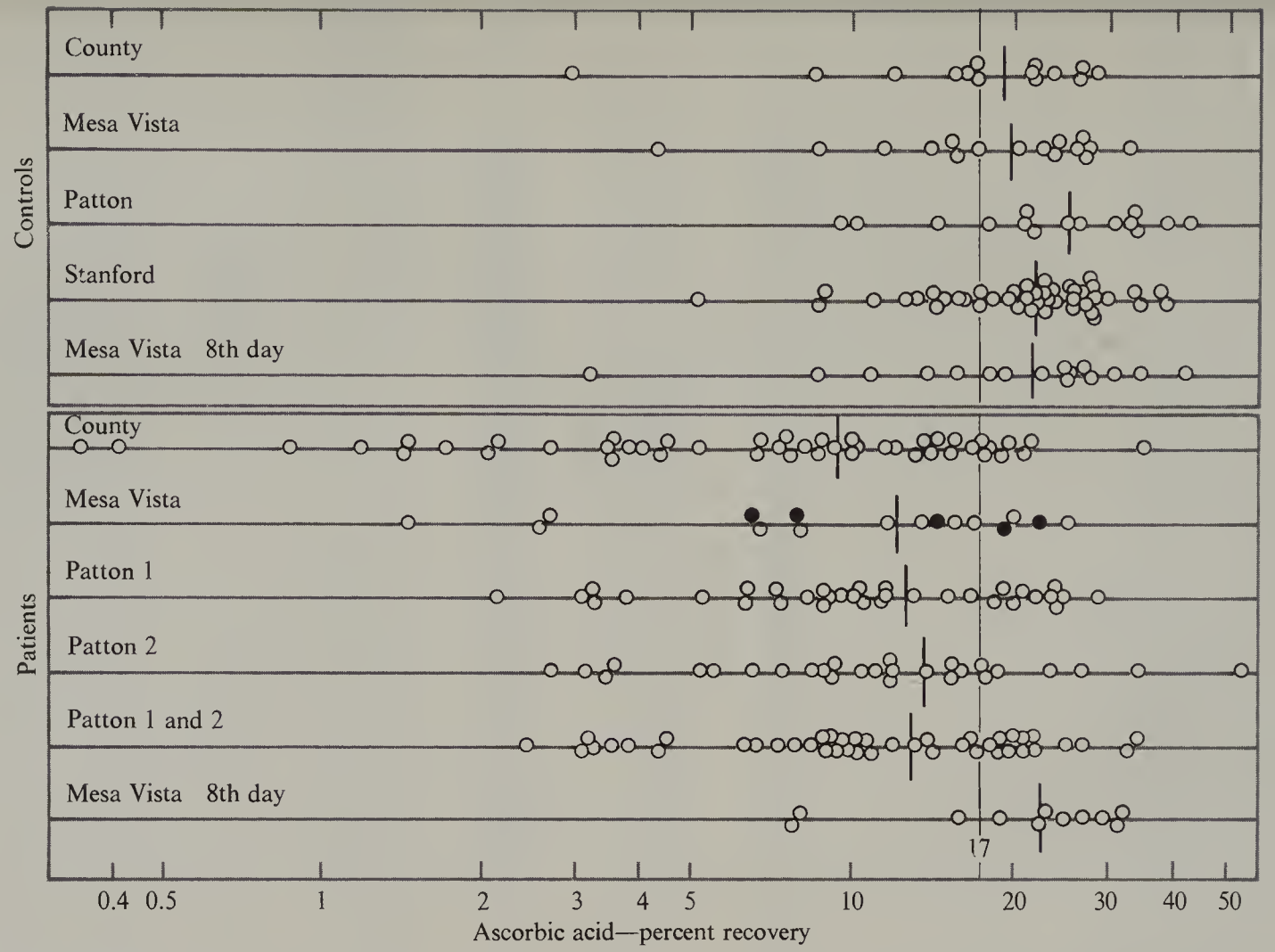


FIGURE 2-1.
Values of percentages of an oral dose of L-ascorbic acid found in the urine during the six-hour period after ingestion of the dose.

eliminated or its logarithm, and indicated instead a sum of three such functions. The Stanford study, with 44 normal subjects, was carried out to check this point and, as can be seen from Figure 2-1, gave results supporting the earlier indication. A distribution function derived from the Stanford points by a method formulated by us is shown as the upper curve in Figure 2-2. This function is the sum of 44 error functions, representing the 44 experimental values. Each error function is normalized to unit area, centered on its point, and has standard deviation 2.5 times the logarithmic distance to the third nearest neighboring point.

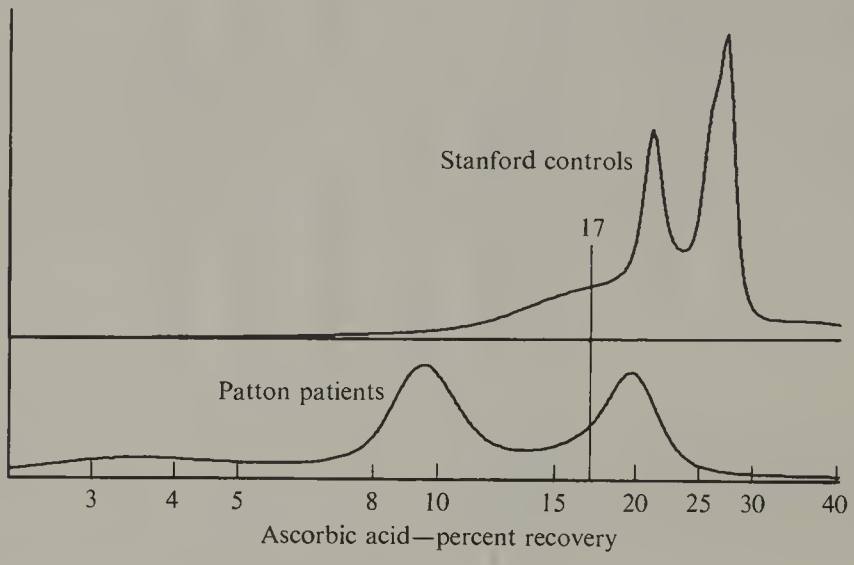


FIGURE 2-2.
Probability-distribution curves, calculated as described in the text, for percent of ascorbic acid recovered in the six-hour urine for 44 Stanford control subjects (above) and for 44 Patton schizophrenic subjects (below).

The distribution function shown in Figure 2-2 clearly indicates that with respect to the handling of ascorbic acid the 44 normal subjects are not essentially similar. The fraction of ascorbic acid eliminated in 6 hours differed from a normal (mean) value because of a number of randomly effective environmental and polygenic factors. The subjects are probably representative of three different populations: the high excretors (above 25 percent, 17/44), the medium excretors (17 to 25 percent, 16/44), and the low excretors (below 17 percent, 11/44). It seems to us unlikely that dietary differences would lead to such a distribution function. The reasonable hypothesis that the three groups result from two alleles *l* and *h* in a single gene locus, and represent the genotypes *ll* (low excretors), *lh* (medium), and *hh* (high) could, of course, be checked by familial studies, which we have not as yet undertaken.

The distribution curve for recovery of ascorbic acid by the Patton–(1 + 2) combined group of 44 schizophrenic subjects is shown in the lower part of Figure 2-2. There is clear indication of three groups, centered on 3.5 percent, 10 percent, and 20

percent, respectively. If the division into separate groups, as indicated in Figure 2-2, is accepted, there are two obvious alternative explanations of the differences between the upper curve and the lower curve. The first explanation is that the factor of decreased intake of ascorbic acid (poor nutrition of the schizophrenic subjects) operates to shift all values of percent recovery down. The normal peak around 27 percent would thus be shifted to 20 percent, that at around 22 percent to 10 percent, and that around 10 percent to 3.5 percent. The alternative is that the groups are not shifted, but instead the number of subjects in these groups is changed, with the top group, around 27 percent, much decreased in the schizophrenic subjects, and the groups around 10 percent and 3.5 percent much increased. Additional studies will be needed to check the reliability of this apparent division into groups and to distinguish between the alternative explanations of the differences between the distribution curves. There is no doubt, however, that there is a striking difference in the distribution of schizophrenic subjects and control subjects with respect to the recovery of an orally administered dose of ascorbic acid.

Let us assume that the upper limit of the low-excretor group is 17 percent elimination of the dose of ascorbic acid in 6 hours. The number of low excretors and the total group number are the following:

Controls: County 7/14, Mesa Vista 6/16, Patton 3/15, Stanford 11/44.
Schizophrenics: County 38/46, Mesa Vista 12/16, Patton–1 24/34, Patton–2 21/28, Patton–(1 + 2) 31/44.

Of the schizophrenic subjects 76 percent are low excretors, 2.5 times the incidence (30 percent) for the controls.

The numbers of low excretors can be used in a second test of the null hypothesis that the schizophrenic group and its control group are selected randomly from the same population. The values of χ^2 for a two-by-two test of these groups lead to the following values of the confidence level of rejection of the null hypothesis:

County	$1 - P$ (two-tailed) $> 99.5\%$
Mesa Vista	$> 96.5\%$
Patton–(1 + 2)	$> 99.93\%$

The four control groups show no statistically significant differences with one another, and may be combined into a single control group, with 27 low excretors in 89 subjects; similarly, the single combined schizophrenic group contains 81 low excretors in 106 subjects. These numbers lead to rejection of the null hypothesis at the confidence level $1 - P$ (two-tailed) > 99.9999 percent ($\chi^2 = 41.57$).

There is no doubt that the schizophrenic patients we studied differed significantly from the control groups in their elimination of ascorbic acid. It is known that

cigarette smokers tend to have low blood levels of ascorbic acid, but among our subjects there were few smokers, and they did not show a significant difference from the nonsmokers. For example, the average excretion for the five Stanford smokers was 22.26 percent, as compared with 22.16 percent for all 44 Stanford subjects. (The Stanford subject with the lowest value, 5.16-percent excretion, was a cigarette smoker; the four others were not in the low group.) The sex of the subjects had no significant bearing on the results.

EFFECT OF INCREASED INGESTION OF ASCORBIC ACID

In the Mesa Vista series the loading test was repeated after extra ascorbic acid (1.23 to 2.04 g) had been administered each day for seven days. The results of the test on the eighth day are shown in Figure 2-1. For the control group there was essentially no change: average recovery increased from 20.0 percent to 21.5 percent, and low excretors decreased from 7/16 to 5/16. For the 11 members of the schizophrenic group who were tested on the eighth day,[2] however, there was a large change: average recovery increased from 11.3 percent for the 11 subjects to 21.7 percent, and low excretors decreased from 9/11 to 3/11. There is a striking difference between the schizophrenic subjects and the control subjects not only in the number of low excretors but also in the response to an increased intake of ascorbic acid. We surmise that many of the schizophrenic subjects had a high degree of "tissue unsaturation," which was rectified by the ingestion of about 10 g of extra ascorbic acid during the week of treatment.

THE TESTS WITH NIACINAMIDE

In Figure 2-3 the fractions of the oral dose of niacinamide found in the urine excreted by the subjects during the next 6 hours are shown. As was found for ascorbic acid, the mean values of the three control groups are consistently higher than those for the two schizophrenic groups by about 45 percent (as compared with 90 percent for ascorbic acid). Comparison of the County schizophrenic group with its control group and of the Patton schizophrenic group with its control group by the Wilcoxon sequence test showed that for each pair the null hypothesis that the two groups of the pair are randomly selected from a population uniform with respect to the handling of

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[2] Five subjects failed to complete the 8-day study because of departure from the hospital.

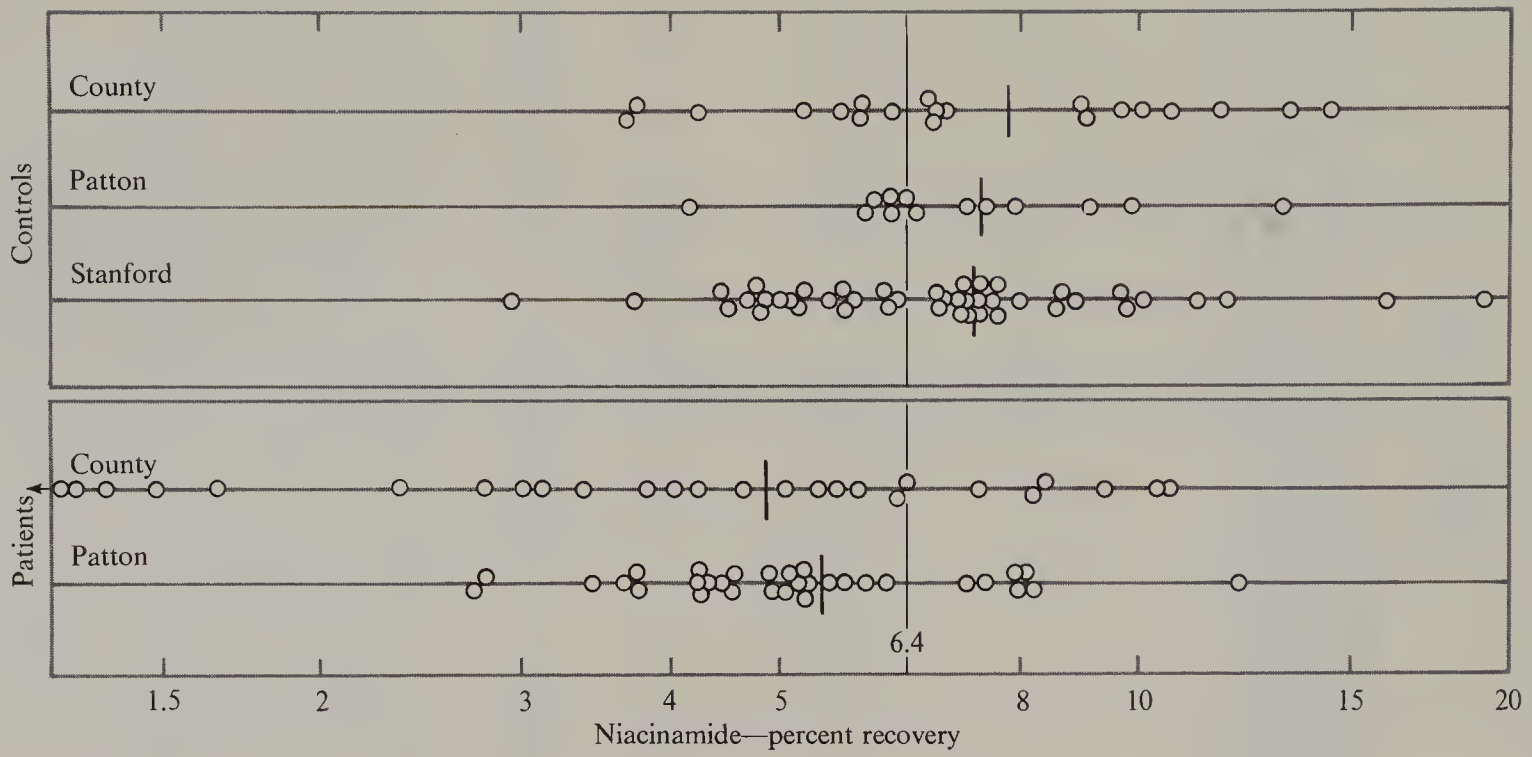


FIGURE 2-3.
Values of percentages of an oral dose of niacinamide found in the six-hour urine.

niacinamide is rejected with statistical significance, at the following values of the level of confidence (1 — P, one-tailed):

County	99.8%
Patton	99.98%

The niacinamide distribution function for the Stanford control group, calculated in the same way as for ascorbic acid (Figure 2-2), is shown in Figure 2-4. It is seen that a division into two or three groups is indicated, with one group consisting of the subjects with less than 6.4 percent of the dose of niacinamide, the low excretors. Of the 44

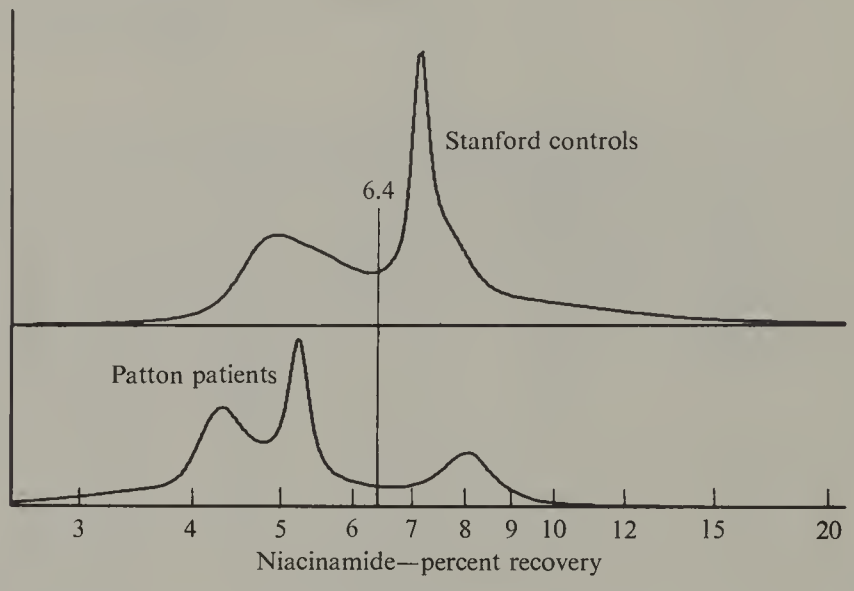


FIGURE 2-4.
Niacinamide-recovery probability-distribution curves for 44 Stanford control subjects (above) and for 32 Patton schizophrenic subjects (below).

Stanford subjects, 19 (43 percent) are low excretors. The second peak indicates the medium excretors, of whom there are 15 (34 percent) if the upper limit of their range is taken (rather arbitrarily) at 8.5 percent. The remaining 10 high excretors (23 percent) have values of recovery from 8.6 to 19 percent. Low excretors constitute 40 percent (8/20) of the County controls, 38 percent (5/13) of the Patton controls, 79 percent (20/26) of the County schizophrenics, and 78 percent (25/32) of the Patton schizophrenics. The values of χ^2 for a two-by-two test of pairs of numbers lead to the following values of the confidence level of rejection of the null hypothesis:

County	$1-P$ (two-tailed) $> 99.9\%$
Patton	$> 99.9\%$

The three control groups and the two schizophrenic groups may be combined, giving 32 low excretors in 77 control subjects (42 percent) and 45 low excretors in 58

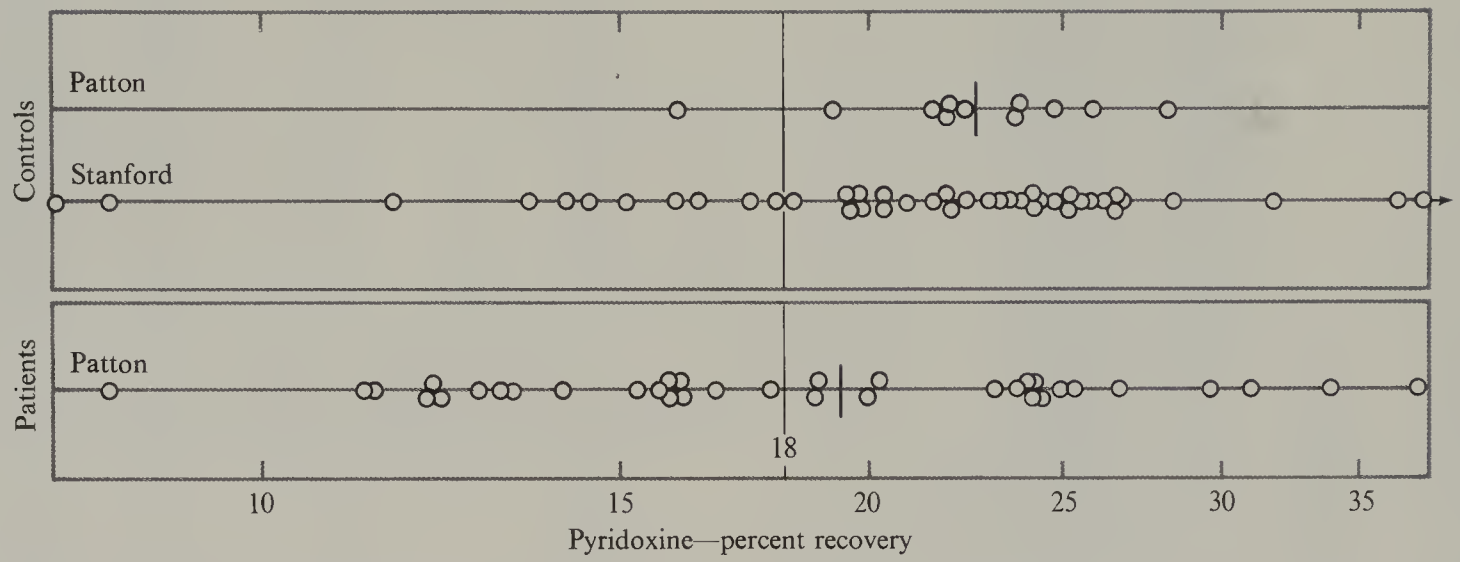


FIGURE 2-5.
Values of percentages of an oral dose of pyridoxine found in the six-hour urine.

schizophrenic subjects (78 percent). The statistical significance of this difference is very high, 99.997 percent ($\chi^2 = 17.52$). We conclude that with respect to their handling of niacinamide the schizophrenic groups in our study are significantly different from the control groups.

THE TESTS WITH PYRIDOXINE

The results of loading tests with pyridoxine for 34 schizophrenic subjects in Patton State Hospital and their 11 control subjects and for 44 normal subjects in the Stanford test are shown in Figure 2-5. The mean value for each of the two control groups is 17 percent higher than that for the schizophrenic group. Application of the Wilcoxon sequence test for the Patton schizophrenic group and its control group leads to rejection of the null hypothesis that the two groups are randomly selected from a population uniform with respect to the handling of pyridoxine at the confidence level $1 - P$ greater than 95.7 percent.

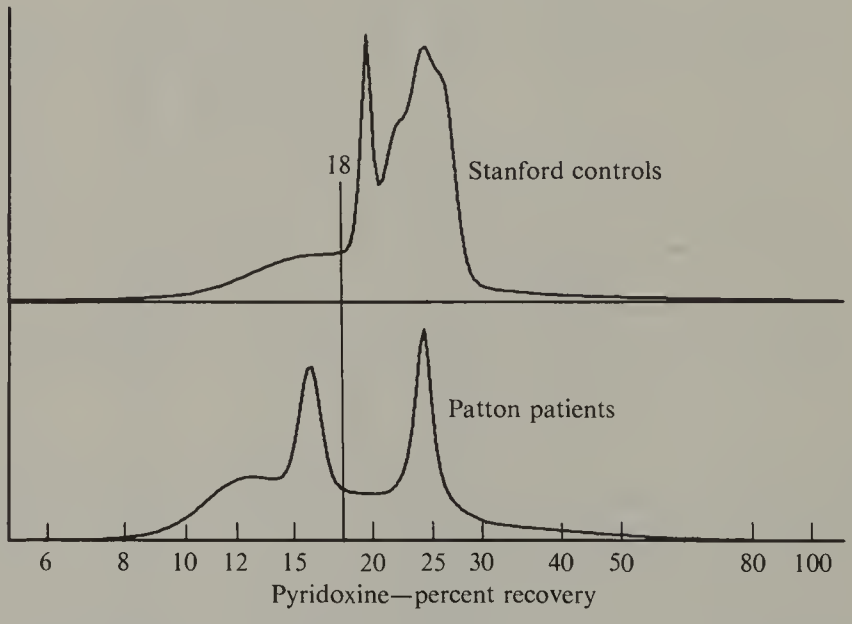


FIGURE 2-6.
Pyridoxine-recovery probability-distribution curves for 44 Stanford control subjects (above) and for 35 Patton schizophrenic subjects (below).

The pyridoxine distribution functions for the Stanford control group and the Patton patients, calculated in the same way as for ascorbic acid (Figure 2-2), are shown in Figure 2-6. It is seen that there are indications of a division into three groups. The group of low pyridoxine excretors, up to 18 percent (vertical line in Figure 2-6), includes 11 of the 44 Stanford control subjects (25 percent), 1 of the 11 Patton control

subjects (9 percent), and 18 of the 35 Patton schizophrenic subjects (51 percent). The null hypothesis is rejected at the 99.2 percent confidence level by comparing Patton schizophrenics with the Patton control group, and at the 99.6 percent confidence level by comparing Patton schizophrenics with Patton controls plus Stanford controls.

CORRELATION OF LOW VALUES IN THE THREE VITAMINS

Loading tests with the three vitamins administered at the same time were carried out for 50 control subjects (Patton 6, Stanford 44) and for 31 schizophrenic subjects (Patton). Data on subjects with low excretion in one vitamin only, two vitamins, or all three are given in Table 2-2.

If low values were the result of poor nutrition there would be positive correlation of the incidence, and the number of subjects low in all three would increase. The numerals in parentheses in Table 2-2 are calculated from the values of the incidences, assuming them to be independent of one another. The differences between observed

TABLE 2-2.
Correlation of Low Excretion in Three Vitamins in Schizophrenic and Control Subjects

Characteristic	Controls[a]	Schizophrenics[b]
Number of subjects	50	31
Incidence of L(AA)[c]	0.320[d]	0.742[d]
Incidence of L(Ni)	0.460[d]	0.806[d]
Incidence of L(Py)	0.240[d]	0.516[d]
L(AA) only	3 (6.6)[e]	2 (2.2)[e]
L(Ni) only	10 (11.9)	3 (3.1)
L(Py) only	1 (4.4)	1 (0.8)
L(AA + Ni)	6 (5.6)	8 (9.0)
L(AA + Py)	4 (2.1)	1 (2.3)
L(Ni + Py)	4 (3.8)	2 (3.3)
L(AA + Ni + Py)	3 (1.8)	12 (9.6)
Not low in any	19 (14.0)	2 (0.7)

[a] Patton (6 subjects) plus Stanford (44 subjects).
[b] Patton.
[c] AA = ascorbic acid, Ni = niacinamide, Py = pyridoxine.
[d] Fraction of subjects with low excretion of the vitamin.
[e] Values in parentheses are calculated from values of incidence, rows 2 to 4, assuming independence in incidence from one another.

and calculated numbers are not statistically significant, but there is some indication of positive correlation, especially for the control group (15 observed low in two or all three vitamins, 11.7 calculated). The values for the schizophrenic group (22 observed, 23.7 calculated) indicate no correlation.

A reasonable possibility is that positive correlation, resulting from poor nutrition (low intake of all three vitamins or poor assimilation of all three vitamins), operates for both groups, and is effectively cancelled for the schizophrenic group by another effect, peculiar to the schizophrenic population, that introduces negative correlation. Let us assume that correlation introduces a factor in the frequency of subjects low in two vitamins and another factor in the frequency of subjects low in three vitamins. The value of the first factor is about 5, and that of the second is about 25 (incidences 0.10, 0.35, and 0.10 for ascorbic acid, niacinamide, and pyridoxine, respectively, then give calculated values within 1.5 of the observed values). An effect that increased the number of subjects low in one vitamin only in the schizophrenic population (relative to those low in two or three) could account for the differences between the correlations for controls and schizophrenics in Table 2-2. This effect might be a change in genotype affecting one vitamin only, thus increasing the probability of hospitalization for schizophrenia.

DISCUSSION AND SUMMARY

Our studies have shown that there is a pronounced difference, with high statistical significance, in the response of groups of schizophrenic patients and control groups to orally ingested doses of ascorbic acid, niacinamide, and pyridoxine, as shown by the fractions of the ingested doses eliminated in the urine during the period of 6 hours immediately following the doses. The observations for ascorbic acid are in general agreement with the results of many earlier studies, summarized by Herjanic in Chapter 14; those for niacinamide and pyridoxine are, we believe, new.

Our results indicate that for each of the three vitamins the population, either schizophrenic or normal, does not show a simple distribution function for the fraction of vitamin eliminated, but instead shows clustering into groups. The upper limit for the fraction excreted in 6 hours by low excretors has been taken as 17 percent, 6.4 percent, and 18 percent for ascorbic acid, niacinamide, and pyridoxine. The low excretors of the individual vitamins in the normal population constitute about 30, 40, and 20 percent, and in the schizophrenic population about 75, 80, and 50 percent,

respectively. About 60 percent of the control population and 94 percent of the schizophrenic population are low excretors for one or more of the three vitamins.

The pattern of excretion of ascorbic acid is changed very little for the control subjects by the ingestion of 1 to 2 g of this vitamin per day for one week, but that for the schizophrenic subjects is shifted so that it becomes the same as for the controls. It is likely that the low excretors have a low body store of the vitamin, and that this store is brought up to the normal value by a sufficiently increased daily intake.

The observations reported in Table 2-2 make possible some statements about the probability of hospitalization for schizophrenia of persons in different categories of vitamin excretion (assuming that the low excretors in the schizophrenic group would remain low excretors if they had been tested at other times, and that the control subjects represent the population as a whole). The ratio of the probability of hospitalization for schizophrenia of the various kinds of excretors to that for persons not low in any of the three vitamins is: low in one vitamin, probability 5 times as great; low in two vitamins, 8 times as great; low in all three vitamins, 40 times as great.

Only 6 percent of our schizophrenic subjects were found by our tests not to be low in any of the three vitamins. A complete understanding of vitamins in relation to schizophrenia has not yet been obtained. There is uncertainty as to the relative contributions of genetic and environmental factors, and to the effect of the schizophrenic episodes and of hospitalization on the biochemical and physiological functioning of the patients. There is no uncertainty, however, about the fact that the great majority, 94 percent, of the hospitalized schizophrenic subjects studied by us show a low urinary excretion of one or more of the three vitamins which we have studied, and that this is an indication of a low content of vitamins in the body, which can be rectified by the methods of orthomolecular psychiatry—the increased daily intake of the vitamins, as discussed in other chapters of this book.

These vitamins are inexpensive and they are almost entirely nontoxic and free of undesirable side reactions, as compared with ordinary drugs. Studies of individual patients might indicate which vitamins are especially needed. We feel, however, that at the present time these vitamin studies of individual patients need not be carried out before megavitamin therapy is instituted, because almost all schizophrenics are low excretors for at least one of the three vitamins, and an increased intake of any of these vitamins has small probability of doing harm, and large probability of doing good.

This work may be summarized by the following statement: observations made by administration of an oral dose of ascorbic acid, niacinamide, and pyridoxine, and determination of the fractions excreted in the urine in the next 6 hours have shown that almost all of the schizophrenic patients studied are low excretors for one or more of the three vitamins. These results strongly support the use of megavitamin therapy for the prevention and treatment of schizophrenia.

EXPERIMENTAL METHODS

Analysis for Ascorbic Acid by Iodine Titration

All the urine samples were collected in 500-ml plastic bottles which contained 1 ml of 1 *N* HCl, to lower the *p*H of the urine and thus inhibit the oxidation of ascorbic acid. The samples were kept frozen at −20°C until analysis. For the experiment using normal subjects at Stanford University, the samples were analyzed immediately after collection for ascorbic acid and were frozen in small glass bottles at −76°C for later analysis for niacinamide and pyridoxine. The analysis was performed as follows: add 1 ml of 1 *N* HCl to a 50-ml conical flask; add 10 ml mixed urine to flask; add about 3 ml of chloroform; add a 1/4 inch magnetic stirring rod; place on magnetic stirrer and adjust to highest speed without splattering; titrate with I_2 solution (6.25 g of I_2 and 20.0 g of KI in 2 liters of water, 0.0123 M) from a 5-ml buret. In making the end-point determination, ignore the pink color that sometimes occurs immediately in the chloroform phase, titrate rapidly until the yellow color of iodine lingers at the point of addition, and then titrate very slowly until a lasting pink color is seen in the chloroform phase. The titrations were usually made in triplicate, and the iodine solutions were standardized every week by titrating weighed amounts of crystalline L-ascorbic acid.

Analysis for Niacinamide by Microbiological Assay

The analysis for niacinamide for all County subjects was done by the microbiological method described by Strohecker and Henning (1966) with use of a strain of *Lactobacillus arabinosus* (ATCC 8014) responding to niacin, niacinamide, and nicotinuric acid. The procedure was very time-consuming, and was discarded after the development of the chromatographic method described below. The measured amounts were converted by an empirical factor to correspond to the results of the chromatographic method.

Analysis of Niacinamide by Gas-Liquid Chromatography

Two 0.5-ml samples of urine for this analysis were stored at −76°C. A Varian-2100 gas-liquid chromatograph with flame-ionization detectors was used. The column

was 5 percent Carbowax 20M on Chromosorb W (regular), with oven at 240°C and injector and detector at 250°C. The internal standard was 1.00 mg methylniacinamide in 1.00 ml of water. Standardization was achieved by analyzing 0.5-ml samples of water containing various amounts of niacinamide between 10 and 1,000 mg, with standardization runs made before and after each set of urine-sample runs. The 0.5-ml sample of urine (or niacinamide solution) was thawed and 100 ml of the internal standard was added. Then 1 μl or 2 μl was injected into the chromatograph. The only large peaks are those of methylniacinamide and niacinamide, and the amount of methylniacinamide in urine is very small compared with the amount added.

Analysis of Pyridoxine by Gas-Liquid Chromatography

Two 0.1-ml samples of urine for this analysis were stored at −76°C in glass vials with teflon-lined caps. The chromatographic column was 1.5-percent OV-101 on Chromosorb G, with oven at 190°C, injector at 210°C, and detector at 220°C. The internal standard was heneicosane. Standardization runs before and after each set of urine analyses were made with 0.1-ml aqueous solutions containing between 10 and 1,000 mg of pyridoxine. The 0.1-ml sample of urine (or pyridoxine solution) was dried in high vacuum, capped, and frozen. Then 0.5 ml of 1 : 1 solution of bis-trimethylsilylacetamide in pyridine and 0.1 ml of pyridine containing 125 μg of heneicosane were added; the container was capped and shaken for 90 minutes, and 1 μl of the solution was injected into the chromatograph.

ACKNOWLEDGMENTS

We thank Dr. Robert Nichols and Mrs. Dorothy Marshall at University Hospital of San Diego County, Dr. L. Pratum of Mesa Vista Hospital, Dr. Halmuth Schaefer of Patton State Hospital, and the staffs of these hospitals for help in the collection of the urine samples.

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3

Quantitative Chromatographic Analysis in Orthomolecular Medicine

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In medical research and medical practice much use is made of analysis of body fluids, such as urine, blood, and spinal fluid. Most of the quantitative clinical tests that are carried out at the present time are for a single substance or a small number of substances. During the last two or three decades some techniques, especially those of chromatographic analysis in its various forms, have been developed that permit the detection and quantitation of scores or hundreds of substances in a single small sample. These techniques have been used, and are now being used, in medical research by a number of groups of investigators, almost all of whom have sought to obtain qualitative or only very roughly quantitative analyses (Jellum et al., 1971).

Three years ago we asked the questions "How many and what substances can be quantitatively measured by techniques so inexpensive that all persons, regardless of their wealth and apparent state of health, could afford to be regularly tested? How much information about health can be extracted from these measurements?" These questions differ from the usual approach, which asks "What substances will be useful in testing for a certain disease? How can those substances be measured?" This latter approach has led to a state of affairs wherein there are so many individual tests that,

regardless of the best efforts of automation, only the sick are usually willing to pay the high cost of analysis and then only after a physician has tried to guess which tests they need, other than a few standard ones. Preventive medicine and low-cost medicine require a new approach.

We have for these reasons been striving to develop a practical method of analysis of body fluids that would permit the quantitative evaluation of the amount of each of several hundred substances in a sample of body fluid with good reliability (standard deviation for repeated measurements usually less than 10 percent). In this report some of the methods that we have been using are described, and the results of the application of one technique to some normal subjects and to some mental retardates are presented.

The composition of the body fluids of a person is determined by his genotype and by environmental factors, especially the food that he has recently ingested, the nature of his digestive processes, the bacteria in his intestines, and bacterial, rickettsial, or viral infections that may be present (also, in some cases, parasites). We have found that the composition of the urine of one person on an ordinary diet, with the usual day-to-day differences, varies greatly from day to day, the average relative standard deviations for the amounts of single substances on successive days being 75 percent or more. This difficulty can be largely overcome by using as the only food for several days a synthetic (essentially complete) diet, Vivonex-100, which consists almost entirely of small molecules, which are completely absorbed into the blood stream in the small intestine (Winitz et al., 1970a, 1970b). We find that the composition of the urine becomes nearly constant within about four days on this diet. This is in agreement with qualitative observations which have been made for 13 ultraviolet-absorbing compounds (Young, 1970). We are also studying the effectiveness of fasting to achieve this result, as well as the extent to which the amounts of some substances are unaffected by diet.

THE DESIRED CHARACTERISTICS OF THE ANALYTICAL METHOD

The goal is to develop an analytical method such that it would be practically possible to check the state of health at frequent intervals and the course of disease during periods of illness for all persons throughout their lives. The practical possibility (largely determined by costs) makes the folllowing requirements:

1. The sample should be collected by the subject himself. This requirement indicates urine as the body fluid to be sampled, with breath as another possibility. A timed sample should not be required.
2. One sample should be sufficient for checking essentially all conditions and all

diseases. To achieve this goal would require quantitative analysis for several hundred substances, preferably by a single analytical procedure.

3. To keep the cost low, the analysis should be carried out by a machine, with the minimum number of operations by human attendants (possibly only introducing the sample into the machine).
4. Objective evaluation of the analytical results should be carried out by machine calculation of amounts of substances and interpretation by reference to information stored in the memory bank of the computer.

TECHNIQUES OF CHROMATOGRAPHIC ANALYSIS OF URINE AND BREATH

In our studies of alternative analytical techniques we have for the most part analyzed samples of urine of normal subjects who have during periods of three to twenty days ingested only the small-molecule diet Vivonex-100 (usually mild-orange flavor) and distilled water, and who have refrained from smoking.

A preliminary study showed chromatographic methods of analysis to be the most promising for our purpose. Our work with five techniques, with consideration of the economic factor, especially the amount of human labor per sample, has led us to the following conclusions about these techniques:

1. Low-resolution ion-exchange separation of ninhydrin-positive substances (including amino acids) in a sample of urine (Figure 3-1). This method of analysis

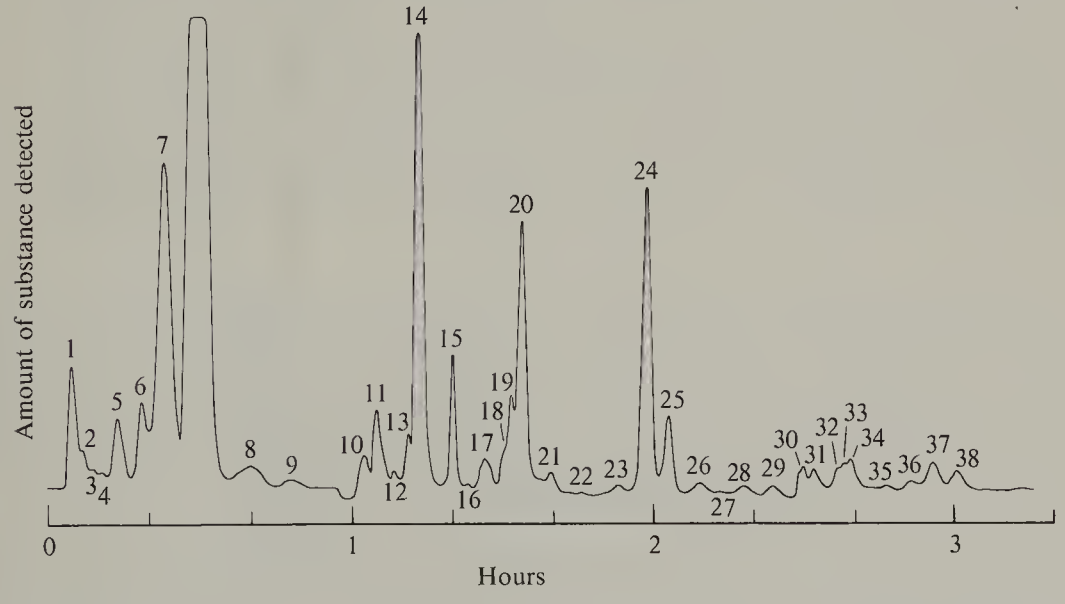


FIGURE 3-1.
Low-resolution ion-exchange analysis of ninhydrin-positive urinary constituents, made with an automated commercially available instrument (Beckman Model 121 Amino-Acid Analyzer). Identification of some peaks is given in Table 3-1.

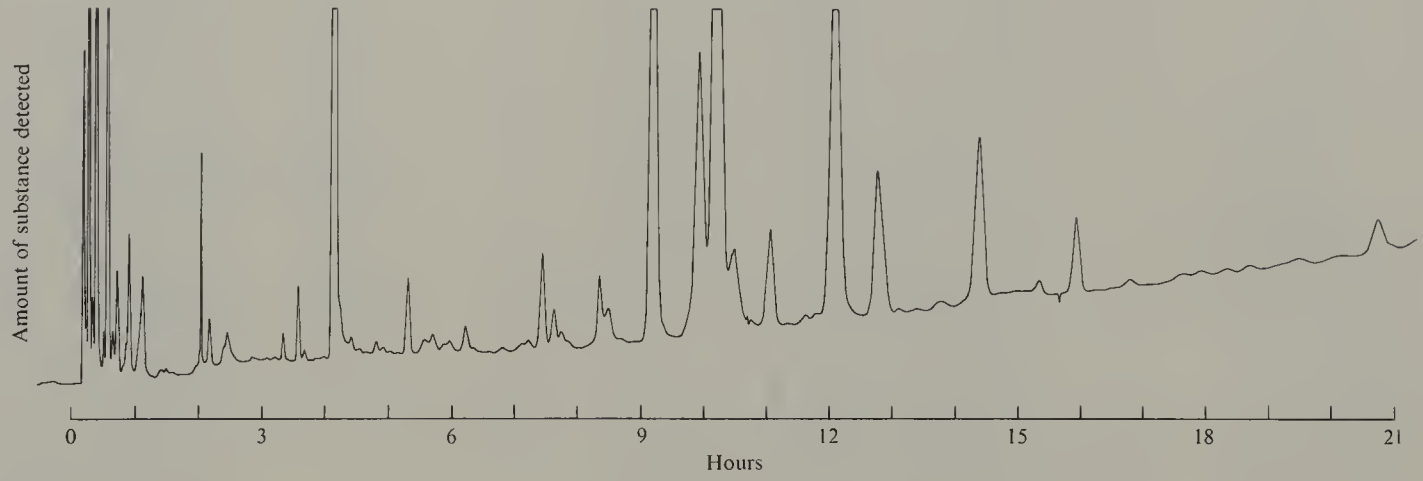


FIGURE 3-2.
High-resolution ion-exchange analysis of urinary constituents absorbing light in the ultraviolet region. This analysis was performed by Carl Burtis.

(Moore and Stein, 1956) is presently in use in most protein and peptide laboratories. A large amount of industrial effort has been expended in automating and refining the technique. For moderate cost about 30 substances can be quantitatively analyzed by this method.

2. High-resolution ion-exchange separation of ultraviolet-absorbing substances in urine (Figure 3-2). This method of analysis, which uses small-diameter columns and pressures from 1,000 to 5,000 psi in order to increase the speed and resolution of ion-exchange chromatography, is relatively new (Burtis, 1970). At present, about 80 compounds can be quantitatively analyzed for moderate cost.
3. Low-resolution gas-liquid partition chromatography of urine sample separated into two fractions by an ion-exchange column, with each fraction then treated to form trimethylsilyl derivatives or other derivatives with increased volatility (Figure 3-3). This method of analysis uses a low-resolution 6-foot packed column (Horning et al., 1963; Horning, 1968). It is very economical and fast for the repetitive quantitative analysis of a few compounds at a time. For moderate cost per sample a 120-substance analysis can be carried out.
4. High-resolution gas-liquid partition chromatography of the vapor from an untreated urine sample (Figure 3-4). This method (Pauling et al., 1971; Teranishi et al., 1972) consists of the collection of urine vapor at 80°C and subsequent analysis on a 1,000-foot 0.03-inch i.d. metal capillary column. This method is new. A 280-substance analysis can now be carried out for low cost, and further improvement is possible.
5. High-resolution gas-liquid partition chromatography of a sample of breath (Figure 3-5). This method (Pauling et al., 1971; Teranishi et al., 1972) consists of the collection of breath volatiles from 15 exhalations and subsequent analysis on a 1,000-foot 0.03-inch i.d. metal column. This method is new. A 250-substance analysis can be carried out for low cost. The breath, however, is subject to greater contamination by the immediate environment of the person than urine. Breath analysis is probably, therefore, a less practical diagnostic tool than urine analysis.

The last two methods now seem to be the most promising. Much work remains to be done on identifying the substances and determining the significance of the analytical results in relation to health and disease. It is not unlikely that in the course of time still more powerful and practically convenient techniques will be discovered.

We suggest that it is now possible, using method 4, to provide quantitative analysis of over 200 urinary constituents, with computerized reduction of this urinary profile in comparison with other urinary profiles, for a cost of $5 to $10. This cost includes all expenses: collection of the sample, supply of the apparatus (with a profit for the manufacturer), analysis, overhead, computation, and report. Our cost estimate is based on laboratories performing 12,000 analyses per year.

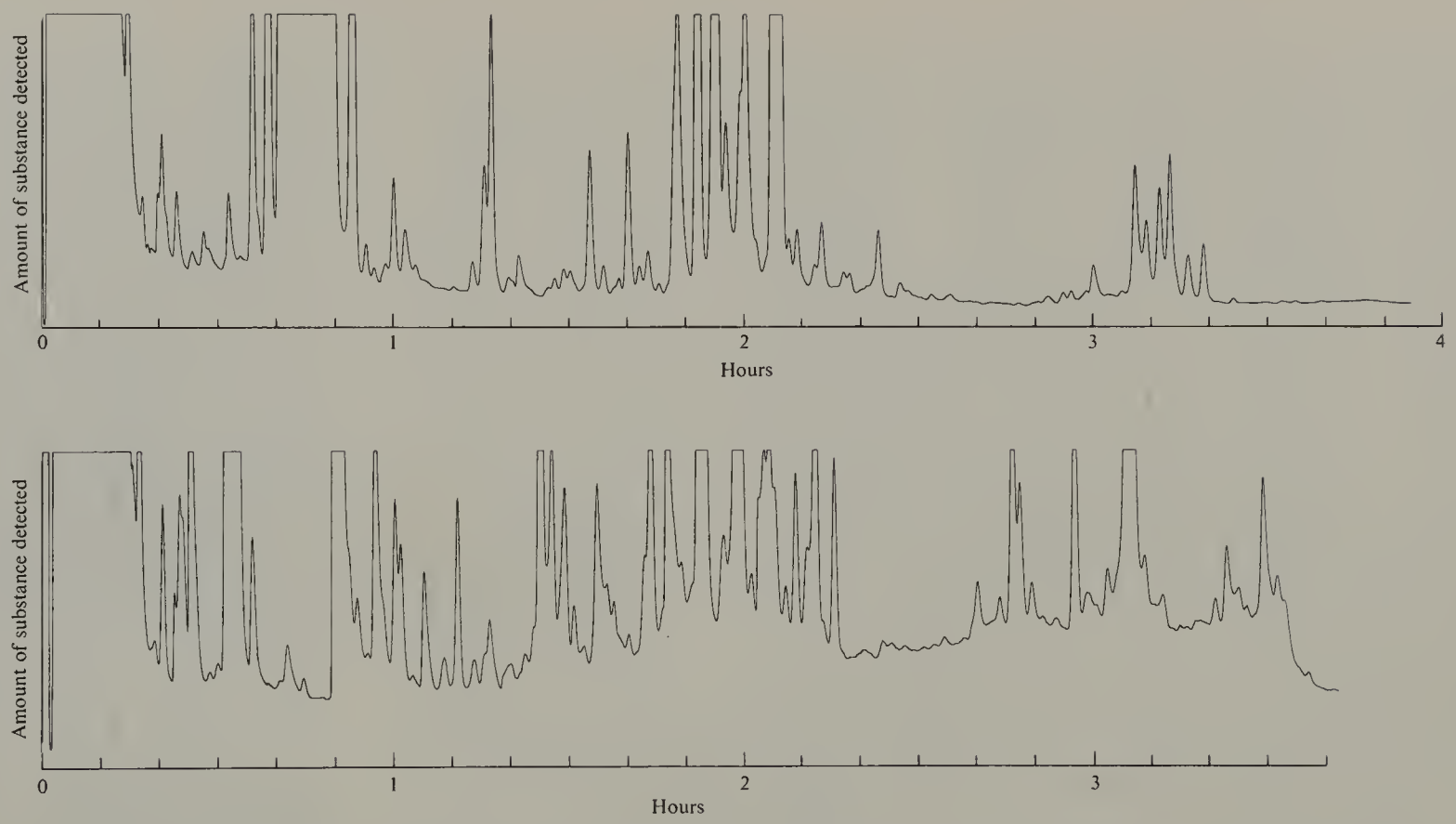


FIGURE 3-3.
A. Low-resolution gas chromatogram of the basic-neutral urine fraction from DEAE Sephadex column. B. Low-resolution gas chromatogram of the acid urine fraction from a DEAE Sephadex column. The chromatograms 3A and 3B were obtained in our laboratory with an extensively modified Varian Aerograph Model 2100 gas chromatograph with flame ionization detector. The temperature was programmed to increase from 20°C to 170°C at the rate of 0.5°C per minute. The DEAE Sephadex was prepared by washing with 0.5*F* NaOH followed by washing with water and stored suspended in 0.01*F* *p*H 5.0 pyridine acetate buffer. A 1 cm × 10 cm column was poured and washed with 1.5*F*, *p*H 5.0 pyridine acetate buffer followed by washing with water; 1 ml of urine was applied to the column and then the column was washed with 50 ml water followed by 75 ml 1.5*F* *p*H 5.0 pyridine acetate. These washes are collected, freeze dried, reacted at 80°C for 90 minutes with 0.5 ml BSTFA, and injected into the chromatograph. The column was OV-101, packed in a six-foot glass tube. Temperature was linearly programmed from 50°C to 250°C at 1°C per minute.

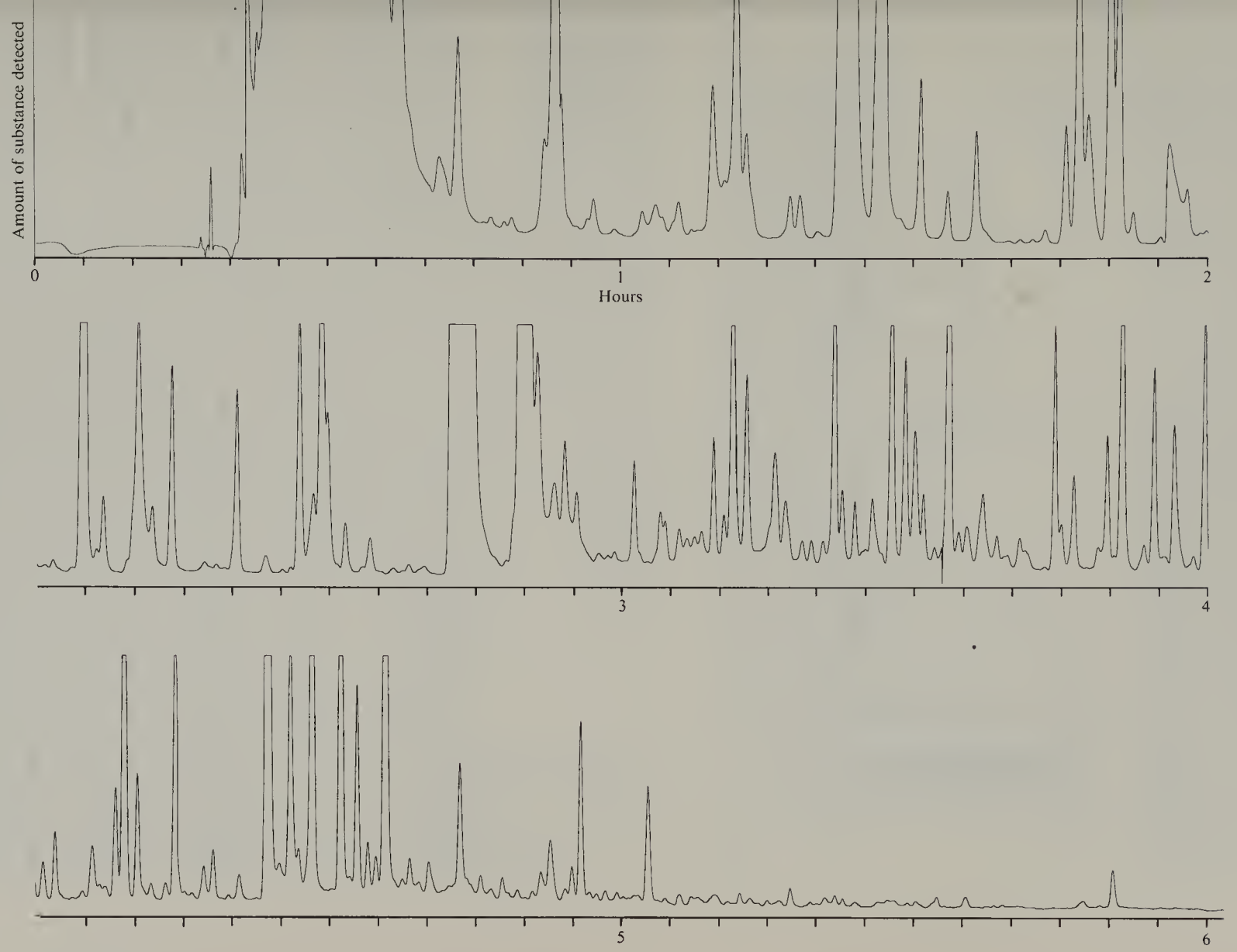


FIGURE 3-4.
High-resolution gas chromatogram of urine vapor. The chromatogram was made in our laboratory with an instrument not commercially available. The temperature was increased from 20°C to 170°C at the rate of 0.5°C per minute.

Figure 3-6 shows experimental reliability measurements for the urine-vapor method. For comparison, similar measurements for low-resolution ion-exchange chromatography are also shown. The cost per substance analyzed is 20 times greater for the low-resolution ion-exchange method than for the urine-vapor method, but

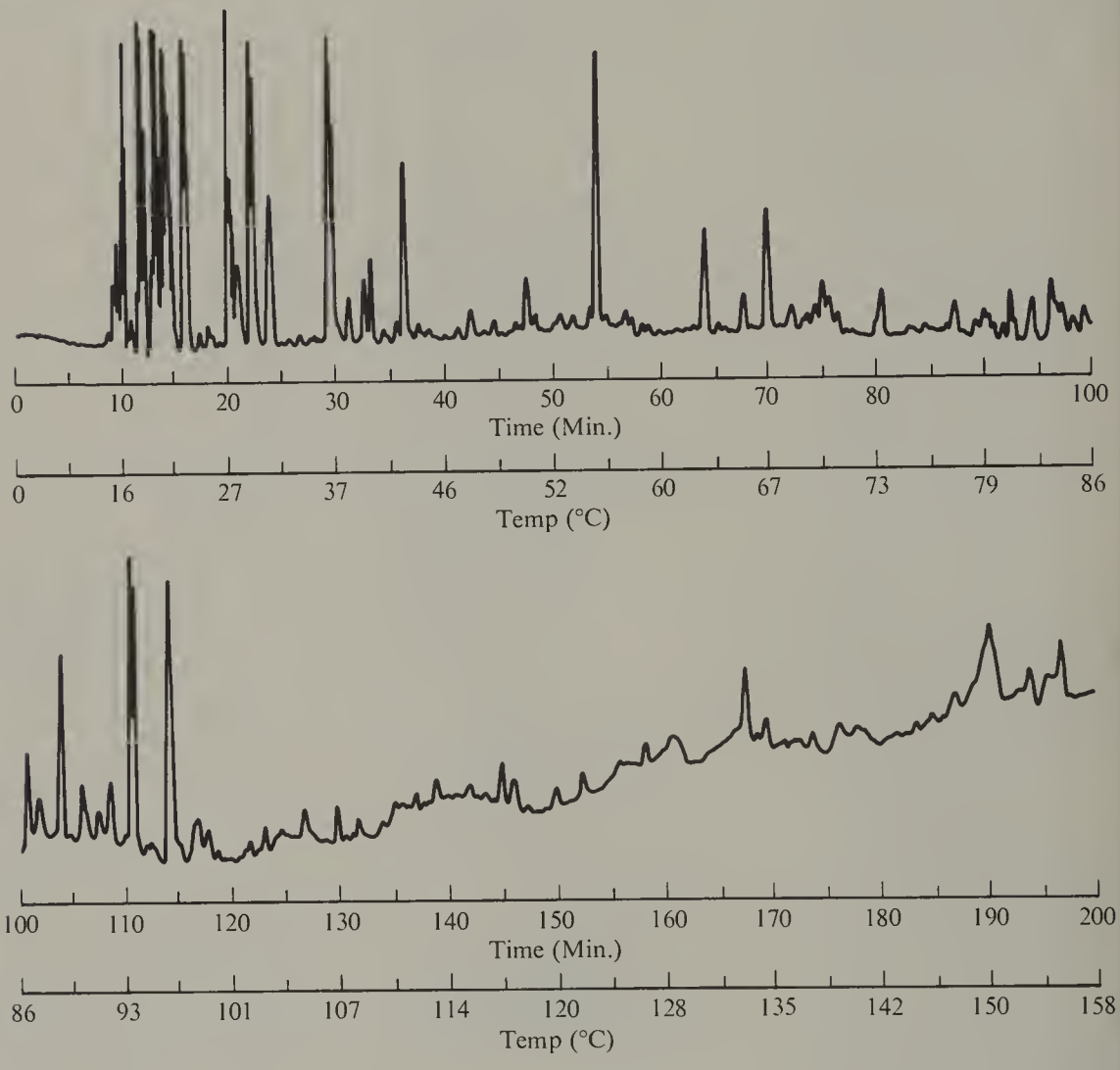


FIGURE 3-5.
High-resolution gas chromatogram of breath, made in our laboratory with use of a noncommercial instrument. This curve is from Pauling et al. (1971).

the machines for ion-exchange analysis are already installed in many hospitals and research institutions. The computational equipment and procedures required for the two methods are identical. We discuss below an example of the use of this profile analysis using the machines that are already available to everyone. The high-cost and synthetic-diet limitations of this example will probably be eliminated by the eventual installation of cheaper high-resolution machines.

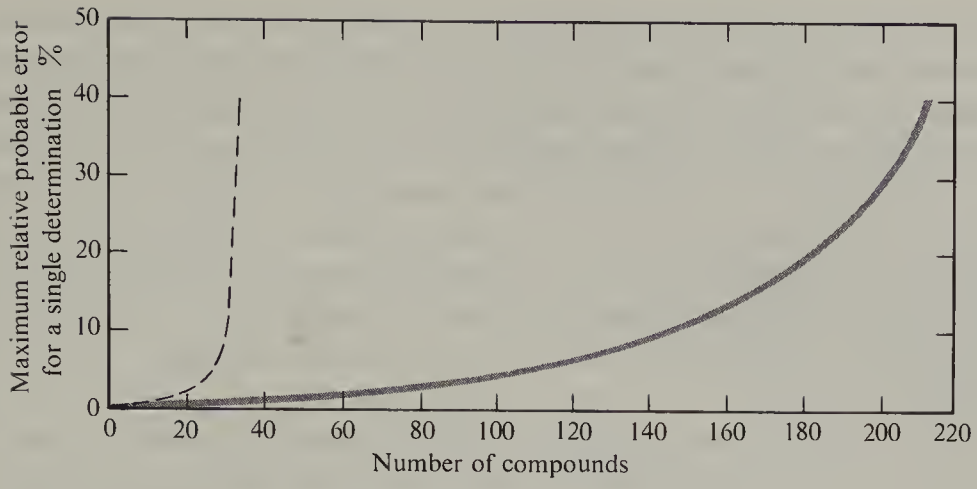


FIGURE 3-6.
A plot of the maximum relative probable error (=0.67 × the relative standard deviation of an individual from the mean) versus the number of compounds routinely quantitated in a single chromatographic analysis with relative probable error less than or equal to the maximum relative probable error. The dashed curve is for low-resolution ion-exchange urine analysis for ninhydrin-positive substances, and the full curve is for high-resolution gas chromatographic analysis of urine vapor.

THE STUDY OF A POPULATION OF MENTAL RETARDATES AND A CONTROL POPULATION BY ANALYSIS FOR NINHYDRIN-POSITIVE SUBSTANCES

We have carried out the following experiments and calculations to illustrate the potential usefulness of quantitative analysis of large numbers of urinary constituents as a diagnostic medical procedure. The experiments have been with the usual low-resolution ion-exchange analysis for ninhydrin-positive compounds, which is presently available in most laboratories and hospitals.

The control population consisted of nine persons in the Stanford University chemistry department community, who received for ten to fourteen days only Vivonex-100 (mild-orange flavor) as food and distilled water as the liquid component of the food and as drink. The subjects were non-smokers, and they refrained from intake of any medicines during the study. Samples of urine were taken during the day and night. The day samples and night samples of a subject in general agreed closely with one another, as described below. Analyses were made by the first method mentioned above, low-resolution ion-exchange separation of ninhydrin-positive substances.

We were also able to make similar studies of about 250 mentally retarded patients who had been receiving the Vivonex-100 food for two months or more. Most of these patients were also receiving medication; the results for these patients are not

included in our discussion. Twenty-two mental retardates who had not received medication are discussed below. These subjects were severely retarded patients in wards in Sonoma State Hospital, Sonoma, California. The intake of these patients had consisted solely of Vivonex-100 (mild-orange flavor) and tap water for one month or more before the urine samples were collected. It seems likely that the ingestion of tap water rather than distilled water does not have a significant effect on the analytical results. The Vivonex-100 ingested by the mental retardates was from a different batch than that ingested by the controls, and there might have been a small difference in composition of the food for the mental retardates and for the normal controls.

The low-resolution ion-exchange analysis for ninhydrin-positive substances was carried out with a Beckman Model 121 automated amino acid analyzer. Amino acid analyses were performed by Fred C. Westall at the Salk Institute, La Jolla, California. A 0.1-ml sample of urine (stored at −76°C) was applied to both the short column and the long column of the apparatus. Quantitative determinations were made for 39 substances or overlapping groups of substances (Figure 3-1). The values for the six smallest peaks were unreliable, and were omitted in our treatment. Nineteen of the 33 peaks used in the evaluation were identified as amino acids, and one as urea (Table 3-1). Peaks 1 and 2 consist of several substances.

Timed urine samples could not be obtained for the mentally retarded subjects, and a method of normalization was used for all samples to give a constant value to the sum of the areas of the peaks. Of the 50 samples studied, three were identical (numbers 1, 2, 3, day urine of control subject VIII on the eleventh day on diet), nine (numbers 21 to 26, 11, 27, 28) were day samples of control subject V on the 0, 1, 3, 5, 7, 9, 11, 13, and fourteenth day on diet, and 18 were night–day pairs (tenth night, eleventh day on diet) for the nine normal subjects. The samples for the mental retardates were day samples. Subjects 29 to 46 were undiagnosed mental retardates on Vivonex-100 for over one month, with no medication. Subjects 47 and 48 were phenylketonuric mental retardates on Vivonex-100 for over one month, with no medication. Subjects 49 and 50 were phenylketonuric mental retardates on a low-phenylalanine version of Vivonex-100.

The average normalized peak area and standard deviations for the 33 peaks are given in Table 3-1 for all 50 samples and also for the tenth day and eleventh night samples for the control subjects and the samples for the 22 mental retardates. The average percentage deviation (ratio of the standard deviation to the mean) is 33 percent for the control subjects and 63 percent, almost twice as great, for the mentally retarded subjects, despite the greater constancy of their environment (they were confined to the ward and largely to their beds).

A simple check for abnormality in the patterns was made by counting high peaks (more than twice the average for the 28 control analyses) and low peaks (less than one-fifth of this average). For the nine control subjects (average for night and day) the

number of high peaks averages 0.66 per subject and the number of low peaks averages 0.40 per subject; the corresponding values for the 22 mental retardates are 3.64 and 2.16, respectively, about five times as large. Sample 11, which was very dilute, gave 13 low values by this test, disagreeing with other samples for the same subject, which showed only one low value. This sample and sample 29, which also was very dilute, are not included in the foregoing discussion.

No striking pattern of high and low peaks was obvious except for the two untreated phenylketonuric patients, 47 and 48, who were concordantly high in peaks 1, 14, 30, and 38 and low in peak 2 (47 also low in peak 12, 48 low in peak 10). For these two the phenylalanine peak (38) was eighteen times as large as the average, whereas for the two phenylketonuric patients receiving the low-phenylalanine Vivonex it was three times the average (subject 49) and six times the average (subject 50).

We have formulated several objective tests of quantitative lack of concordance of pairs of samples, and have found that they give closely similar results. The simplest is the pair noncorrelation index (PNI), given by the following equation:

$$\mathrm{PNI(AB)} = \frac{1}{N}\sum_{i=1}^{N}\frac{|A_i - B_i|}{A_i + B_i}. \tag{3-1}$$

In this equation A_i and B_i are the areas of the ith peak for the two samples A and B, and N is the number of peaks. This pair noncorrelation index is the average of the deviation of the two values of the peak area from their mean.

The 1,225 values of PNI for the 50 samples with one another calculated for 33 peaks show many interesting features.

The triplicate analyses 1, 2, and 3 in pairs give PNI = 0.044, 0.049, and 0.034, showing a reliability of the analytical technique to about 4 percent.

For subject V analyses of day urine were made on day 0 (before Vivonex diet), day 1 (first day of diet), 3, 5, 7, 9, 11, 13, and 14 (day of resuming ordinary food). The values of PNI for the pairs of successive analyses are the following: day 0 to day 1, 0.226; 1–3, 0.228; 3–5, 0.154; 5–7, 0.130; 7–9, 0.102; 9–11, 0.114; 11–13, 0.140; 13–14, 0.120. It is seen that from the third day on the values are nearly constant, and considerably smaller than for the day 0 and day 1. The average of the 21 values for pairs of days 3 to 14 is 0.132. A decrease by about 0.10 (from 0.226 for 0–1) is achieved by three days or more on the Vivonex-100 diet. We may assume that a value of PNI approaching 0.13 means essential identity of the samples. About 30 percent of the 1,225 values of PNI lie below 0.2, 40 percent between 0.2 and 0.3, 20 percent between 0.3 and 0.4, and 10 percent between 0.4 and 0.6.

To obtain more information from the analyses we have made use of another quantity, the weighted noncorrelation index (WNI). This quantity involves the comparison of the two samples A and B not only with each other but also with the average peak areas for all control subjects. If two samples, A and B, are concordant in a certain peak in that both show an unusually large deviation from the average, this

TABLE 3-1.

Some Results of Analysis of 50 Urine Samples for Ninhydrin-positive Substances

Peak	Substance	Averages for 8 normal subjects						Averages for 20 retardates		Averages for 3 analyses of sample 8011	
		Day/Night (16)		Day (8)		Night (8)					
		Amount	σ (%)	Amount	σ (%)	Amount	σ (%)	Amount	σ (%)	Amount	σ (%)
1		3.96	15	3.66	18	4.16	13	4.72	110	3.65	2
2		0.62	31	0.56	15	0.66	38	0.45	42	0.53	3
3		~0[a]	—	—	—	—	—	—	—	—	—
4		~0[a]	—	—	—	—	—	—	—	—	—
5	tryptophan	1.88	22	1.61	17	2.05	23	0.84	32	1.56	2
6	lysine	1.90	77[b]	1.81	68	1.84	88	2.28	53	2.08	1
7	histidine	8.16	(32)[c]	8.41	31	8.34	31	8.13	39	12.33	1
8		0.58	24	0.49	25	0.62	25	0.46	27	0.51	7
9	arginine	0.17	(15)[c]	0.17	13	0.17	16	0.19	52	0.29	53
10		1.09	22	0.98	20	1.14	25	0.90	39	1.07	4
11		1.63	34	1.40	30	1.74	38	1.29	44	1.85	1
12		0.16	(64)[c]	0.13	53	0.18	68	0.09	68	0.18	10
13		3.26	85[b]	3.47	97	2.76	65	0.71	79	1.20	4
14	urea	34.73	19[a]	33.74	18	36.27	18	19.98	56	39.60	2
15		3.19	28	2.79	30	3.37	28	2.11	46	3.82	4
16	aspartic acid	0.07	42[c]	0.07	31	0.08	34	0.29	76	0.10	10
17		0.53	30	0.49	28	0.55	33	0.21	62	0.74	2
18		0.92	23	0.83	22	1.00	20	0.54	50	0.81	1
19	threonine	1.47	43	1.68	36	1.33	45	1.94	50	1.64	3

20	serine	12.08	24[c]	11.74	27	11.98	23	11.03	35	9.43	3
21	glutamic acid	0.50	21	0.43	27	0.53	22	1.17	111	0.48	4
22	proline	0.05	38[c]	0.05	30	0.06	29	0.27	173	0.04	49
23		0.15	39[c]	0.16	36	0.14	44	0.11	45	0.24	4
24	glycine	15.89	29[c]	18.71	24	14.30	30	32.94	33	11.95	1
25	alanine	2.93	39	3.31	35	2.39	35	4.91	44	2.06	1
26	cysteine	0.36	24	0.32	27	0.37	29	0.30	42	0.26	5
27		0.09	56[c]	0.09	55	0.07	65	0.06	52	0.03	10
28	ABA[e]	~0[a]	—	—	—	—	—	—	—	—	—
29	valine	0.28	22	0.27	10	0.28	35	0.29	67	0.29	5
30	methionine	0.73	15	0.71	29	0.79	10	0.97	32	0.76	4
31		~0[a]	—	—	—	—	—	—	—	—	—
32	isoleucine	0.52	21	0.47	11	0.55	25	0.42	39	0.49	7
33		~0[a]	—	—	—	—	—	—	—	—	—
34	leucine	0.71	25	0.63	6	0.77	29	0.57	40	0.71	3
35		0.11	76[c]	0.09	65	0.17	53	0.24	72	0.07	20
36		0.27	26	0.23	15	0.29	29	0.16	64	0.25	1
37	tyrosine	0.58	37	0.58	33	0.64	40	0.63	49	0.55	3
38	phenylalanine	0.45	34	0.40	25	0.48	37	1.26	228	0.45	8
39		~0[a]	—	—	—	—	—	—	—	—	—
	Mean	3.03	34(32)[d]	3.03	31	3.03	35	3.03	63	3.03	35
	Median	0.62	19(26)[d]	0.58	27	0.66	30	0.63	50	0.66	30

[a] These peaks were omitted, because they were small and often absent from the chromatograms.

[b] These two peaks were used in WNI calculation but were omitted from the chromatogram normalization because of their large variation among different normal subjects.

[c] All peaks with average percentage in normal chromatograms greater than 8% or less than 0.2% were omitted from WNI calculation. $\sigma(\%)$ is equal to (standard deviation for a single measurement) (100)/average for all measurements.

[d] The first values are for all 33 peaks, the second (in parentheses) for the 22 peaks used in the WNI calculation (not including those marked [c]).

[e] ABA = α-amino-n-butyric acid.

concordance (representing a similar deviation from the normal pattern) should be given extra weight. We have done this in a simple way, by writing

$$\text{WNI} = \frac{\text{PNI}}{\Sigma Q_i}. \tag{3-2}$$

Here Q_i has the value 0 when either A_i or B_i is less than Av_i (the average peak area for the ith peak), and the value $(A_i - Av_i)/\sigma Av_i$ or $(B_i - Av_i)/\sigma Av_i$, whichever is the

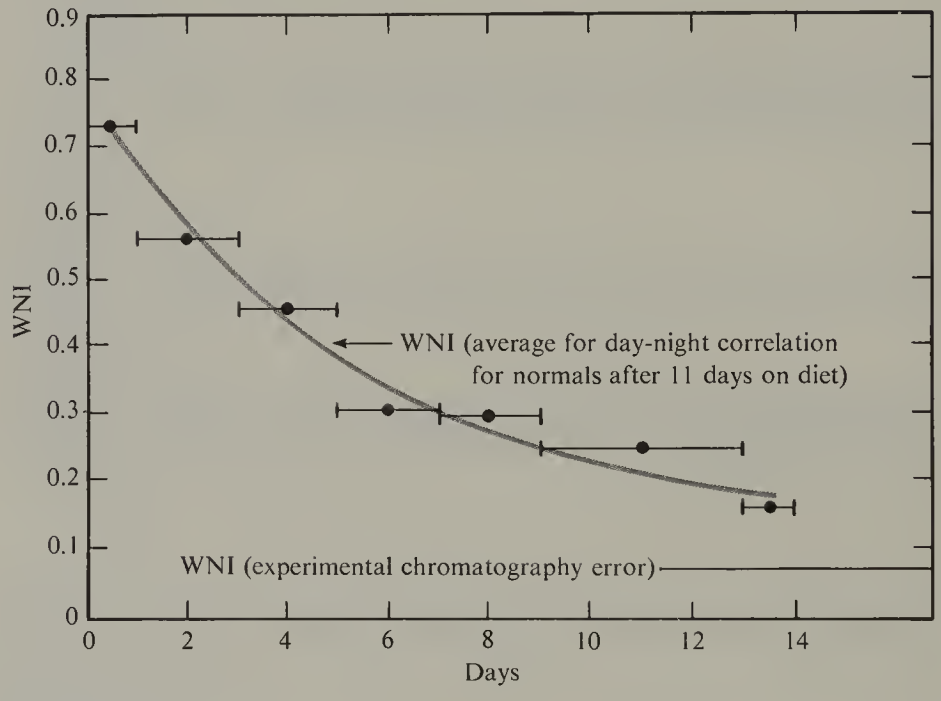


FIGURE 3-7.
The value of WNI for low-resolution ion-exchange analysis of 22 substances versus the days of equilibration of normal subject V on the Vivonex-100 synthetic diet. The pairs of chromatograms used for calculation of the individual values of WNI are indicated by the horizontal lines joining the days on which the urine was collected.

smaller, when both A_i and B_i are greater than Av_i. σAv_i is the standard deviation of the ith peak for a single sample in the group of samples.

Figure 3-7 shows the WNI values for successive days during the equilibration of control subject V on the synthetic diet.

Values of WNI for day versus night for each of eight control subjects are given in Table 3-2, and also the average values for each subject with the others, both day and night. The reliability with which two samples from the same person can be picked from a group of 48 samples is given in Table 3-3. It is clear that reliable determinations of individual patterns are possible with only 22 peaks, providing dietary control is used. We hope that with 200-peak analyses the same determinations of individual

TABLE 3-2.

Values of the Weighted Noncorrelation Index for Control Subjects

Subject	D–N[a]	D–N next lowest[b]	D–D average[c]	N–N average[d]	D–N average[e]
I[f]	0.454	0.535	1.453	1.620	1.721
II	0.401	(0.308)[h]–0.627	1.255	1.150	1.600
III	0.373	0.493	1.960	1.588	1.913
IV	0.336	(0.308)[h]–0.730	1.391	2.137	1.622
V	0.580	0.622	1.357	0.980	1.486
VI	0.256	0.333	2.088	2.667	2.874
VII	0.647	1.300	2.222	1.543	2.394
VIII	0.616	0.684	1.284	1.223	1.600
IX[g]	—	—	—	1.277	—
Average	0.458	(0.573)[h]–0.666	1.626	1.576	1.901

[a] WNI for eleventh day sample and tenth night sample of same subject. [b] Next lowest WNI to [a].
[c] Average WNI for eleventh day sample of subject with each of eleventh day samples of seven other control subjects.
[d] Average of WNI for tenth night sample of subject with each of tenth night samples of eight other control subjects.
[e] Average of WNI for eleventh day and tenth night samples of subject with tenth night samples of eight other control subjects and eleventh day samples of seven other control subjects, respectively.
[f] Day sample for subject I was measured three times. Average WNI for the three measurements are used in Table 2.
[g] The day measurement for subject IX was unreliable, because the sample was too dilute.
[h] II-day and IV-day had WNI = 0.308.

TABLE 3-3.

Reliability of WNI Selection of Day–Night Pair

Subject	Rank in 48 comparisons[a]	Rank in 16 high–low comparisons[c]
I	1	6
II	2[b]	1
III	1	2
IV	2[b]	2
V	1	1
VI	1	10
VII	1	11
VIII	1	2

[a] Value of WNI for each day sample I to VIII with each of 47 other samples, including night sample for the same subject.
[b] The day sample of subject II and the day sample of subject IV had WNI = 0.308. This caused the only failure of WNI in picking individual patterns, and probably results from the difference between normal day and normal night patterns (see Table 3-2).
[c] Comparison was made of the number of high peaks (above average) and low peaks for the 16 samples for subjects I to VIII.

TABLE 3-4.

Average WNI of Eleventh-day Samples for Normal Subjects with One Another and with Samples for Retardates, Using 33 Peaks (See Table 3-1)

Subject	*WNI (average)*	Subject	*WNI (average)*
	Normal		
I	1.231	V	3.240
II	1.167	VI	1.503
III	1.314	VII	1.203
IV	1.583	VIII	1.037
		Mean = 1.535	
		σ = 0.711	
	Retardate		
29	14.732	40	1.957[a]
30	4.858	41	5.674
31	7.034	42	6.378
32	5.640	43	5.870
33	9.715	44	3.237
34	1.928[a]	45	12.687
35	5.699	46	6.036
36	4.111	47	6.917
37	2.145[a]	48	3.723
38	5.762	49	2.611[b]
39	1.958[a]	50	4.353[b]

[a] It is likely that these retardates do not have a genetic abnormality involving amino-acid metabolism (see text).

[b] Samples 49 and 50 are from phenylketonurics who were being treated by administration of low-phenylalanine Vivonex-100.

patterns will be possible without dietary control, and we are presently doing experiments to test this possibility.

The day and night average WNI values given in Table 3-2 show that there is a characteristic difference in pattern of urine collected in the bladder during sleep and urine collected in the bladder during wakefulness and activity. In only two cases is the day–day average WNI or night–night average WNI larger than the day–night average WNI. The null hypothesis that there is no difference between day and night pattern is rejected with $\chi^2 = 19.88$ (one degree of freedom), P (one-tailed) = 0.0000083. The average day and night patterns are given in Table 3-1.

The advantages of this quantitative procedure using WNI over a qualitative or semi-quantitative procedure are illustrated by the failure of a calculation that uses only the information about whether a peak is above or below average, summing this information for the 22 peaks. It is shown in Table 3-3 that this method picks only two

perfect comparisons, even though the sample is restricted to the 16 samples from normal subjects.

In the study of the analyses of the urine samples for the mental retardates (samples 29 to 50) we have first checked the values of WNI with the day samples for eight normal subjects. (The sample from Subject IX is omitted because of evidence of abnormality; see Table 3-2.) Samples 34, 37, 39, and 40 have values of WNI with the eight control samples less than 2.957 (within 2σ of mean; Table 3-4). It is accordingly likely that these four mental retardates do not have a genetic abnormality involving amino-acid metabolism.

A check can be made by examining the values of WNI for these four subjects with one another and with other mental retardates. These values (including those with representative samples 33 and 45) are given in Table 3-5. It is seen that for 34, 37, 39, and 40 with one another the values are low, 0.713 to 2.766, and with 33 and 45 they are higher, 3.369 to 6.882, showing the concordance of these four with one another as well as individually with the control subjects.

On the other hand, 41, 43, and 46 show strong correlation with one another (WNI 0.559 to 0.818) and noncorrelation with the controls (WNI 5.674 to 6.036) and most of the other mental retardates, as is seen from Table 3-6, in which 40 and 47 (a phenylketonuric) are introduced for comparison. It is accordingly likely that the subjects 41, 43, and 46 have a similar genetic abnormality involving amino-acid metabolism. We have not yet determined the nature of this abnormality. The two untreated phenylketonuric subjects, 47 and 48, show good correlation with one another (WNI = 0.080), less good with the treated phenylketonurics (WNI 0.333 and 0.268 with 49, 0.499 and 0.446 with 50), and poor averages, 6.917 and 3.723, with all others.[1] The average values of WNI for the treated phenylketonuric patients 49 and 50 with the eight normal samples are 2.611 and 4.353, respectively. We conclude that the low-phenylalanine treatment is biochemically effective for 49 but not for 50.

TABLE 3-5.
Values of WNI for Some Pairs of Retardate Samples

	33	34	37	39	40	45
33	0.000	4.782	6.510	5.713	4.844	2.504
34		0.000	0.942	0.891	1.138	6.882
37			0.000	2.766	1.662	3.369
39				0.000	0.713	5.105
40					0.000	4.354
45						0.000

[1] The value of WNI for the comparison of samples 47 and 48 is unusually low because peak 38 is phenylalanine and peak 1 is a mixture including phenylalanine, and such a small number of peaks are used in this type of analysis that the term Q in WNI can be dominated by a pair of very large peaks. Variations of this extreme extent were not present in the other 48 samples.

How many days must a subject be on the synthetic diet before these genetic patterns can be recognized with use of 22 peaks? We expect that WNI is a combination of experimental error (WNI exp), dietary variation (WNI diet), genetic variation (WNI genetic), and health variation (WNI health). Health variation may be taken to include variations in disease state, age, environmental stress, and individual nutritional state. The following equation may provide an approximation to the interrelationship of those quantities:

$$(\text{WNI})^2 = (\text{WNI exp})^2 + (\text{WNI diet})^2 + (\text{WNI genetic})^2 + (\text{WNI health})^2. \quad (3\text{-}3)$$

Analyses 1, 2, and 3 (same sample) have an average WNI of 0.07. Therefore, WNI exp = 0.07. WNI for subject V after eleven days of equilibration is 0.245. Assuming subject V to have been in a constant state of health during the eleven days, we calculate $\text{WNI}_{\text{diet-days}} = 0.235$. Evidently about four days of equilibration on Vivonex-100 should be sufficient dietary control for most studies.

It is to be expected that the extent of dietary control required will decrease as the number of peaks increases. When the requirement for dietary control decreases to a few hours of fasting or less, this method of machine evaluation of individual health will have far surpassed anything offered to the average person by the present medical establishment. Orthomolecular medicine, the provision of the optimum amounts of the substances normally present in the body, may then be supplemented by orthomolecular diagnosis, wherein the amounts of substances normally present in the body of each person are routinely measured.

SUMMARY

It would be desirable to have a low-cost method for quantitative analysis of body fluids, with determination of the amounts of two or three hundred substances, to make it possible to check the state of health of all persons at frequent intervals and to

TABLE 3-6.

Values of WNI for Some Pairs of Retardate Samples

	40	41	43	46	47
40	0.000	1.852	3.525	2.508	7.052
41		0.000	0.704	0.559	4.661
43			0.000	0.818	4.351
46				0.000	4.328
47					0.000

follow the course of disease during periods of illness. A discussion of presently available methods of analysis has led us to the conclusion that gas-liquid partition chromatography of urine vapor and breath is the most promising method. An indication of the possibilities is provided by a discussion of the results of analysis of 50 urine samples by a less powerful method (low-resolution ion-exchange chromatography of ninhydrin-positive substances). Of 18 subjects with undiagnosed severe mental retardation, four were found to be indistinguishable from normal subjects by this test; it is accordingly likely that these four do not have a genetic abnormality involving amino acids. Three of the 18 were found to be closely correlated with one another and not correlated with normal subjects or the other 15 retardates. It is likely that these three have the same genetic abnormality leading to severe mental retardation. The nature of this abnormality has not yet been determined. We are continuing this work, with emphasis on the analysis of urine vapor and breath, with normal subjects, mental retardates, schizophrenic subjects, and subjects with many other diseases.

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4

The Genetics of Schizophrenic and Schizoid Disease

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The contribution of genetic factors to the etiology of schizophrenia has been confirmed decisively. Because the investigations that have led to this result have uncovered questions cutting across several fields of inquiry, a fresh look at some central aspects of the schizophrenia problem is warranted. These questions and the factual background underlying them are the main concerns of this article. Because emphasis is placed on formulating testable hypotheses, the evidence is organized in support of a particular genetic theory.

THE BASIC EVIDENCE

During the first half of this century, systematic family studies demonstrated that the distribution of schizophrenia is that of a genetic disease. Relatives of schizophrenics

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were found to be afflicted with the illness much more frequently than members of the general population. The child of a schizophrenic parent, for example, was found to have a risk of schizophrenia about 15 times that of a member of the population at large. It was found that, among all classes of relatives, the closer the genetic relationship to a schizophrenic proband (or index case) is, the greater is the likelihood of schizophrenia in the relative. Finally, and most telling of all, monozygotic twins were found to be concordant with respect to schizophrenia about four times as often as dizygotic twins. Several authorities have critically reviewed these basic data (Slater, 1968; Rosenthal, 1967; Shields, 1968). But, despite the supporting evidence, a genetic etiology for schizophrenia was not widely accepted, especially in this country. It was pointed out that the investigators did not pay enough attention to important procedural matters, such as providing sampling safeguards and insuring against bias on the part of the investigator. But the paramount objection to a genetic interpretation of the evidence was the objection that the whole research strategy was faulty. The results of these studies, it was held, were just as compatible with transmission of schizophrenia through the social environment as with transmission through genes. The closer the genetic relationship, the closer the social relationship. Were genes or was noxious social learning responsible for the familial clustering of schizophrenia?

Recently, several studies have been aimed at closing those methodological and conceptual gaps. In these newer studies diagnoses either were made by raters who did not know the genetic background of the subjects or were taken unchanged from medical records. Care was taken to remove sampling biases and, most importantly, control groups were used. The strategy permitted separation of the effects of genes from the effects of social environment through the use, as subjects, of children reared in adoptive or foster homes.

The results of one such study are shown in Table 4-1 (Heston, 1966). The experimental subjects were individuals born to schizophrenic mothers, and the controls were individuals born to parents who had no record of psychiatric disturbance. The members of both groups had been permanently separated from their biological mothers in the first month of life and reared mainly in foster or adoptive homes. The subjects, as adults, were assessed through psychiatric interviews and review of every available record—for example, school, police, Veterans Administration and medical —and then evaluated by a team of clinicians. The significant excess of schizophrenia found among those subjects whose biological mothers were schizophrenic seems impossible to explain except on a genetic basis. Moreover, among those same experimental subjects, and thus also linked to schizophrenia by the evidence, was an even greater excess of various apparently nonschizophrenic disorders. The latter finding, which is reflected in nearly every entry in Table 4-1, is a central concern throughout this article.

The preliminary results from a very similar study which stressed exemplary investigative safeguards were much the same. Rosenthal et al. (1968) reported that

TABLE 4-1.

Results of a Study of Individuals Born to Schizophrenic Mothers and Reared in Adoptive or Foster Homes, and of Controls Born to Normal Parents and Similarly Reared

Item	Control	Experimental	Exact probability (Fisher's test)
Number of subjects	50	47	
Number of males	33	30	
Age, mean (years)	36.3	35.8	
Number adopted	19	22	
MHSRS, means*	80.1	65.2	0.0006
Number with schizophrenia	0	5	0.024
Number with mental deficiency (I.Q. $<$ 70)†	0	4	0.052
Number with antisocial personalities	2	9	0.017
Number with neurotic personality disorder‡	7	13	0.052
Persons spending more than 1 year in penal or psychiatric institution			
Number	2	11	0.006
Total years incarcerated	15	112	
Number of felons	2	7	0.054
Number serving in armed forces	17	21	
Number discharged from armed forces on psychiatric or behavioral grounds	1	8	0.021
Social group, first home, means§	4.2	4.5	
Social group, present, mean§	4.7	5.4	
I.Q., mean	103.7	94.0	
Years in school, mean	12.4	11.6	
Number of children, total	84	71	
Number of divorces, total	7	6	
Number never married, $>$ 30 years of age	4	9	

* The MHSRS is a global rating of psychopathology moving from 0 to 100 with decreasing psychopathology. Total group mean, 72.8; S.D., 18.4.

† One mental defective was also schizophrenic; another had antisocial personality.

‡ Considerable duplication occurs in the entries under "neurotic personality disorder"; this designation includes subjects diagnosed as having various types of personality disorder and neurosis whose psychiatric disability was judged to be a significant handicap.

§ Group 1, highest social class; group 7, lowest.

biological children of schizophrenics reared in adoptive homes exhibited "schizophrenic spectrum" disorders in significant excess over similarly reared controls. The "schizophrenic spectrum"—an expression coined in a quite reasonable attempt to find a term that would encompass the various disorders seen among biological relatives of schizophrenics—included schizophrenia, possible schizophrenia, borderline states, certain paranoid disorders, schizoid disorders, and the condition known as inadequate personality.

Karlsson (1966), as one result of his study of schizophrenia in Icelandic families,

found that 6 of 29 persons, some of them siblings, born to a schizophrenic parent but reared in foster homes developed schizophrenia. None of their 28 foster sibs who were reared in the same homes developed schizophrenia. This difference, too, is significant. Karlsson did not ascertain any disorders other than typical schizophrenia among his subjects.

In two ingeniously designed research projects, adopted individuals served as the starting point. Wender et al. (1968) studied the biological and adoptive parents of ten adopted schizophrenics and the adoptive parents of ten normal persons. The biological parents of the schizophrenics were found to exhibit significantly more psychopathology than either group of adoptive parents. In a similar but wider ranging study conducted by Kety et al. (1968), psychopathology, again reported as "schizophrenic spectrum" disorders, was found to be concentrated in significant excess among the biological relatives of adopted schizophrenics. The adoptive families of schizophrenics were indistinguishable from the adoptive and biological families of adopted controls. Since the psychopathology found in these studies was significantly greater among the group of biological relatives of the schizophrenic probands than among the adoptive relatives who actually lived with them, this evidence too strongly favors genetic over social transmission of schizophrenia.

The results of the studies of adopted and foster children—results which are strikingly consistent from study to study, considering the vagaries of research in this area —present seemingly insurmountable difficulties for adherents of environmental theories of schizophrenia. The evidence must surely compel acknowledgment of a genetic contribution to schizophrenia, and probably to related disorders as well. To go further, however, requires information on other types of genetic relationships and larger numbers of subjects. Happily, the older family studies can now meet these needs. For perhaps the most important contribution of the recent studies of adopted and foster children is the fact that they have confirmed the results of the older studies in all material respects. The familial clustering of psychopathology that had been documented in such detail has been linked to one critical variable, a genetic relationship to schizophrenia.

THE SCHIZOID

The presence of so much psychopathology other than typical schizophrenia among relatives of schizophrenics was first noticed by physicians on visiting days in the earliest asylums. Isaac Ray, writing in 1863, gave a good description (1968). Because the relatives' disabilities resembled schizophrenia, investigators associated with the Munich school called these disabilities "schizoid" (schizophrenic-like). Describing the schizoid individual, delimiting schizoid from psychiatric and general populations, and placing the schizoid in relation to the schizophrenic were central concerns of

the psychiatry of that day. After perhaps the longest detour in the modern history of science, we have come full circle in returning to the same concerns. Meanwhile, problems of nomenclature have developed.

To me, "schizoid" and "schizophrenic spectrum" seem to denote precisely the same disabilities, except that the latter term also includes schizophrenia. One consideration that may have led Kety, Rosenthal, Wender, and their co-workers to coin the new term is the obvious danger of confusing "schizoid" with "schizoid personality." The latter term, a diagnosis in the American Psychiatric Association and World Health Organization nomenclature, although descended from descriptions of the abnormal relatives of schizophrenics, has evolved and changed in meaning so that it is no longer applicable to most of those relatives. For example, it was not often applied to relatives of schizophrenics by the rating clinicians in the studies of adopted and foster children. But other diagnoses currently considered applicable to such individuals also fit these relatives imperfectly, so no formal categorization is now available. Because of a central trait of the schizoid—his clinical resemblance to the schizophrenic—and because of the desirability of maintaining continuity with older studies, I use the term "schizoid" as a name for the schizophrenic-like disabilities seen in relatives of schizophrenics, or for the individual manifesting such disabilities.

Nearly all observers of the schizoid have noted his clinical resemblance to the schizophrenic, but clinical criteria adequate to reliably distinguish the schizoid from members of a general or a psychiatric population or even from other kinds of abnormal persons with a coincidental genealogical connection to a schizophrenic are most imperfect (Planansky, 1966; Essen-Möhler, 1946). Although unsatisfactory, the only means of identifying many—perhaps most—schizoids remains genealogical, and a clinical understanding of the schizoid can best be gained by reading descriptions of abnormal relatives of schizophrenics (see Alanen, 1966; Kallmann, 1938; Kringlen, 1967; Slater and Shields, 1953, for good examples). The circularity thus introduced is regrettable but inescapable. The schizoid exists, and he sometimes shows as much impairment psychiatrically as a typical schizophrenic.

Several problematical behaviors have been associated with the schizoid. Among males, antisocial behavior has been found commonly enough to warrant the older subdesignation "schizoid psychopath." Entries in the police records of the schizoid psychopaths in my study reflected impulsive, seemingly illogical crime such as arson, unreasoning assault, and poorly planned theft (Heston, 1966). Social isolation, heavy intake of alcohol, and sexual deviance have been noted frequently. Other schizoids, both male and female, have been described as eccentric, suspicion-ridden recluses. The main disability of still other schizoids, mostly females, has been found to be incapacitating attacks of panic or unreasoning fear in response to ordinary social challenges.

On a more technical level the resemblance to schizophrenia is more apparent.

Rigidity of thinking, blunting of affect, anhedonia, exquisite sensitivity, suspiciousness, and a relative poverty of ideas—in variable combinations and intensities—characterize both the schizoid and the schizophrenic, though such characteristics are less prominent in the former. Though schizoids do not show a well-marked thought disorder, delusions, and hallucinations, descriptions of some of the behavioral lapses of schizoids, especially the schizoid psychopath, are bizarre enough to suggest micropsychotic episodes.

Slater took a different approach. He listed a series of explicatives, partially reproduced in Table 4-2, used by relatives of schizophrenics when describing their abnormal but nonschizophrenic relatives (Slater and Shields, 1953). Slater went on to

TABLE 4-2.

Explicatives Used by Relatives of Schizophrenics in Describing Their Schizoid Relatives. (After Slater and Shields, 1953)

Paranoid eccentricities:	suspicious, sensitive, sullen, touchy, grouchy, morose, resentful, unforgiving, difficult, quarrelsome, self-conscious, jealous, litigious, critical, and others.
Eccentricities:	giggly, opinionated, pedantic, narrow-minded, meticulous, obstinate, humorless, rigid, little-minded, spiritualist and many others.
Lack of feeling:	passive, cruel, calculating, placid, hard and stingy, unsympathetic, cold, withdrawn, little-feeling, and others.
Reserve:	shy, serious, haughty, snobbish, studious, unforthcoming, taciturn, unsociable, seeks solitude, and so on.
Anergic:	dependent, tired, slack, unreliable, subservient, and so on.

say (p. 83) that "the same or similar words or phrases occur in descriptions of abnormal personalities from other kinds of families, but much less frequently, not in such concentrated form, and they are usually submerged by descriptions of a very different tone."

Because Kallmann's investigations of the families of schizophrenics were by far the most extensive that have been made, his concept of the schizoid is of critical importance (Kallmann, 1938). From his description (p. 102) it is clear that he relied heavily on the schizoid's clinical resemblance to the schizophrenic. Kallmann regarded the distinguishing features of the schizoid to be the "fundamental symptoms of schizophrenia in the milder form of characterological abnormalities . . . dominating the personality of the individual in question." Kallmann also looked analytically at traits other than those obviously associated with schizophrenia or schizoidia that seemed to occur in excess among relatives of schizophrenics, with the aim of

including or excluding them from the group of schizoid traits. On various grounds he excluded all the traits that he considered.

One of the traits which Kallmann considered and rejected, mental deficiency, perhaps deserves another look. About 6 to 10 percent of schizophrenics (see Hallgren and Sjögren, 1959) and their first-degree relatives (see Heston, 1966; and Kallmann, 1938) are mentally subnormal, as compared with 3 percent of the general population. The expected reciprocal relationships, an excess of schizophrenics among mental defectives or their relatives, was found by Penrose (1938) and Böök (1953) among mental defectives but not by Reed and Reed (1965) in their monumental survey of the relatives of mental defectives. Also, Kallmann found a much higher rate of mental deficiency (10.8 percent) among relatives of simple schizophrenics, where there is a clinical commonality of sorts, than among relatives of other subtypes in the Kraepelinian classification. The evidence for or against an association between schizophrenia and mental deficiency is inconclusive, and more data are needed before the matter can be decided.

Obviously there is much yet to be learned before we can describe and delimit schizoidia. However, the same thing can be said of schizophrenia itself, and in this regard study of the schizoid may lighten some dark corners. Schizophrenia is defined operationally, not etiologically. It is the clinician who determines whether schizophrenia is present. But of course the limits of the clinical entity may not correspond to those of the etiological entity. In fact, the linking of schizoidia to schizophrenia by genetic evidence raises serious questions about the etiological reality of the clinical definition of schizophrenia. There has always been a fuzzy border about schizophrenia along which several named entities, including abortive, ambulatory, borderline, latent, pseudoneurotic, pseudopsychopathic, and reactive schizophrenia and the "schizotype" of Meehl (1962), have seemed to lie. These terms may best be viewed as attempts to cope with an operationally defined border between schizoidia and schizophrenia that is clinically imprecise because it is biologically unreal.

QUANTITATIVE ASPECTS

Given a schizophrenic who has a monozygotic twin, the empirical probability that his twin will also be schizophrenic has been found to be about 0.46 (Table 4-3). Most of the remaining 54 percent of monozygotic twins of schizophrenics have also been found to be abnormal. From clinical descriptions included in five studies (Kringlen, 1967; Slater and Shields, 1953; Essen-Möller, 1941; Tienari, 1963; Pollin et al., 1965) it appears that nearly all of the abnormal though nonschizophrenic co-twins were schizoid. Overall, only about 13 percent of the monozygotic twins of schizophrenics have been regarded as normal or nearly normal, and, because most of the errors inherent in this sort of research tend to increase the proportion of apparent

normals, this is surely an overestimate. But, while a critic could easily quibble about any of the proportions in Table 4-3, a crude but critical conclusion is inescapable: monozygotic twins of schizophrenics are about as likely to be schizoid as schizophrenic. What then is inherited? These considerations led Essen-Möller (1941) to regard schizoidia as the basic inherited trait, and Kringlen, in a careful and sensitive analysis of twin research, including his own major study, seems to have reached a similar conclusion, although he regarded the predisposition as less specific (Kringlen, 1967). At the very least a prima facie case has been made for considering the whole

TABLE 4-3.
Data on Monozygotic Twins of Schizophrenics

Investigator	Pairs	Schizophrenia	Other significant abnormality*	Normal or mild abnormality
Essen-Möller (1941)	9	0	8	1
Slater (1958)	37	18	11	8
Tienari (1963)	16	1	12	3
Kringlen (1967)	45	14	17	14
Inouye (1961)	53	20	29	4
Gottesman and Shields (1966)	24	10	8	6
Kallmann†	174	103	62	9
Total	358	166 (46.4%)	147 (41.1%)	45 (12.6%)

* Investigators' diagnoses: ? schizophrenia, schizophreniform, transient schizophrenia, reactive psychosis, borderline state, schizoid, suicide, psychopathic, neurosis, and variations of these diagnoses.
† From Shields et al. (1967).

group of schizoid and schizophrenic disorders as alternative expressions of a single genotype. Moreover, because monozygotic twins are identical genetically, there is presumptive evidence that the range of variability within pairs can, in principle, be accounted for by environmental factors. The genes allow a range of outcomes.

A critical point to be established is the proportion of schizoids or schizophrenics among the first-degree relatives (parents, sibs, children) of schizophrenics. Table 4-4 gives Kallmann's results. No one else has investigated so many relatives of schizophrenics, and few others have conducted field studies intensive enough to identify schizoids. The more intensive modern studies have tended to show somewhat larger proportions of afflicted relatives (Heston, 1966; Alanen, 1966; Lidz et al., 1966). So did Slater among dizygotic twins of schizophrenics (Slater and Shields, 1953). The proportions found by Gottesman and Shields (1966, 1967) and by Ödegard (1963) were somewhat smaller. Kallmann's values may be taken as fair average estimates of the proportion of schizoids or schizophrenics among first-degree relatives of schizophrenics.

Table 4-4 also shows the results of four studies of the children of two schizophrenics. An estimated 66 percent of the children of these matings were schizoid or schizophrenic; again, this is surely an underestimation because the subjects were still quite young. The results of one such study, that of Lewis (1957), were not included. Lewis did not give ages, and he stated that his follow-up was incomplete. Rosenthal has recently reviewed these studies (1966).

An important unknown must now be considered. There is no adequate estimate of the proportion of schizoids in the general population. Then, is the clustering of

TABLE 4-4.
Percentages of First-degree Relatives Found to be Schizophrenic or Schizoid

Relationship	Number of individuals	Schizophrenia* (%)	Schizoid (%)	Total: schizoid plus schizophrenic (%)
Children†	1000	16.4	32.6	49.0
Siblings‡	1191	14.3	31.5	45.8
Parents‡	2741	9.2	34.8	44.0
Children of two schizophrenics§	171	33.9	32.2	66.1

* Age-corrected rates. † From Kallmann (1938). ‡ From Kallmann (1946).
§ From Kallmann (1938), Kahn (1923), Schulz (1940), and Elsässer (1952).

schizoids among relatives of schizophrenics greater than might occur by chance? Although the proportion of schizoids found in families of schizophrenics is surely greater than that expected by even the most pessimistic observer of the general population, a better answer is that neither the relatives of other kinds of psychiatric patients nor the controls used in psychiatric studies have been found to be afflicted in significant numbers with disorders of a schizoid character or with any kind of behavioral disorder to the extent seen in relatives of schizophrenics. Further evidence—the small proportion of schizoids found among descendants of normal relatives of schizophrenics—is discussed below.

While the lack of data for the general population and the related lack of data for the families of schizoid probands preclude estimates of gene frequency, it should be noted that schizoid disorders surely afflict a large proportion of the population. With only isolated exceptions, schizophrenia afflicts about 1 percent of any population. If each schizophrenic has five living first-degree relatives (about the number in Kallmann's study), a simple extrapolation yields an estimate of 4 percent for the proportion of schizoids plus schizophrenics in the general population. This crude estimate can only make the point that any population, and especially any psychiatric population (persons identified because they came to psychiatric clinics or hospitals), is likely

to contain large numbers of schizoids. One of the most neutral implications of this conclusion has an obvious application to the choosing of control groups for research in schizophrenia.

GENETIC HYPOTHESIS

The most parsimonious explanation of the data is given by the hypothesis that a defect in a single autosomal gene accounts for the genetic contribution to both schizoid and schizophrenic disease (the "dominance hypothesis"). By including schizoid disease (schizoidia), this hypothesis extends that of Slater (1958). The view that schizoidia and schizophrenia are a single disease genetically is supported by their clinical similarity and is virtually required by the finding that the disorders occur with equal probability in monozygotic twins of schizophrenics. Further support for the hypothesis is presented in Figure 4-1. The proportions of affected first-degree relatives fit reasonably well with the theoretical proportions expected under the dominance hypothesis.

Kallmann presented some data on second-degree relatives (1938). Among 822

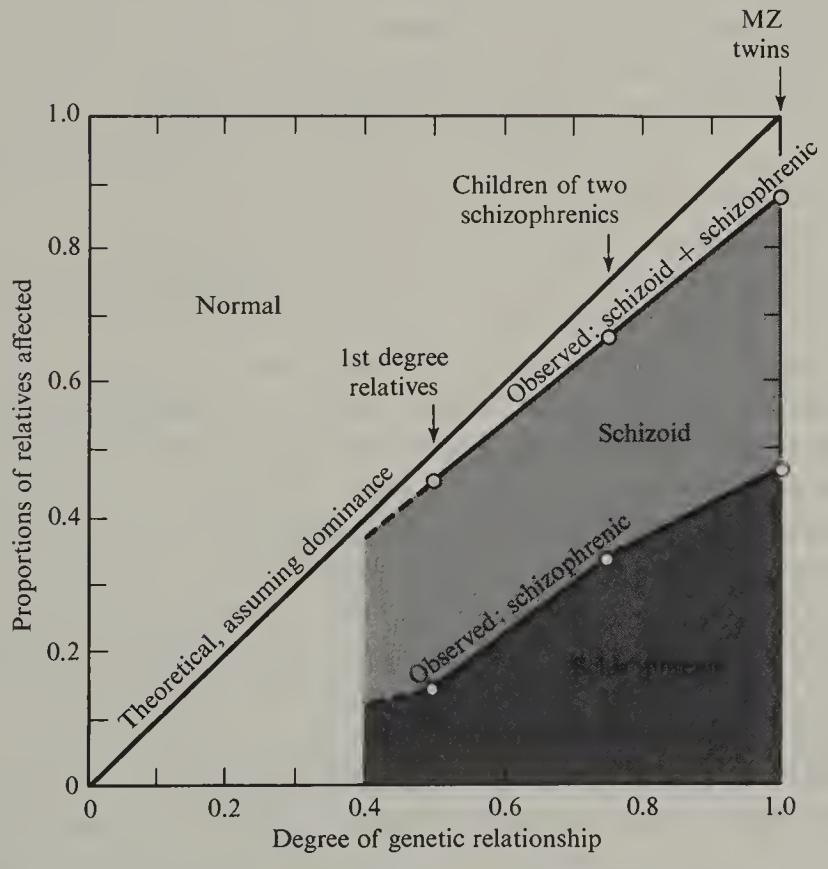


FIGURE 4-1.
Observed and expected proportion of schizoids and schizophrenics.

grandchildren of his schizophrenic probands he found 4.3 percent to be schizophrenic and 22.8 percent to be schizoid. The corresponding rates for nephews and nieces were considerably lower (3.9 and 6.2 percent). However, Kallmann pointed out that the normal sibs of his schizophrenic probands contributed many more nephews and nieces than the schizoid or schizophrenic sibs did. While the total of 27.1 percent for affected grandchildren is certainly close to the 25 percent expected under the dominance hypothesis, the proportions of affected nephews and nieces may or may not be compatible with that hypothesis.

The segregation of schizophrenia and schizoidia within families fits well with the dominance hypothesis. In Kallmann's study, which included three generations, the normal children of his schizophrenic probands produced few schizophrenic or schizoid children (1.8 and 2.6 percent, respectively), no more than might be expected in a general population. This is in contrast to the corresponding values of 13.7 and 33.4 percent for the children of the schizoid or schizophrenic children of Kallmann's schizophrenic probands (1938).

The matter cannot be so simple, of course. The mechanisms involved in a disease like schizoidia-schizophrenia will surely be found to be extremely complex. Even phenylketonuria, which only a few years ago provided a prototype of rigorous simplicity for behavioral genetics, has turned out to be enormously complicated by secondary biochemical effects and by other, mostly unknown, factors (Johnson, 1968). Heterogenity is also likely. Probably the most completely known genetic disease in humans, glucose-6-phosphate dehydrogenase deficiency, occurs in at least 18 variants, each one presumably due to an amino acid substitution at a different place in the same enzyme (Harris, 1968). But research must proceed from hypotheses based on present understanding. From that viewpoint, and for practical purposes, it is not at all unreasonable to proceed on the working assumption that most schizoidia-schizophrenia is associated with defects in a single basic biochemical or physiological pathway, transmitted by a single mode of inheritance. It matters little that new research will no doubt turn up complexities that cannot even be imagined today.

Apart from insights gained from analogies to other genetic diseases, there are factual reasons for expecting that many elements in addition to a single main gene go into the mix that results in schizoidia-schizophrenia. First of all, there remain small deviations from the theoretical expectations under the dominance hypothesis, deviations which have been cited by Shields (1968). These mainly take the form of a greater resemblance between relatives than can be explained by simple dominance. For example, the monozygotic twin of a severely afflicted individual is more likely to be schizophrenic than the twin of a mildly affected individual. If only a single gene were involved one would expect the risk of schizophrenia for a monozygotic twin of any schizophrenic to be equal to that of any other. Likewise, the larger the proportion of schizophrenic relatives, the greater is the risk of schizophrenia for any given individual. Another sort of problem is that of accounting for the variability seen among

schizophrenics; this becomes more difficult when schizoids are included. Although there are no grounds for expecting any particular degree of resemblance between affected persons, it has often been argued that, if only one gene were involved, the range of observable phenotypes should be smaller than is the case. And the persistence of schizophrenia presents a problem. Before the introduction of antipsychotic drugs, schizophrenics reproduced at a rate 30 percent lower (Böök, 1953), and schizoids at a rate 22 percent lower (Kallmann, 1938), than the rate for the general population. Such reproductive deficits should have lowered the rates of occurrence of a disorder due to a main gene of large effect far below the presently observed rates for schizophrenia.

Attempts to account for such findings have led to widespread espousal of polygenic theories of schizophrenia (Kringlen, 1967; Ödegard, 1963; Rosenthal, 1963). As Gottesman and Shields have pointed out (1967), the facts are explained adequately by polygenic theory. Most polygenic theorists have regarded schizophrenia as a threshold trait. But clinically schizoidia and schizophrenia seem to form a continuum of psychopathology, much as first described by Kretschmer (1925). If there is a threshold it probably falls between the schizoid and the normal condition, but it seems that any such "threshold" is as likely to be a function of lack of diagnostic precision as a function of the disease. It is not necessary to consider other aspects of the polygenic argument here. Known modifiers of the phenotypic expression of the disease point toward plausible solutions of the problems encountered by the dominance hypothesis and toward resolution of the apparent differences between main-gene and polygenic theories.

MODIFYING FACTORS

One class of modifiers must be environmental events in the broadest sense—events occurring from conception onward that produce some change in the organism. The nature-nurture dilemma is unreal. It is change in the environment of the cell that induces change in the genetically mediated metabolic systems of the cell. The functional state of the cell is a result of the interplay of these determinants. But realization that phenotypic traits depend on interaction between gene and environment imposes conditions on research aimed at assessing the environment contribution. Genes function within cells. They interact with chemical, thermal, or other physical events and not with the abstractions ("stress," for example) that too often have passed for environmental data. The ultimate questions implicit in the concept of gene-environment interaction are, for example: How does a noxious learning experience alter the environment of the cell? What response is elicited from the genetic program of the cell? How is the later operation of the cell modified? Of course, such questions cannot be approached directly today. But unless the environmental contribution is too

variable from case to case to allow generalization, it should be possible to build up a series of associations between environment and behavior that would point toward the environmental events that enter into the gene-environment interaction. The critical requirement is that such associations be potentially translatable into events that occur at the level of the gene. Despite all the research that has been done on the effects of environment on the development of schizophrenia, and despite the scope for environmental factors demonstrated by the differences between members of monozygotic twin pairs, practically no associations that meet this requirement have been established. Clinicians have learned to predict the effects of environmental features on their patients, but it is difficult to see any etiological clues in this body of experience. On general clinical grounds it makes sense to continue to study the effects of environmentally stimulated autonomic and endocrine responses. An association between lower birth weight and the development of schizophrenia in one member of a monozygotic twin pair has been reported (Pollin et al., 1965), but it must be quite imperfect in view of the failure of other investigators to confirm it (Kringlen, 1967; Gottesman and Shields, 1966). Perhaps differences in autonomic responses among children of schizophrenics that were described in a preliminary report from a wide-ranging prospective study (Mednick and Schulsinger, 1958) are the most promising associations so far defined. Almost everything remains to be done.

A second class of modifiers consists of complex traits that have been linked to schizophrenia by decades of empirical research. Somatotype has been found by several investigators to be associated with major modification of schizophrenia. Mesomorphs are underrepresented among schizophrenics, and especially underrepresented among schizophrenics younger than 25. Ectomorphs are correspondingly overrepresented. Schizophrenic mesomorphs are predominantly paranoid and have a shorter mean period of hospitalization than other schizophrenics. Parnell (1958), who has reviewed the subject and contributed his own data, found all these associations to be statistically significant. A relation between intelligence and the prognosis in schizophrenia is well known: the higher the intelligence the better the prognosis. But higher intelligence may also affect the expression of schizophrenia. Lane and Albee (1965) found that the I.Q. of children who later became schizophrenic was seven points lower than that of their siblings who remained nonschizophrenic. There are a host of other established associations between complex traits and schizophrenia—for example, patterns of autonomic nervous system reactivity, immunological phenomena, resistance to certain chronic diseases, and tolerance of wound shock. Some such traits appear to be only oddities, given our present knowledge; others are known to be linked to favorable or unfavorable prognosis in schizophrenia, and still others are known only to be more frequent or infrequent among schizophrenics. Several reviews of these findings are available (Gellhorn and Loofburrow, 1963; Ross et al., 1950; Huston and Pepernik, 1958; Rosenbaum, 1968; Freeman, 1958; Rees, 1952).

The large number of such complex traits and the magnitude of the modification of schizophrenia associated with some of them must mean that they have a significant role in the ecology of the disease. For one thing, they suggest a plausible solution to the puzzle posed by the persistence of high rates of schizophrenia. Sir Julian Huxley et al. (1964) postulated that the gene responsible for schizophrenia conferred sufficient physiological or reproductive advantages to maintain a balanced polymorphism. They listed several physiological traits found in schizophrenics that could be due to pleiotropism. Although the number of traits listed seems large, widespread pleiotropism might result from a mutation at a regulatory locus (Britten and Davidson, 1969). But many modifying traits are clearly not due to pleiotropism, and some of those—particularly differences in somatotype and intelligence—which demonstrably affect the outcome in schizophrenia must have conferred general biological advantages through much of man's history as well. In either event, schizophrenics possessing advantageous traits would be expected to reproduce at relatively higher rates than those not possessing such traits. Over time, the evolutionary process would, theoretically, act to establish sets of favorable traits that, on the average, would tend to accompany schizophrenia. Theory aside, the popular association between genius and insanity, thought to be erroneous by Kallmann, was given some substance by Karlsson's finding that creative achievements and schizophrenia occurred in the same family lines (1968). I reported a similar impression; however, the evidence was not gathered systematically (Heston and Denney, 1968). Although the problem posed by the persistence of schizophrenia remains theoretical and unsolved, further exploration of modifying traits provides as likely a path as any other now in view toward solution of the puzzle.

Modifying traits also suggest an approach to the problem of deviations from strict expectations under the dominance hypothesis. As pointed out above, polygenic theory can account for such deviations. But traits like somatotype and intelligence are themselves almost certainly polygenic. Polygenic modifiers of a single main gene explain the same facts, and indeed would yield the same mathematical results as simple additive polygenic theory per se. A multitude of genes summating to produce schizophrenia directly or a single main gene plus groups of genes summating to produce modifying traits account equally well for findings such as the tendency of monozygotic twins to be concordant with respect to severity of illness.

CONCLUSION

A main gene of large effect modified by multiple factors, including polygenic traits, suggests a number of testable hypotheses. Biochemical or other effects of a main gene should be present in schizoids as well as in schizophrenics. In family studies, the critical test of the place of the schizoid would be his reproductive performance in

matings with normal individuals; 50 percent of the offspring of such matings should be schizoid or schizophrenic. However, polygenic modifiers should, on the average, maintain lesser degrees of disability in particular families. Thus, schizoid parents should have fewer schizophrenic but more schizoid children than schizophrenic parents. There is incomplete support for this contention in Kallmann's study (1938) of the grandchildren of his schizophrenic subjects: the schizoid children of his schizophrenic probands had more schizoid and fewer schizophrenic children than their schizophrenic siblings, but members of the third generation, the grandchildren of the probands, were too young to yield decisive evidence. Along the same lines, it would be expected that nearly all schizophrenics should have at least one schizoid or schizophrenic parent. Although the work of Kallmann and the intensive family studies of Alanen (1966) and Lidz et al. (1966) support this expectation, more rigorous evidence is needed. The traits that favorably modify schizophrenia should be more apparent among schizoid than among schizophrenic relatives of schizophrenics. One would hypothesize, for example, that the more mesomorphic or more intelligent among the children of schizophrenics would tend to have less severe illnesses and to have more children than the less mesomorphic or less intelligent. These hypotheses, and many more that are implicit in the preceding discussion, constitute a significant refinement of the genetic hypotheses so far explored in schizophrenia.

SUMMARY

The importance of genetic factors in the development of schizophrenia has by now been established beyond reasonable dispute, although it is clear that environment also plays its etiologic role. The results of recent research have refocused attention on schizoid disorders, a term applied to psychiatric disorders resembling schizophrenia which afflict relatives of schizophrenics. The many conceptual and research problems presented by the schizoid are considered.

Schizoids and schizophrenics occur with about the same frequency among monozygotic twins of schizophrenics. About 45 percent of the sibs, parents, and children of a schizophrenic are schizoid or schizophrenics, as are about 66 percent of the children of two schizophrenics. From the known risk of schizophrenia for the population as a whole, it is estimated that at least 4 percent of the general population will be afflicted with schizoid-schizophrenic disease.

Since monozygotic twins are identical genetically, it appears that the same genotype is compatible with either schizophrenic or schizoid disease. The proportions of affected first-degree relatives and the segregation of affected individuals within families closely approximate theoretical expectations based on the hypothesis of a defect in a single autosomal dominant gene. However, modifying traits play a

significant role; this is discussed and integrated into the main genetic hypothesis. Emphasis is placed on hypotheses testable by future research.

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5

Perceptual Defect and Role Handicap: A Theory of the Etiology of Schizophrenia

RUTH V. KIRK

"Could that be a cause of mental illness?" The speaker was a 24-year-old woman who had been hospitalized twice for schizophrenia. Recovered, she was referred for psychological testing to help plan her vocational rehabilitation. Testing had shown aberrations in perceptual functioning which I had previously observed in schizophrenics and was aware were part of the syndrome. In explaining to her the test findings, I mentioned the perceptual difficulty as a kind of disability which could make an academic course (requiring large amounts of reading) stressful to her despite her superior I.Q. My reply to her question, "I don't think it's necessarily a cause of mental illness, but it certainly can be a source of stress," elicited the story of her two breakdowns. The first was precipitated by unrelenting pressure on her by her parents to perform well in school, as all her siblings did. The patient, however, was convinced by her experience of failure, despite consistent efforts to learn certain subjects, that some people just cannot learn certain things, although they may learn others very well. The constant strife over her poor academic performance was, she said, the main source of stress within her family. The patient said that her second breakdown occurred when she was training to become a nurse. She tolerated the

hard work and practical aspects of nursing training in the hospital very well; the schizophrenic break occurred after several weeks of intensive reading and study.

My main area of specialized interest in working toward a degree in Clinical Psychology was the diagnosis and treatment of learning disabilities in children. Thus I was particularly aware of perceptual handicaps, and that they are often associated with disturbed behavior.

Schizophrenia was presented in our texts and by our instructors as the most baffling of mental disorders, very poorly understood despite the voluminous research literature. Researchers could demonstrate a relationship between schizophrenia and some specific "cause," such as heredity, faulty biochemistry, psychological stress within families, or emotional trauma, yet there were always others who could explain the findings in some reasonable way and produce researches of their own to show that none of these "causes" can explain the etiology of schizophrenia. The alternate explanations for the relationship could be demonstrated by properly controlled studies.

Perhaps because I was a student who was committed to no one of these possible causes of schizophrenia, I was profoundly impressed by the statements of an intelligent, articulate person who had twice been ill with schizophrenia and had twice recovered. In thinking about what I knew of schizophrenia, perceptual disorders, and this particular patient, the theory of etiology of schizophrenia presented in this chapter formed in my mind. It was like seeing the pieces of a complex puzzle fitting neatly into place, with research findings complementing and reinforcing each other, rather than conflicting.

Another patient, this time the 7-year-old daughter of a schizophrenic mother, led me to see another aspect of the theory. The child was referred for psychological testing because she was believed to be retarded. She had two normal siblings and another who also appeared retarded. Testing showed her to be of low-average intelligence, emotionally very withdrawn, and severely perceptually handicapped. She came in with her father after visiting the referring psychiatrist, to whom she had refused to speak, despite patient, kindly approaches on his part. She stood silently listening as I explained the testing to her father. While describing the perceptual handicap, demonstrating reversals of letters and words, and telling of the confusion this can cause a child who is trying to learn to read, I wrote the example of "on" and "no" and said that the perceptually handicapped child may see it one way or the other unpredictably so that instructions and corrections from the teacher are not understood and the child appears unable to learn. Turning to the little girl, I asked, "Did anything like that ever happen to you in school?" Her face became suddenly radiant, and she said, "Oh, yes, yes!" Her father's comment was "Well, I'll be damned! That's the first words she's said today!" It was clear that my understanding of her problem with perception resulted in an immediate change in her emotional state, from depression and extreme withdrawal to a cheerful readiness to communicate. The fact that her siblings who were learning normally were also emotionally

normal despite having to live with the same schizophrenic mother (who was alternately in and out of hospital) made it clear that the child's emotional response was both to her own disability and to the fact that her disability was not understood by others. Inquiry revealed that among the children of schizophrenics (who were known to professionals of my acquaintance) there was a very large proportion of perceptually handicapped, learning-disabled children—far more than would be anticipated in the general population, so the genetic studies suddenly acquired new meaning for me.

My theory of the etiology of schizophrenia is now presented, substantially as it originally appeared (Kirk, 1968), but with some revisions for greater clarity.

THE THEORY

Introduction

The immense literature on schizophrenia abounds in discoveries of single associations between the symptoms of the disease and certain other factors. Braithwaite (1960) says in speaking about "sciences like psychology and the social sciences which make great use of tendency statements" that "to assert an isolated tendency statement is to say very little." Such isolated statements in themselves are not explanations. A theory, on the other hand, interprets information; it explains.

In this paper a theory of the etiology of schizophrenia is proposed. The aim is to link the main experimental data and observations concerning the disease, providing, in Beck's (1962) words "a single scheme of interpretation for a whole group of apparently disconnected facts."

The procedure will be to assess first the main types of investigation concerning schizophrenia (Table 5-1). This assessment is presented in tabular form, so that the data can be readily summarized and the relative strengths of the various associations can be compared by the reader. Second, evidence is cited in support of defective perception as a central factor in schizophrenia. Third, taking defective perception as a starting point, and with the aid of a diagram, a complex social interaction process is outlined which organizes the previously summarized data into an explanatory pattern. Fourth, the proposed theory is stated in summary form. Fifth, a preliminary test of the theory is made by checking whether it can explain the specific symptoms and characteristics of the disease.

Assessing the Main Types of Investigations

In Table 5-1, representative reports of the main types of investigations into the nature and etiology of schizophrenia have been brought together. An attempt to assess

TABLE 5-1.

Factor as related to schizophrenia	Investigators	Evidence for relationship	Evidence against relationship	Theory assessment		
				1	2	3
Unspecified genetic factor.	Kallmann, 1946 Böök, 1960 (review article) Jackson, 1960 (review article)	The closer the blood relationship to a schizophrenic, the more likely it is that a person will develop schizophrenia. CONCORDANCE *Relationship* — *% concordant* Parents . . . . 10% Siblings . . . . 12% Children: One S. parent . . 16% Two S. parents . . 68% Twin studies: Dizygotic . . . 13% Monozygotic . . 85% Not separated . . 91% Separated . . 77%	Kallmann's methods are questioned. Adequate diagnosis is crucial. Evidence from epidemiological studies tends to undermine genetic evidence. Association could be the result of environment.	Yes	No	No
Genetically determined error in biochemical function interferes with the mechanism of perception.	Huxley et al., 1964	About 5% of people have this genetic factor, hence are "schizoprone." A fourth of these develop schizophrenia in response to faulty perception plus stress; the nature of the stress is not specified.		Yes	No	Yes
Family dynamics, interaction, communication, psychological stress on child.	*Pro:* Lidz and Fleck, 1960 (review article) Bowen et al., 1957 Boatman and Szurek, 1960 *Con:* Clausen and Kohn, 1960 Prout and White, 1956 Schofield and Balian, 1959	Schizophrenics are more likely than others to have weak fathers or "rejecting, inconsistent, overprotective, domineering, overtly loving, but covertly hostile" mothers. "Schizophrenogenic" mother who places child in "double bind" situation—not possible to respond correctly—either response punished.	Type of maternal behavior is related to social class more than to schizophrenia, 90 siblings of 60 schizophrenics experienced as much mental trauma but schizophrenics reacted differently. Parental deprivation as causal not substantiated. Histories of nonschizophrenic controls usually were disturbing—more trauma experienced than by schizophrenics.	?	No	?

Extreme physical and psychological trauma.	Eitinger, 1961 Bettelheim, 1960	Concentration camp victims with no hercditary taint developed schizophrenia after starvation, depersonalization, loss of family, hopelessness.	Clinical study only—no information on victims not schizophrenic.	Yes	Yes	No
	Rogler and Hollingshead, 1965	Schizophrenics in Puerto Rican slums, in contrast to matched sample of nonschizophrenics, had experienced a "critical year" of personal trauma, physical and psychological, prior to onset of illness.	See above for more typical environment. These cases may be explained this way, but few schizophrenics have experienced such extremes of deprivation; death of loved ones a universal human experience.	Yes	Yes	No
Biochemical abnormality.	Weckowicz, 1961 (review article)	Hundreds of studies have shown differences in body chemistry between schizophrenics and others.	Many of these differences have been shown to be artifacts of hospitalization, and can be eliminated by changes in diet or activity level. Inconclusive findings with respect to metabolism of epinephrine, ceruloplasmin, serotonin, taraxein.	Yes	No	No
	Kety, 1960 (review article)	Emotional reactions and chemical imbalance tend to perpetuate and exacerbate each other.				
Adverse intra-uterine conditions.	Pasamanick et al., 1956	The incidence of psychosis is higher among children whose births were difficult and/or when there were abnormalities during pregnancy. Evidence from epidemiological studies.		Yes	No	No
	Sontag, 1960 (review article)	Numerous animal studies relate enduring behavior disorders to prenatal factors such as poor nutrition, altered oxygen supply, emotional disturbance of mother.				
Prenatal environmental factors.	Boatman and Szurek, 1960	Strain for parents just before birth of child is related to onset and exacerbation of child disorder—clinical study.	No information about strains experienced by parents of other children.	Yes	Yes	No

(continued)

TABLE 5-1 *continued*

Factor as related to schizophrenia	Investigators	Evidence for relationship	Evidence against relationship	Theory assessment		
				1	2	3
Perceptual deficit, defect, disorder, distortion.	Weckowicz and Blewett, 1959	Degree of disturbance in size and distance constancy is correlated with severity of thought disorder in schizophrenics.		Yes	No	No
	Shakow, 1963	Slowness of establishing set. Slowness of response.		Yes	No	No
	Weckowicz et al., 1960	Slowness of learning. Unrealistic perception. Variability much greater.				
	Buss and Lang, 1965 Lang and Buss, 1965 (review articles)	Underlying the multiple psychological deficits of schizophrenics is a basic defect in sensori-motor functioning.		Yes	Yes	No
	Lane and Albee, 1965	Pre-morbid group IQs of schizophrenics of grade 2, 6, and 8 level, when compared with those of siblings, show up as consistently lower, showing that intellectual deficit *precedes* onset of illness by *years*.		Yes	No	No
	Kephart, 1960 Strauss and Lehtinen, 1947 Bender, 1956 Kirk, clinical observations	Symptoms and psychological test protocols and schizophrenics resemble those of children with learning disabilities due to perceptual defects. This is true of at least the following tests: Wechsler Intelligence Scales. Bender Visual-Motor Gestalt Test. Doman-Delacato Developmental Profile.		Yes	Not as yet	Not as yet

them is made by listing the evidence for and against the association which a particular investigation claims to have discovered. Beyond this, the investigator's report as a theory of etiology is assessed by asking:

1. Does the report demonstrate one or more factors with which the disease is typically associated?
2. Does it postulate one or more mechanisms that can account for the observed associations and so begin to explain the formation of symptoms?
3. Is this supposed mechanism specific enough to be tested?

Defective Perception and Schizophrenia

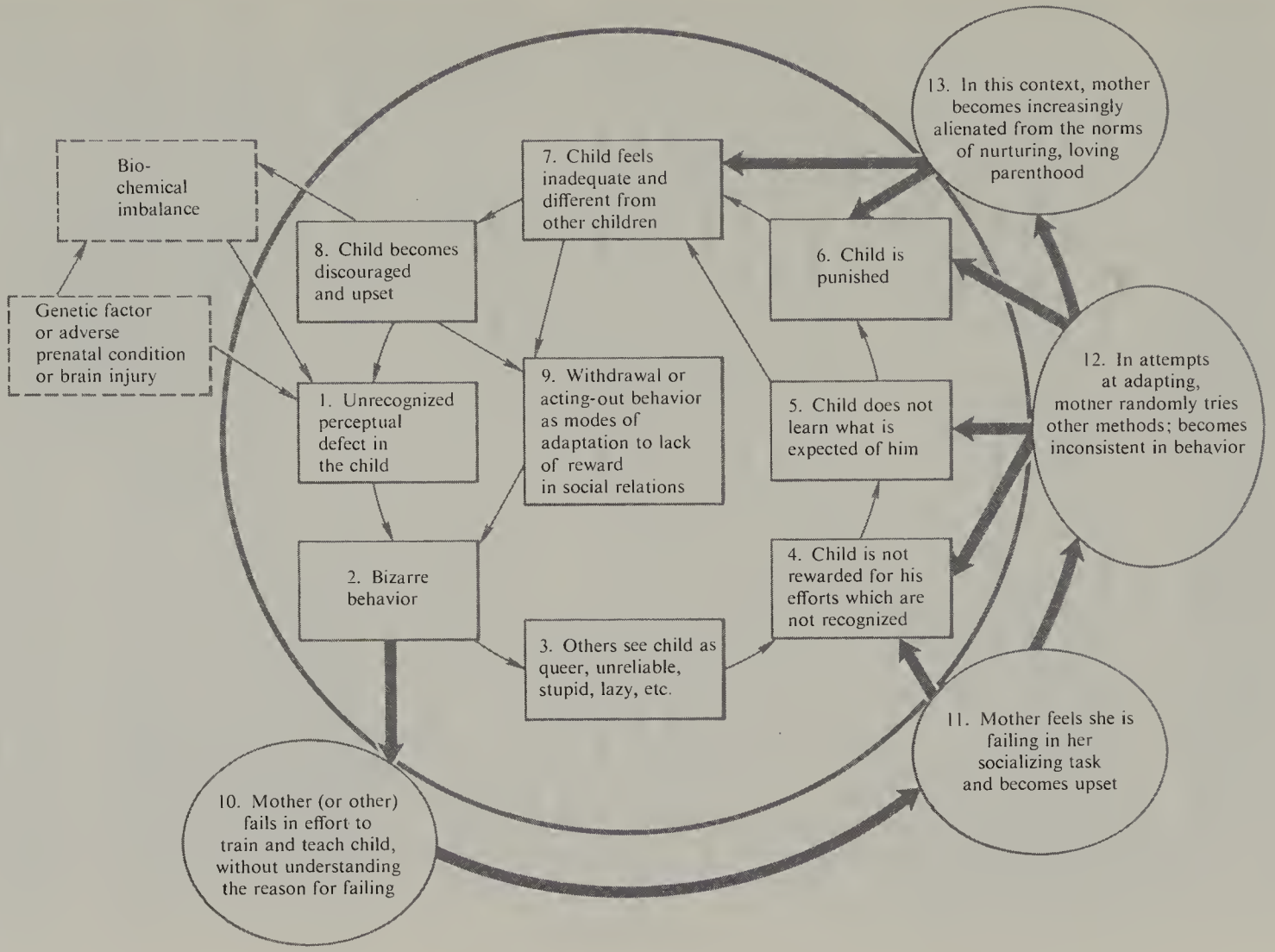
On the basis of the available evidence, then, the association between defective perception and schizophrenia emerges as the strongest, most consistent, most generally agreed-upon association. This is hardly surprising, since perceptual disorders have long been thought of as a symptom of the illness. Some of the investigators already cited have established connections with other variables, such as severity of thought disorder (Weckowicz and Blewett, 1959), genetic factor and biochemical abnormality (Huxley et al., 1964), and anxiety (McReynolds, 1960). McGhie and Chapman (1961), starting from an investigation which was psychoanalytic in orientation, were led by their observations to reject the proposal that early schizophrenic symptoms are defensive activities related to unconscious conflicts, and to suggest that the basic pathological breakdown is particularly to be found in the process of perception. Fish (1961) reaches the conclusion that early phases of acute schizophrenia are due to "overactivity of the reticular system producing an undue diversion and disruption of central processes by sensory input." Thus he sees anxiety as a result of disturbed perception and the resulting disruption of thought processes. Hoffer and Osmond (1963) report that certain schizophrenic symptoms are associated with measurable aspects of visual perception, specifically that schizophrenic patients are less able than nonschizophrenics to decide if an investigator is looking into their eyes. Most of these investigators have not, so far, been able to state the complex interrelated mechanisms which could explain the development of the complex symptomatology of the disease. Chapman (1966) gives evidence which relates disturbances in perception to the immobility of the catatonic, to cognitive disturbances, to visual imagery, and to the development of delusions and hallucinations, illustrating his ideas with material from interviews with acute schizophrenics. He suggests that the time is ripe for finding a way of integrating the vast number of disparate findings into a theory rather than looking for some major new etiological factor.

Defective Perception and Social Interaction

The accompanying diagram, like the line of thought which is to follow, starts out with the postulation of an unrecognized perceptual defect in a child. The origin of this perceptual defect could be a genetic factor, possibly a biochemical abnormality; adverse prenatal conditions; or brain injury at birth or at some later date—or any combination of these.

The number headings that follow refer to the corresponding numbers on the diagram (see page 79).

1. If one assumes that a perceptual defect in one or more sensory modalities exists, one can readily deduce some of the effects on the growing child. He can be affected by his poor or distorted perception in several ways, namely: (*a*) He will become aware that he cannot do something that others of his age and intelligence *can* do, such as read, spell, throw accurately, or discriminate between similar sounds. (*b*) When he listens to others talk of what they perceive, he will not entirely understand, because he does not perceive things as they do. His disability will perhaps include poor perception of language itself. (*c*) When he acts on the basis of his deficient perceptions, he will not find consensus; that is, his behavior will not be understood by others, and will be seen as bizarre.
2. The perceptual defect, then, results in behavior that seems bizarre to adults and other children, who are not aware that the child is not perceiving things as they do.
3. Because he is behaving in a bizarre manner and not learning normally, others tend to regard the child as queer and unreliable. When he talks of what he perceives, people will tell him he is mistaken or, more bluntly, stupid. If he is unable to judge distances, so that he trips over and bumps into obstacles, he will be thought of as clumsy. When he is unable to keep his attention focused long enough to complete a task, people will be likely to interpret this as laziness.
4. Because his efforts are not recognized as such, the child is not rewarded for them, nor is he rewarded by his own feelings of accomplishment, since many of his attempts are unsuccessful ones.
5. The net result of the perceptual handicap is that the child does not learn the things he is expected to learn, both because the handicap in itself makes learning difficult (and the learning of some of the more complex skills, such as reading, extremely taxing), and because his best efforts may often go unrecognized and unrewarded.
6. If he and others have no knowledge of his perceptual defect, he will, in effect, be punished for things he cannot understand nor avoid doing. He will also be punished for failing at tasks he cannot master despite consistent effort.


Bio-chemical imbalance
Genetic factor or adverse prenatal condition or brain injury
1. Unrecognized perceptual defect in the child
2. Bizarre behavior
3. Others see child as queer, unreliable, stupid, lazy, etc.
4. Child is not rewarded for his efforts which are not recognized
5. Child does not learn what is expected of him
6. Child is punished
7. Child feels inadequate and different from other children
8. Child becomes discouraged and upset
9. Withdrawal or acting-out behavior as modes of adaptation to lack of reward in social relations
10. Mother (or other) fails in effort to train and teach child, without understanding the reason for failing
11. Mother feels she is failing in her socializing task and becomes upset
12. In attempts at adapting, mother randomly tries other methods; becomes inconsistent in behavior
13. In this context, mother becomes increasingly alienated from the norms of nurturing, loving parenthood

7. Even if he is not punished directly, he will probably feel himself to be somehow different and less adequate than other children.

8. The child's conscious or unconscious reaction of discouragement and emotional upset to the unrecognized fact of his perceptual disability and his own sense of his difference from others can take various forms, but it is bound to be present.

9. Because social relations are unrewarding to him, the child may withdraw from others and live chiefly in a fantasy world in which his own perceptions are not tested against the perceptions of others and hence are less disturbing, or not disturbing at all. This is the autistic reaction. Alternatively, the child's emotional reaction to his handicap may be one of violent, aggressive, uncontrolled behavior, that of a person who tries to force his own perceptions on other people. This is the acting-out reaction.

   This inevitable emotional reaction to the experience of impaired perception is likely to compound the feeling of difference in at least two ways. First, in children with perceptual defects, these defects are much more pronounced when the child is upset, angry, or tired than when he is rested, happy, and relaxed. Hence, the emotional reaction will tend to increase the perceptual handicap. Second, the emotional reactions of withdrawal, aggression, or lack of control will often be construed as infantile or bizarre behavior unacceptable to others, possibly leading to rejection of the child or to punishment which he may feel to be rejection.

   To sum up the argument so far, the perceptual defects, the reactions of other people, and the child's emotional reactions to both (including, of course, his physiological reactions) appear to constitute a vicious circle which will tend to spiral downward unless the defect is somehow corrected or compensated for and the emotional reactions are neutralized or reversed. Chapman (1966) has described this process to some extent, and has illustrated it with quotations from interviews with young schizophrenics.

   The child whose perceptions are thus not only deficient or distorted but also are made unstable by his emotional reactions will have difficulty in identifying with anyone, since he can have no stable models. This instability of models is, of course, much greater for the child with a "schizophrenogenic" mother. This is true because her behavior toward the child is actually unstable and unreliable. According to the proposed theory, a child with such a mother, if his own perceptions were normal, might become neurotic, but not schizophrenic. He would, in time, find other models with whom to identify, and could come to realize that it is his mother, not he, who is "different." But a child with faulty perception, compounded by his own and others' reactions to it—for whom nothing and no one in the external world of reality is stable—will have no basis for

forming a sturdy ego. His natural tendency would be to regard his own inner bodily needs and his fantasies built around these needs as the only stable realities of his life. Hence, he would, in schizophrenic fashion, tend to respond mainly to these inner needs and fantasies, rather than to external reality.

The next link in the chain can be best understood in terms of Kirk's (1964a, 1964b) concept of "role handicap."

The notion of "role handicap" helps to clarify how the kind of interpersonal communication (or, more accurately, miscommunication) that is characteristic of schizophrenics and their families develops. Roles are learned patterns of interpersonal conduct governed by particular norms. In that sense they involve our learning that certain responses are generally to be expected in particular social situations. Let us now think of an individual who has learned the proper role for a certain situation, but who, when he finds himself in that situation finds that it is not at all what his training has led him to expect. The behavior of other people is sharply different from his anticipations. Such a discrepancy between the learned and thus expected situation and the encounter with the one actually experienced constitutes a constraint for normative role performance, and such a structural constraint has been called "role handicap."

If the role-handicapped person can gain the key to the meaning of the actual behavior of others he may be able to adjust his behavior accordingly, and thus overcome his role handicap and relate to them in an altered but effective manner. But if he does not gain understanding of the nature of the changed situation he is likely to act in ways that are inappropriate and that may alienate him from the relational norms that were supposed to govern his role. This concept of role handicap, when considered in combination with a learning handicap in the child, can explain the genesis of the syndrome of behavior on the part of the mother which has been called "schizophrenogenic."

10. To see how this kind of behavior by the mother could be generated toward a perceptually handicapped child, let us again follow the sequence illustrated in our diagram. Because role performance depends in part on getting adequate responses from persons significant to him, not only does the child require adequate responses from the mother, the mother also, if she is to feel adequate in her role as a nurturing, loving parent and teacher, requires adequate responses from the child. But the bizarre behavior of the child means to the mother that she is failing in her efforts to teach and train the child, without understanding why she is failing.

11. The mother of such a child, feeling that she is failing in her task, becomes upset; she feels she is failing, not only because of the child's bizarre behavior, but also because she becomes aware that others see the child as queer, stupid, or lazy.

12. She thus feels handicapped in her role as mother, and will be likely to try to adapt in at least two ways. Because her child responds differently from others to her usual methods of discipline and training, her efforts are likely to give way to a random succession of methods, in the hope of finding a successful one. Since she does not have the key to understanding what is wrong, her random attempts at adaptation compound the child's difficulty by forcing him to cope not only with his own perceptual defect, and hence learning handicap, but also with the inconsistency of his mother's approach, which fails to be rewarding and may actually be punishing.

13. As each new method is tried and falls short of success the mother, feeling more and more inadequate, is likely to begin blaming the child, if she has not already done so at an earlier stage. Her hostility, coupled with her feeling of guilt (because of both her failure and her hostility), would be likely to make the child feel even less secure and his performance even less adequate than it would be without this emotional strain, so that again a vicious cycle is in operation. In this cycle, the child's withdrawn or hostile behavior perpetuates the mother's inconsistent, rejecting, "schizophrenogenic" behavior, which in turn exacerbates the child's tendency to bizarre behavior, and tends to alienate the mother even further from the norms of nurturing, loving, parental behavior toward this child who is so unrewarding to her. Thus, the mother develops an ambivalent attitude toward the child, with love and rejection felt simultaneously.

    The adult who is closest to the child (usually the mother) will suffer more of a handicap in her role toward him, but such significant persons as fathers, teachers, and siblings will also be likely to meet with responses based on the child's faulty perception, and they and the child will be prone to reduce their interaction with each other, thus reducing their mutual frustration. Although the other people will not suffer much from this reduced contact because they experience other, more normal relationships, the child himself will become increasingly isolated and withdrawn as social interaction tends to be continually frustrating for him.

In recent years, I have had occasion to take several histories in which this kind of complex vicious-circle process was clearly visible. Even more significant, a reversal has been observed when perceptual defect was diagnosed and appropriate perceptual training was begun. Parents of perceptually handicapped children experience a profound relief and a corresponding shift toward a positive desire to help their child overcome his handicap, once they understand what the child's problem is. In such cases, the key to overcoming the role handicap lies in the parents' knowledge of the underlying defect, so that the social milieu, instead of being rejecting and hostile,

becomes positive, accepting, and loving, working toward the child's better functioning rather than exacerbating the difficulty.

A case history may serve to illustrate this reversal of the vicious cycle of parental and child behavior.

> J., an 8-year-old boy, the son of a university teacher, was the younger of two children in the family. For two or three years he had been gradually withdrawing from contact with family members, and within the six months prior to testing the withdrawal had extended to withdrawal from other children, both at school and in the neighborhood. Despite a bright-normal IQ, J.'s school work was poor, and he spent most of his time in his room with the door closed. His parents were having marital problems, and were told by their doctor that they were rejecting their son emotionally and that this withdrawal was a reaction to his knowledge of their rejection of him.
>
> Psychological testing showed that J. had many signs of minimal cerebral dysfunction, including deficiencies in both auditory and visual perception, as well as fluctuating attention, hyperactivity, and inadequate language development. (His Verbal IQ was 22 points lower than his Performance IQ.) When these difficulties and the handicap they caused in the school situation were explained to his parents, their previous ambivalent attitudes toward him changed to loving concern. They undertook to launch J. on a vigorous program of exercises and training designed to decrease these handicaps (Delacato, 1963).
>
> Over a period of ten months, J. became actively involved in both family and school activities, and developed a lively, friendly personality. His Verbal IQ increased by 15 points, and his test protocol no longer showed the evidences of perceptual handicap. These improvements took place and the gains were maintained after treatment was stopped, in spite of the fact that the emotional stress in the home became worse, resulting in the separation of J.'s parents.

The downward spiral of reactions to perceptual defect by the child and others is not likely to occur to any great extent until after the child is no longer an infant. One reason for this is that satisfactory performance by a baby is relatively simple and does not require as accurate and stable perception as is necessary for the more skilled performances required of the older child or adolescent. Also, everyone expects infants to be infantile in their emotional responses. But by the time the child is 3 or 4 years old and has learned to walk and talk he is expected to begin behaving as others do, and is punished in subtle or not-so-subtle ways if he does not conform to these expectations.

In order to construct a theory of the etiology of schizophrenia it was only necessary to arrange into a new pattern the data summarized previously in this paper. The first step in forming the new pattern was to think of the perceptual deficiency associated with schizophrenia as a predisposing factor, rather than simply as a symptom of the disease. It predisposes in the sense that it constitutes a learning handicap for the child, and that learning handicap leads to a role handicap for the mother. The interaction of these two handicap patterns was shown to lead to alienation on the part of the mother and to withdrawal or acting-out behavior on the part of the child.

Statement of Theory

The theory of the etiology of schizophrenia can now be formulated. A deficiency in the processes of perception resulting from a central nervous system malfunction is necessary to produce schizophrenia. The origin of the defect could be genetic, the result of some type of injury to the brain (either physical or chemical), or it could be biochemical. Given such a perceptual deficiency, the nature of the individual's social environment and his interaction with it determines whether or not schizophrenic symptomatology will develop.

Preliminary Test of Theory

The theory will now be tested in a preliminary way by examining it in the light of the specific symptoms and characteristics of the disease.

HALLUCINATIONS

A hallucination, by definition, is a perception (in one or more of the sense modalities) which would not be perceived by other people similarly situated. There is a type of hallucination which is common in very young children, who have not yet learned to distinguish between external reality and their own fantasies. In testing his fantasies against external reality as perceived by himself and by others, the child with normal perceptions finds that these fantasies are the products of his imagination; thus he can learn to distinguish between them and external reality. But a child who is perceptually handicapped regularly sees (or hears, tastes, smells, touches) things in ways that differ from the perceptions of others, and differ in unpredictable ways. Such a child has the basis of hallucination, as do all young children, but without the normal child's adequate equipment for reality testing. Because of his perceptual handicap, he is unable to perceive external reality as others do; he has no built-in basis for learning the difference between this reality and his own fantasies. Thus, he would be likely to confuse his fantasies more frequently with reality; that is, to hallucinate. (See Chapman, 1966, for observations of this kind of process in schizophrenic patients.)

WITHDRAWAL

In the kind of situation just described, the reality sense of other people will be likely to disturb, for the child with faulty perception, the reality of his own perceptions,

thus leading him to withdraw from others as the best defense. To illustrate this idea, consider the situation of a dyslexic child who has a confusion in laterality. He may see the word "on" and perceive it as "no" sometimes and as "on" at other times. He will be told that it is "on" no matter how he happens to be perceiving it at the time. Also, he may see "no" and perceive it as "on," in which case he will also be told he is wrong. In this situation, his only escape from his confusion and from the ridicule of others would be to withdraw entirely from the reading situation.

The idea of withdrawal as a defense reaction to impaired perception is supported by evidence from an experiment performed by Lawes (1963). This experiment demonstrated that in normal adults under the sensory and social stimulation of an ordinary conversation the symptoms produced by phencyclidine are similar to those of early schizophrenia—such symptoms as thought disorder, vertigo, disorders of perception and attention, affective reactions, and body image disturbances being common. But under conditions of social isolation and sensory deprivation, the administration of the drug to the same normal subjects produced no such symptoms, or the symptoms were much reduced in intensity. This finding lends support to the view that withdrawal from other people can reduce or eliminate the disturbance experienced by a person with defective perception. Chapman (1966) describes the function of withdrawal as a defense against disturbed perception, quoting from recordings of interviews with young schizophrenics.

THOUGHT DISORDER

Perceptual defect readily explains the source of this most definitive of the symptoms of schizophrenia, since the abilities to form associations and concepts, to abstract, and to think logically are all based on accurate and stable perception. For example, if there is a disturbance in the perception of size and distance, how can one firmly understand such abstract ideas as "tall," "far," or "little"? Or how can one be sure that 50 feet is one-half of 100 feet? Bizarre associations and misinterpretations can easily be explained by poor auditory perception. There are many words which differ from each other only in a single similar sound, while the rest of the word is the same. Suppose that a person cannot readily distinguish that slightly different sound. He may understand "sought" or "fought" when someone says "thought," or "fence" when what is said is "sense." One can understand how confusing the most ordinary statements could become to a person so handicapped and how difficult he would find it to follow just a social conversation, let alone a logical sequence of thought. Lawson et al. (1964) have collected both clinical and experimental data which suggest that faulty perception of speech by schizophrenic patients may be due to their relative inability to perceive a sentence as an organized meaningful whole, even when the individual words are perceived accurately.

PARANOID DELUSIONS

If a person perceives things differently from other people he will, as was shown earlier, be punished through ridicule and in other ways for errors of which he cannot be aware. This could lead him to believe that other people are against him, or that he is a chosen emissary of God or some supernatural power and thus different from and superior to the ordinary people with whom he lives. In either case, he would be protected by his delusions from the reality sense of other people, with the net result that his deficient or distorted perceptions would be less disturbing to him.

CATATONIA

Various investigators (for example, Kephart, 1960), have demonstrated that visual and tactual perception depends upon movement. Therefore it seems reasonable to suppose that the immobility of the catatonic patient serves as a defense against distorted perception. This immobility can be thought of as a kind of self-induced sensory and social deprivation which can make perceptual and body-image distortions less disturbing. Chapman (1967) not only describes this process but also quotes young schizophrenics who have experienced it and tell precisely what it feels like.

AFFECTIVE FLATTENING

The flattening of affect characteristic of schizophrenia can be understood as a conditioned reaction. Since emotional arousal increases perceptual distortion; this increased distortion and its concomitant disturbance would be avoided if emotional arousal did not occur. Therefore, a person who has distorted perception may become conditioned to avoid becoming emotionally aroused. This avoidance behavior would be powerfully reinforced by the fact that the person would thereby avoid the disturbance that his increased distortion precipitates. The withdrawal behavior would go along with and reciprocally reinforce avoidance of emotional arousal, with the end result of a progressive flattening of affect.

AGE OF ONSET

The fact that the onset of schizophrenia typically occurs in late adolescence or early adulthood is congruent with the hypothesis that perceptual defect is the crucial factor in its etiology. For it is only as the individual is leaving childhood and entering adulthood that society insists that he leave the world of fantasy behind him and conform consistently to the demands of external reality. A person who has been handicapped by defective perception and his own emotional reactions to it may get along well enough until the demands of external reality as they exist in his social group become

insistent. At that point, the weak ego becomes overwhelmed, and a catastrophic downward spiral of emotional reaction, disturbed body chemistry, further impaired perception, thought disorder, and exacerbated emotional reaction takes place. Such a downward spiral corresponds to the onset of schizophrenia as a recognizable disorder; in acute cases, it corresponds to "decompensation."

ACUTE VERSUS PROCESS SCHIZOPHRENIA

Acute schizophrenia in an adult, with its sudden onset and more hopeful prognosis, could be explained as a result of perceptual defects caused by a delayed-action gene (as in Huntington's chorea), organic damage (brain injury), or a biochemical imbalance from severe malnutrition, as in slums and concentration camps. In this case the individual may have had normal perception during his childhood and hence have been able to form a relatively sturdy ego and a basically sound sense of reality. The relatively sudden disruption of perception would be frightening and upsetting to him and lead to acute and sudden symptom formation. But with a basically sound ego structure, he would be able to compensate and overcome his symptoms faster and more completely than could a person whose whole ego stucture is weak because he has never had adequate perception. This latter kind of individual would develop process schizophrenia, which is slow and insidious in onset. His sense of reality would be grossly underdeveloped and his ego would have no stable foundation. He would, therefore, have little chance of recovery, although his symptoms might appear to be milder. In this connection, we note that psychiatrists and others who have experimented with LSD and other psychotomimetic drugs report experiencing both perceptual disturbances and psychotic symptoms such as acute anxiety and disrupted thought processes. This has enabled them to understand the world of the psychotic better than before, but has not permanently disrupted their normal ego functioning.

SCHIZOTYPE

The hypothesis of perceptual defect interacting with social environment also explains Meehl's (1962) "schizotype," or schizoid personality. A person who has a perceptual defect in one modality could be sufficiently handicapped by it to develop a schizoid personality, yet might be able to compensate with accurate perceptions in the other modalities to the extent that reality testing is impaired but not destroyed. Also, a child whose mother is able to remain consistent, loving, and stable in her behavior toward him in spite of being frequently punished by his lack of adequate response would have a better chance of compensating for a perceptual defect than one with an unstable, inconsistent, rejecting, "schizophrenogenic" kind of mother. Finally, if the modality in which the perceptual defect occurs is not crucial to adequacy in the culture to which the person belongs it will handicap him less than if it is crucial in his

culture. For example, accurate perception of distance would be crucial in a hunting culture, but not in ours, where the perception of laterality is crucial because it is basic to reading.

The McGill cross-cultural study on the symptomatology of schizophrenia (Murphy et al., 1963) has gathered data which suggest that, while the visual and auditory modalities are important in all cultures, the tactile and olfactory modalities may play an important role in schizophrenia in some of the nonliterate cultures, notably in Africa. In these cultures, tactile and olfactory hallucinations are frequent symptoms in schizophrenia, but such symptoms are rarely reported in our culture.

Summary

This theory postulates that a child's unrecognized perceptual defect leads to a learning handicap for the child, and to a role handicap for the child's parent or parents. A complex interaction between the two handicaps has been shown to create a vicious circle which tends to perpetuate and exacerbate the problems of both child and parent and, in extreme cases, leads to the development of schizophrenic symptoms on the part of the child and to alienation on the part of the parents. Ways in which this process can explain the development of the specific symptoms and characteristics of the disease have been outlined and described.

The theory is congruent with the bulk of the separate findings of many investigators. It postulates mechanisms which account for the observed associations and explains symptom formation. The postulated defect is measurable and its working can be observed, so that tests of the theory are possible.

Potentially, one of the most important values of this theory is that it indicates several ways in which to work at preventing schizophrenia.

To begin with, locating children who are likely to be perceptually handicapped could be done by several means, namely, locating children with schizophrenic relatives, particularly parents; locating children born to mothers who have suffered complications of pregnancy or birth; locating children who have suffered head injuries or severe illness; and testing children as they enter Kindergarten. This could be done routinely and inexpensively with use of the Kirk XO Test (Kirk, in press). This is a brief, simple, group-administered test of the temporal and spatial organization of perception and of visual-motor speed and control.

The first three could be done through use of computerized hospital records, and would locate the great majority of children likely to have perceptual difficulties. The fourth way would also locate the great majority of children so handicapped.

Once these "high-risk" children are identified, several positive preventive measures could be undertaken:

1. Administer suitable biochemical tests (such as the mauve spot urine test) to discover the children likely to benefit from megavitamin treatment, and see that such treatment is given to those who need it.
2. Inform all parents of perceptually handicapped children of the nature of perceptual defects so that the vicious cycle of parent–child interaction cannot get started, and the parents could be motivated to institute action aimed at correcting the disability or at least avoiding exacerbation of the problem.
3. Institute special training in perceptual-motor functioning at school or at home, or both, so that whenever possible the underlying perceptual defect is corrected as far as possible. Kephart (1960), Barsch (1965), Cruickshank (1967), Frostig (1967), and Delacato (1963), among others, have developed systems of working at improving perceptual functioning. In my own clinical experience, the method of neurological organization advocated by Delacato (1963) has shown itself to be particularly effective.[1] The simplicity of this method, and its ready adaptability to groups, would make it particularly practical for a preventive program in the schools.
4. Until and unless the disability is overcome, the child's teacher should be made aware of the problem, so that teaching methods and materials could be adapted to compensate for the disability. For example, teaching can be accomplished through the perceptual modalities which function most nearly normally.

Another way of approaching the problem of prevention would be to prevent the original perceptual deficiency. There are several positive steps that could be taken:

1. Provide adequate nutrition for people of all ages (but especially pregnant women, nursing mothers, and children) by supplying supplementary foods and vitamins free to those who cannot afford to buy them, and teaching people the importance of adequate diet.
2. Provide medical care to every pregnant woman, including instructions as to proper diet, exercise, the dangers of drugs, what to expect during labor and delivery, and danger signals that she should be aware of.
3. Blood tests should be done as a matter of routine. In cases of Rh incompatibility, syphilis, and other conditions which may harm the fetus, proper preventive or curative treatment should be undertaken promptly.
4. Test for conditions in the mother that indicate possible damage to the fetus (such as rubella in the first trimester), and make abortion in such cases readily and legally available.

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[1] However, Delacato's concept of "cortical hemispheric dominance" is open to question and its importance has been overemphasized (see Robbins, 1966).

5. Through parent education and the provision of day-nurseries, attempts should be made to have all infants and young children receive the loving care, sensory stimulation, and opportunity for development of motor coordination that are necessary for achieving good perceptual functioning.

Such a positive program of prevention could result in greatly reducing the numbers of people who become schizophrenic, and could provide the perceptually handicapped children with optimum help at the time in their lives when help can be most effective. Far too many of these children suffer years of frustration and failure, resulting in a great deal of emotional hurt, before their problems are understood and they are helped. Many such children never receive the understanding and help which could assure their optimum functioning and happiness.

The cost of instituting such a wide-ranging, comprehensive program of preventive measures would be high, but probably less than the present cost of long-term, often life-time, institutional care for schizophrenics. Saving even a fraction of the suffering caused by perceptual malfunctioning, even when it does not result in schizophrenia, would be well worth the price.

The practical problems in the way of achieving the goal of prevention are many, and are related to the fragmentation and inadequacy of professional services as well as to the social problems which beset societies today, particularly in the large cities. Yet, having outlined a theory that can explain how schizophrenia comes about, I am encouraged to realize that there are growing numbers of my colleagues who are aware of these problems and that some have pioneered in the successful treatment of schizophrenia. We can be hopeful that the ways and means of preventing this scourge which are already known will be instituted and, as time shows the value of prevention, these measures can become more widespread and more complete, with new techniques being added to those already known.

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6

The Adrenochrome Hypothesis of Schizophrenia—1972. The Role of Rheomelanin Formation in Some Toxic Effects of Catecholamine Derivatives

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INTRODUCTION

Almost two decades have passed since the adrenochrome hypothesis of schizophrenia was first enunciated (Hoffer et al., 1954). According to this hypothesis schizophrenia is caused by the action of adrenochrome, an indole derivative of epinephrine, whose presence in human tissue has never been shown. However, a great deal of information about certain aspects of epinephrine and norepinephrine metabolism in mammals has been amassed.

Extensive studies have been made of the transformation of epinephrine in the body to metanephrine, to vanillylmandelic acid (VMA), and to related substances through the action of two tissue enzymes, catecholamine-O-methyltransferase and monamine oxidase. Similar reactions have been established for norepinephrine. The incorporation of data from this branch of biochemistry into medicine has greatly enriched clinical practice. Other aspects, including the indole pathway of epinephrine (Figure 6-1) and norepinephrine degradation, are not yet widely considered important in mammalian physiology. Although adrenochrome formation has been demonstrated in vitro (Heacock, 1959, 1965), it is rarely mentioned in mammalian physiology.

There is increased interest in indole derivatives today because some of them affect biological systems. For example, indole derivatives such as lysergic acid, bufotenine, N,N-dimethyltryptamine, psilocin, psilocybin, harmine, and reserpine affect brain function; all but reserpine are brain poisons used as intoxicants. Some indole derivatives are known to produce seizures (Feinberg and McCullough, 1944) and to have other toxic effects on nerve tissue (Silberberg, 1967). Moreover, some indole derivatives or the processes involved in their metabolism damage other tissues as well, despite the widespread notion that most of them are benign or even beneficial. Even a highly beneficial one (for example, the plant-growth-stimulating substance indole-3-acetic acid) changes during riboflavin-catalyzed photo-oxidation to other indole



FIGURE 6-1.
The indole pathway of epinephrine degradation.

derivatives that are injurious to plants and even to metazoa (Fukuyama and Moyed, 1964).

The indole products of catecholamine metabolism when they were given a role in tissue melanin formation engaged the attention of such researchers as Raper (1928), Green and Richter (1937), and Harley-Mason (1948, 1950). Interest in these indole derivatives of catecholamines, called aminochromes, broadened when the adrenochrome hypothesis of the etiology of schizophrenia was formulated by Hoffer et al. (1954), and became even greater when it was shown that, although catecholamines injected into normal persons are almost entirely changed to VMA and its derivatives (La Brosse et al., 1961), radioactively tagged catecholamines injected into stressed persons produce some metabolites that cannot be identified as constituents of the VMA pathway (Goodall and Alton, 1969).

Today, information about the physiologic and clinical significance of indoles derived specifically from catecholamines is incomplete, but there is reason to believe that they are clinically significant. It is important to review the relevant literature in order to delineate the problems whose solutions may be of benefit in medical practice.

REVIEW OF THE PREVIOUS LITERATURE

In retrospect, the first suggestion of the existence of the indole pathway of epinephrine degradation was Vulpian's (1856) report of the formation of a red substance when adrenal medullary tissue is exposed to air. Epinephrine was isolated from the adrenal glands half a century later, and the red substance was subsequently shown to be derived from this hormone. It was later identified as the indole derivative adrenochrome (Green and Richter, 1937), and its formation in vitro by the spontaneous oxidation of epinephrine was demonstrated. The reaction was found to be accelerated by oxidizing enzyme systems in plants and animals (Heacock, 1959, 1965). Early observers found that the then uncharacterized red compound turned into a yellow one (Kisch, 1930), and later in vitro studies showed that the red adrenochrome can change to its yellow isomer, adrenolutin (Ehrlén, 1949; Lund, 1949). In addition, it became evident that aminochromes polymerize to melanin (Heacock, 1965). None of the compounds intermediate between the aminochromes and melanin has yet been identified.

The Oxidative Cyclization of Epinephrine to Adrenochrome in Mammals

Data on the indole pathways of epinephrine metabolism in intact mammals in vivo are few and inconclusive. Bacq et al. (1951) published indirect evidence of the formation of indole derivatives after the injection of epinephrine in dogs. However, Schayer and Smiley (1953) found no aminochromes in the urine after the injection of epinephrine into rats.

The data on the occurrence of aminochromes in man are similarly controversial. The study of La Brosse et al. (1961) failed to reveal any aminochromes in the urine after the administration of epinephrine to normal and psychotic persons. Moreover, although some observers reported finding adrenochrome in the blood (Hoffer, 1958; Hoffer and Osmond, 1959; Payza and Mahon, 1960), Szara et al. (1958) could not detect this compound in human blood plasma, although another fluorescent compound was found by means of the method designed to detect adrenochrome. Feldstein (1959) likewise was unable to detect adrenochrome in the blood serum. On the other hand, Koch (1966) published evidence that aminochromes were present in the urine of a psychotic patient who received norepinephrine intravenously. He concconcluded that his experiments strongly suggested that chrome indoles are formed in vivo from epinephrine and norepinephrine by the action of phenolases. Veech et al. (1960, 1961) reported finding substances that had properties of aminochromes in the urine of psychotic patients. A possibly related group of studies is that of Mandell et al. (1961a, 1961b) and Kollar et al. (1964), who described what they called a

"stress-reactant indole" in the urine of stressed human subjects, without, however, establishing its biochemical origin.

Despite these in vivo ambiguities, there is evidence that animal tissues cyclize epinephrine to adrenochrome in vitro (Raper, 1928; Green and Richter, 1937; Kaliman, 1961; Kaliman and Koshlyak, 1961; Pastan et al., 1962; Van der Wende and Spoerlein, 1963; Axelrod, 1964; Sweat and Bryson, 1965). In man, Axelrod (1964) showed that an enzyme in salivary gland tissue cyclizes epinephrine to adrenochrome. Other in vitro studies using plasma or whole blood also showed the cyclization of epinephrine (Hoffer and Kenyon, 1957; Payza and Hoffer, 1960; Payza and Zaleschuk, 1960; Billiewicz-Stankiewicz et al., 1964; Hoffer, 1965). In many of the experiments, the products of epinephrine oxidation were not definitely identified as indole derivatives. Cohen et al. (1958), Berthiaume et al. (1960), Geller et al. (1960), and Yuwiler et al. (1961) concluded that the enzymic oxidative cyclization of epinephrine in serum was doubtful, but the methods used did not resolve the problem. The transformation of epinephrine to adrenochrome in mammalian tissues in vitro is accelerated by adrenal corticoids (Sweat and Bryson, 1965) and slowed by reducing agents (Heacock, 1965; Sweat and Bryson, 1965). At present it is impossible to define the conditions that determine whether epinephrine will follow its best recognized pathway (the VMA pathway) or will be degraded via another (the indole pathway). In this connection it is interesting that the activity of the enzyme known to degrade epinephrine via the VMA pathway, catecholamine-O-methyltransferase, may be inhibited by cyclopropane (Gardier et al., 1967). Although there is now no information on what determines how much indole derivative is formed from epinephrine and other catecholamines in vivo, it is nevertheless useful to consider the toxic and other biochemical effects of aminochromes and related indole compounds.

Isomerization of Adrenochrome to Adrenolutin in Mammals

There is ample evidence that adrenochrome is isomerized in vitro (Heacock, 1959, 1965). Studies in animals indicate that adrenochrome can exist only briefly in the circulating blood and that it has different metabolic fates in different species. In rabbits the injection of adrenochrome results in the urinary excretion of adrenolutin and its sulfate ester together with some unchanged adrenochrome, according to Fischer and de Landtsheer (1950) and Fischer and Lecomte (1951). They also state that most of the adrenochrome leaves the circulation rapidly and is conjugated and metabolized in the liver. Schayer and Smiley (1953) found an unstable unidentified yellow compound in the urine of rats injected with adrenochrome. Noval et al. (1962) distinguished three metabolites in the urine of rodents after administration of adrenochrome. One metabolite was a yellow fluorescent compound, a sulfate conjugate

of adrenolutin. Another was a sulfate conjugate of 5,6-dihydroxy-N-methylindole; and the third metabolite also appeared to be a conjugate of 5,6-dihydroxy-N-methylindole. They suggested that adrenochrome is metabolized via two pathways, one involving adrenolutin and the other through 5,6-dihydroxy-N-methylindole. In carnivores (for example, the cat and dog) the metabolism of adrenochrome is different, according to Fischer and Lecomte (1951). In these animals the injection of adrenochrome leads to the excretion of approximately 15 percent unchanged chemical, mainly a "reduction product" of adrenochrome, and approximately 10 percent of other indole products.

The fact that adrenochrome semicarbazone does not become isomerized (Sohler et al., 1967) suggests that the reaction can occur only when both oxygen atoms attached to the benzene ring are free.

Fate of Adrenolutin in Mammals

Adrenolutin has long been known to be formed from adrenochrome (Heacock, 1959, 1965). The foundation of work on this substance was established by the theoretical analysis of its structure by Ehrlén (1949), by the isolation of the compound in crystalline form and its correct identification by Lund (1949), and by its unambiguous synthesis by Balsiger et al. (1953). These contributions were extended by the more recent work of Heacock and Mahon (1958). Noval et al. (1962) reported that injection of adrenolutin into rodents resulted in the appearance of a sulfate conjugate of adrenolutin in their urine. As will be discussed below, adrenolutin changes to rheomelanins (blood soluble melanins; Hegedus and Altschule, 1968, 1970a) when added to oxalated or heparinated human blood or plasma.

Toxic Effects of Indole Derivatives

The processes by which indole derivatives produce cytotoxic effects are only partly understood. One type of phenomenon is the poisoning of several enzyme systems that are particularly important in the brain (Randall, 1946; Meyerhof and Randall, 1948; Alivisatos et al., 1960; Hochstein and Cohen, 1960, 1963). Another phenomenon is of a different type; when indole derivatives polymerize in vitro to melanins (or to their as yet unknown immediate precursors) hydrogen peroxide is generated. If this occurs in vivo, it might damage cell membranes and other lipid-containing cellular components (Hochstein and Cohen, 1963). The brain is deficient in hydrogen-peroxide-destroying enzymes and hence is very sensitive to the toxic effects of hydrogen peroxide (Cohen and Hochstein, 1963). Hydrogen peroxide induces the cyclizing of epinephrine; hence it is possible that the polymerization of indole compounds

derived from epinephrine may lead to the increased production of these substances, thereby instituting a vicious circle.

As regards the epinephrine-derived indole derivatives themselves, the available data form a consistent body of evidence that shows that they affect carbohydrate metabolism. The effect of adrenochrome on intermediary metabolism has been studied by many observers in rat brain minces, homogenates, and extracts added to various salt solutions that contained substrates, buffers, co-factors, and the like, but not plasma or serum. Randall (1946), Meyerhof and Randall (1948), Hochstein and Cohen (1960, 1963), and Woodford (1959) all found inhibition of glycolysis, although there were differences of opinion about which enzymes were inhibited. Walaas and Walaas (1956) observed no metabolic effect of adrenochrome on rat whole diaphragm but did find some depression of hexokinase extracted from it. Park et al. (1956) reported uncoupling of oxidative phosphorylation in hamster liver mitochondria when betahydroxybutyrate was used as the substrate. Although these observations have great theoretical importance, their relevance to the present study is not immediately apparent. Most of them did not use intact tissue and in some of the earlier studies the purity of the adrenochrome used is questionable. The only observer who did use intact cells was McGuire (1964), who studied erythrocytes and found their oxidation of glucose to be greatly stimulated by incubation with adrenochrome.

As regards toxicity in intact organisms, adrenochrome in certain doses has been reported to have no effect on the electroencephalograms of normal persons but to cause changes in those of epileptic patients (Szatmari et al., 1955). This resembles the effect of another indole derivative, LSD, which aggravates the manifestations of focal cerebral lesions (Korein and Musacchio, 1968). However, in some experiments certain batches of what was said to be adrenochrome caused electroencephalographic changes in normal persons (Grof et al., 1963). The literature on the production of aberrant mental function by administering adrenochrome has been collected by Grof et al. (1963). These authors reported mental changes and discussed negative findings that occurred when other batches of the compound were used. Grof et al. (1963) questioned the purity of these batches. The currently available evidence indicates that adrenochrome, or some derivative of it, is a brain poison with hallucinogenic properties.

OUR STUDIES

Our studies were designed to define the metabolic changes of catecholamines in human blood and the effects of the changed chemicals on the blood. Accordingly, a method was developed, hereafter referred to as the Hegedus method, which involves the synthesis of the expected metabolites, the incubation of the chemicals with blood

or with plasma, and the study of the changed chemicals after incubation in the plasma by means of differential ultraviolet and visible spectroscopy.

First, the indole derivatives obtained from epinephrine were studied, since previous workers had shown that the enzymes of the VMA pathway of epinephrine degradation are not active in blood (Tryding et al., 1969). The indole derivatives of epinephrine, adrenochrome, and adrenolutin-monohydrate[1] were synthesized in our laboratory. Studies on adrenolutin had been retarded for years by the widespread impression that stable adrenolutin-monohydrate could not be made. This is no longer true; work done in Heacock's and our laboratories established a method by which adrenolutin-monohydrate can be made in a stable form (Heacock and Mahon, 1958; Hegedus and Altschule, 1967b).

The required amount of venous blood was drawn from a subject. Some was collected in 10-ml sterile test tubes each containing 25.0 mg potassium oxalate, and some was collected in 10-ml sterile test tubes each containing 143 USP units of heparin. The oxalated bloods were combined in one Erlenmeyer flask and the heparinated bloods in another under sterile conditions. Four mg of each chemical to be studied was weighed in a separate sterile rubber-stoppered 125-ml Erlenmeyer flask. After each of the combined samples was made uniform by being gently swirled, 10 ml of either the mixed heparinated or oxalated blood was added to each flask, which was immediately swirled gently ten times. The rest of the blood was treated the same way but without the addition of a chemical; it was used as the reference for the spectrophotometric measurements. All the samples and the references were placed in an incubator kept at 38 ± 1°C. Each specimen was gently swirled by hand ten times every two hours during the work day; the rest of the time they were left in the incubator without agitation.

After 24 hours of incubation each flask was gently swirled ten times and 2.5 ml of blood was taken with a sterile pipette from each and placed in a centrifuge tube; this was centrifuged at about 2800 rpm for 20 minutes. The plasmas were separated and were diluted with nine volumes of distilled water for the spectroscopic measurements, which were made with a Cary 11 or Cary 14 recording spectrophotometer using 0.1-cm path-length quartz cuvettes. These spectrophotometric measurements were repeated after 32 to 35 hours of incubation and with the heparinated samples after 48 to 50 hours of incubation also. The oxalated blood incubated with adrenochrome and adrenolutin showed so much hemolysis after 48 hours of incubation that it was not possible to see the supernatant plasma after centrifugation. When the incubations were carried out only in the plasma, centrifugation was not necessary because no precipitate formed. The rheomelanins remained in solution for as long as observed, up to several weeks. Later this method was changed slightly for the development of a routine test.

[1] The chemicals adrenochrome and adrenolutin-monohydrate now are commercially available from K & K Lab., Inc. 121 Express Street, Plainview, New York 11803.

The anticoagulant used is highly important. The three tested were Acid-Citrate-Dextrose (ACD) mixture (Formula A, NIH), heparin sodium, and potassium oxalate. The *p*H of the blood taken with appropriate amounts of each was found to be, respectively, 6.8, 7.4, and 7.4. The acidity is important, because, for example, after adrenochrome is added to ACD-collected blood a fine black dust-like precipitate—evidently melanin—forms during incubation. The amount of change found in such blood is much less in spectroscopic absorbance values than in blood taken with either of the other two anticoagulants. Moreover, the use of ACD-collected blood decreases

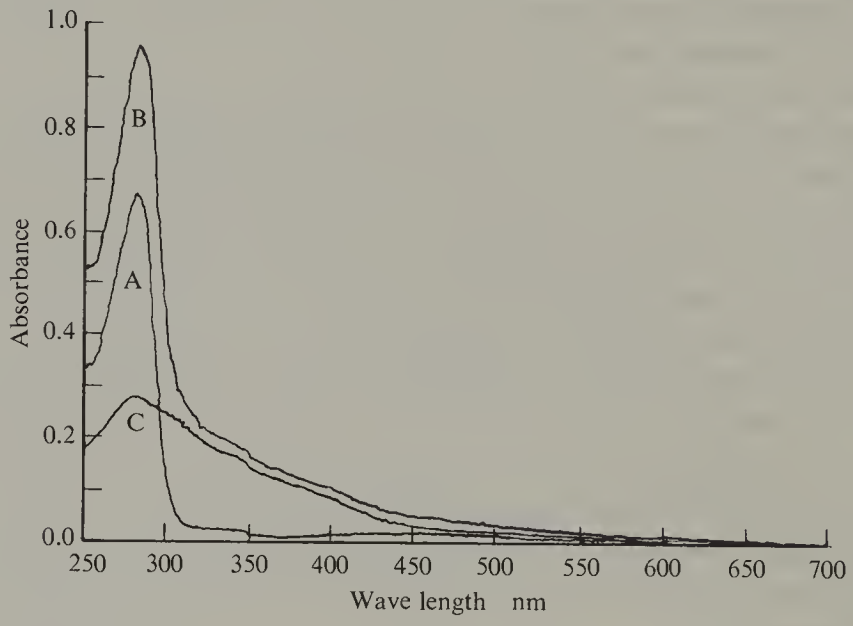


FIGURE 6-2.
The spectrum of heparinated plasma incubated with or without epinephrine. Curve A is the spectrum of a heparinated plasma incubated alone for 24 hours, and read against water. Curve B is the spectrum of the same heparinated plasma incubated with epinephrine for 24 hours and read against water. Curve C is the spectrum of plasma in curve B read against the plasma in curve A.

the frequency of abnormal findings by more than 50 percent. Accordingly all the findings discussed here will refer to heparin- or oxalate-collected blood or its plasma.

One of the basic processes in the Hegedus method that was used is differential spectroscopy. The need for differential spectroscopy is shown in Figure 6-2. This figure gives the results obtained from heparinated plasma in which epinephrine was incubated for 24 hours, and from a sample of the same plasma alone incubated simultaneously. Curve A is that of the plasma without added epinephrine, read against a water reference. In this dilution of 1 : 10 there is almost no absorption in the visible range; a sharp peak appeared in the ultraviolet region, having its maximum at around 280 nm. The peak is the well-known plasma protein peak; it is evidently

produced by the aromatic residues of tryptophan, tyrosine, and phenylalanine in the protein.

Curve B is that of the same plasma incubated with epinephrine; it is also read against water. The peak is at around 280 nm and the curve looks the same as curve A, except for the gradual rise in absorbance starting at almost 450 nm and continuing to about 310 nm, where it starts to rise sharply. It is evident that the difference between A and B is because of a broad band of absorption that raises the 280 nm peak. The nature of this broad band is not clear, however, unless differential spectroscopy is used; that is, unless the spectrum relative to that of the same plasma incubated without epinephrine is recorded, as in curve C. Curve C is the broad absorption, with a maximum at about 280 nm, that is produced by rheomelanins.

The absorption typical of epinephrine-derived rheomelanins also develops when adrenochrome or adrenolutin is incubated with the same plasma (Figure 6-3). It can

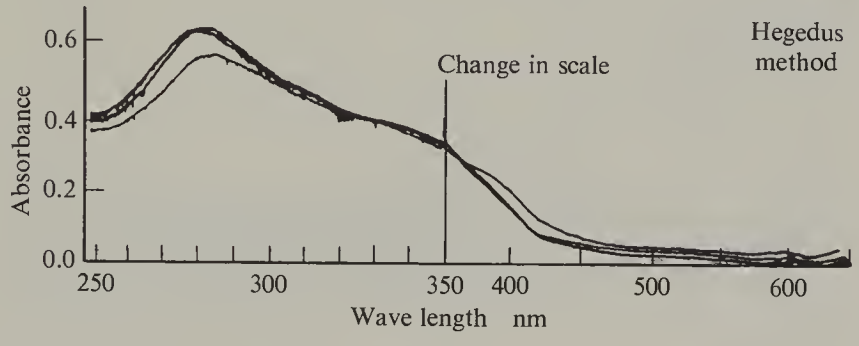


FIGURE 6-3.
Spectra of heparinated plasma incubated with either epinephrine, adrenochrome, or adrenolutin-monohydrate for 24 hours. They were read against the same heparinated plasma incubated without the chemicals for 24 hours.

be seen that when a plasma sample that contains rheomelanins is read against water the plasma protein peak at about 280 nm dominates the picture and obscures the rheomelanin peak (Figure 6-2).

The same phenomena occur when whole blood is incubated with epinephrine, adrenochrome, or adrenolutin; that is, only differential spectroscopy reveals completely the closely similar chemical changes found after incubation. As an example, adrenolutin was incubated in heparinated whole blood for 24 hours, and a sample of the same heparinated blood without adrenolutin was incubated simultaneously. Curve A in Figure 6-4 is the curve obtained with plasma from whole blood incubated alone and read against water. A small peak appeared in the visible region, having its maximum at around 418 nm; this peak is characteristic of hemoglobins. The peak at around 280 nm appeared again as in plasma (curve A in Figure 6-2). Curve B is that obtained with the plasma from the same blood incubated with adrenolutin; it is also read against water. In this curve the small peak is at around 400 nm instead of at

around 418 nm as in curve A. Evidently the rheomelanins (or their precursors) of adrenolutin changed the hemoglobin to hemes and porphyrins, which have an absorption at around 400 nm. The other peak appeared at around 280 nm, as in curve A, but with a higher absorbance value. This curve has a gradual rise in absorbance starting at about 650 nm and continuing to about 310 nm, where it starts to rise sharply. It appears that the difference between A and B is because of a broad

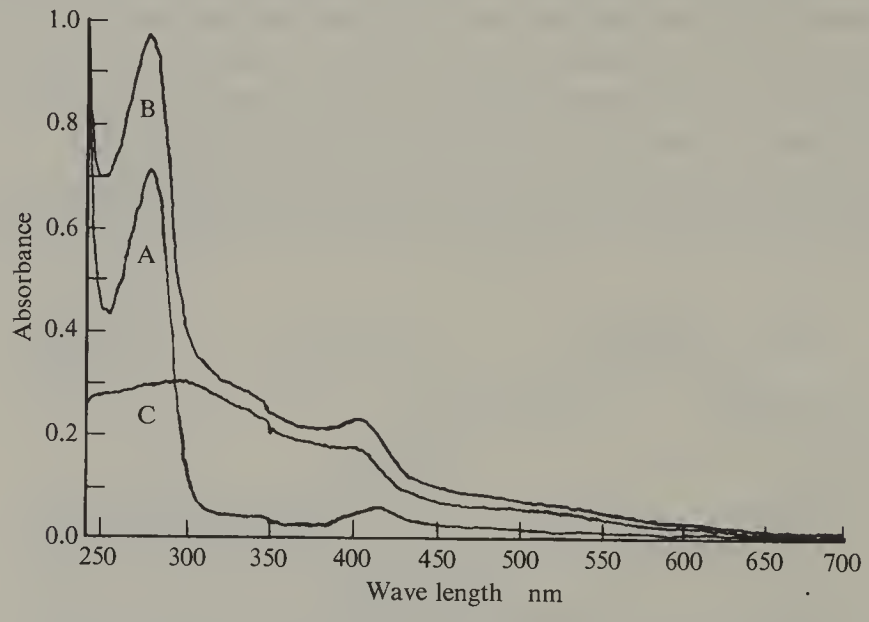


FIGURE 6-4.
The spectrum of plasma obtained from heparinated blood incubated with or without adrenolutin-monohydrate. Curve A is the spectrum of the plasma obtained from heparinated blood incubated alone for 24 hours and read against water. Curve B is the spectrum of the plasma obtained from the same heparinated blood incubated with adrenolutin-monohydrate for 24 hours and read against water. Curve C is the spectrum of plasma in curve B read against the plasma in curve A.

band of absorption that raises the peak at around 280 nm. The nature of this broad band becomes clear with the use of differential spectroscopy, as in curve C.

Curve C shows a broad absorption with two peaks. The peak at around 300 nm is produced mainly by rheomelanins, although some products of hemolysis which might absorb around this wavelength also formed after 24 hours of incubation. The position of this peak differs somewhat from that of the 280 nm peaks of Figure 6-3. The reason for this is probably that there are individual differences in the chemical environments of each blood and of the products of hemolysis; this can shift the peak from about 280 to about 300 nm. The other, smaller peak at around 400 nm can also be seen, as in curve B. With epinephrine or adrenochrome the curves are closely similar.

Figure 6-5 shows that when the same amounts of epinephrine, adrenochrome, and

adrenolutin are incubated in aliquots of the same blood, all three compounds yield closely similar curves by differential spectroscopy.

The other methods used in the studies were fluorescence spectroscopy and paper chromatography. Samples taken for fluorescence spectroscopic measurements were prepared the same way as those for differential spectroscopy except that the separated plasmas were diluted with 100 volumes of distilled water. Measurements were made

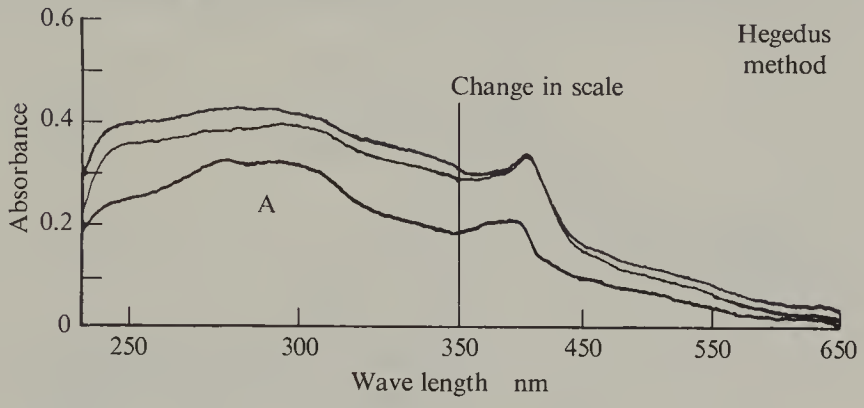


FIGURE 6-5.
Type A spectra of plasmas obtained from heparinated blood incubated with either epinephrine, adrenochrome, or adrenolutin-monohydrate for 24 hours. They were read against the plasma obtained for the same heparinated blood incubated without the chemicals for 24 hours.

after 24, 32 to 36, and 48 to 51 hours of incubation; oxalated blood samples incubated with adrenochrome and adrenolutin for 48 hours showed too much hemolysis to permit separation of the plasma. A Baird-Atomic recording fluorescence spectrophotometer model SF-1 was used.

Paper chromatography runs were also made by the ascending technique, using separated plasmas without dilution after 24, 32 to 36, and 48 to 51 hours of incubation. The spots were made with approximately 10 microliters of plasma. The chromatograms were developed in a solvent system of 5 percent methanol–95 percent water on Whatman No. 1 paper.

The Indole Pathway of Catecholamine Degradation in Plasma and Whole Blood

The transformation to adrenochrome of epinephrine added to human plasma or serum is well documented (Hegedus and Altschule, 1968; Altschule and Nayak, 1970). The subsequent fate of adrenochrome in human plasma was not worked out until recently (Hegedus and Altschule, 1967a, 1968). We showed that adrenochrome

added to normal human heparinated or oxalated plasma changed, even in the frozen state, to a substance with the ultraviolet and visible spectra and the fluorescence of adrenolutin that has been dissolved in the same plasma. Thus curve A in Figure 6-6 shows the ultraviolet and visible spectra of authentic adrenochrome that had been dissolved in plasma immediately before the spectra were made. Curve B shows the spectra obtained when adrenochrome was dissolved in plasma, kept frozen until the color changed to yellow-brown, and then thawed for study. Curve D shows the spectrum of authentic adrenolutin made immediately after it had been dissolved in

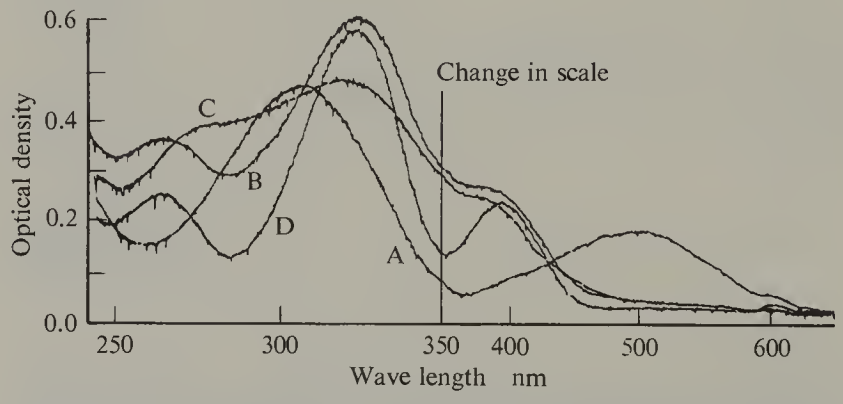


FIGURE 6-6.
The change of adrenochrome to adrenolutin and the beginning of rheomelanin formation in plasma: Curve A, adrenochrome dissolved in plasma immediately before the spectrum was made; Curve B, adrenochrome dissolved in plasma, immediately frozen, and kept frozen until after the color changed, and then thawed for study; Curve C, adrenochrome incubated in plasma until the color changed; Curve D, adrenolutin-monohydrate dissolved in plasma immediately before the spectrum was made

plasma. Curves B and D are almost identical. Curve C was obtained after adrenochrome had been incubated in the same plasma at 37° for 30 minutes (Hegedus and Altschule, 1967a). The main adrenolutin peak at about 320 nm was decreasing and a new maximum at about 280 nm was developing. This 280-nm shoulder obtained by differential spectroscopy is significant in that it indicates the beginning of the change of adrenolutin to rheomelanin. Other points of interest were also noted. The isomerization reaction also occurs somewhat more slowly in heparinated or oxalated aqueous solution made slightly alkaline (*p*H 7.4) with sodium bicarbonate and this also is not prevented by freezing. These preliminary studies suggested that the plasma contains a catalyst that isomerizes adrenochrome. At any rate, the possibility that adrenochrome can exist in blood plasma except for a short time is remote.

When adrenochrome is incubated in human plasma for more than 30 minutes it changes to previously undescribed types of compounds, rheomelanins or plasma-soluble melanins (Hegedus and Altschule, 1968). In fact, as Figure 6-3 shows, the

incubation of epinephrine, adrenochrome, and adrenolutin separately in aliquots of the same plasma for 24 hours gives rise to virtually the same spectral curves. The excitation maxima of all three rheomelanins are around 340 and 404 nm, the fluorescence maxima are around 482 nm. These data were obtained with rheomelanin-plasma solutions diluted 1:50 after 24 hours of incubation with precursor chemicals in concentrations of 2 mg/5 ml plasma. Heparinated plasmas without the added chemicals, studied in the same way, exhibited the following maxima or maxima closely similar to them (Hegedus and Altschule, 1968, 1970c):

Excitation maxima	Fluorescence maxima
293 nm	336 nm
347 nm	437 nm

The paper chromatograms of the three rheomelanins are virtually the same, with Rf values of approximately 0.78. Heparinated plasmas without the added chemicals, studied in the same way, exhibited small pale brown spots with closely similar Rf values of 0.76 (Hegedus and Altschule, 1968, 1970c). These results show that the indole pathway of epinephrine metabolism in plasma is available.

A question naturally arises concerning the possibility that other catecholamines and some related substances might also form rheomelanins by similar pathways in plasma. However, unlike what obtains in the case of epinephrine, indole derivatives of the other catecholamines are not available for study. Accordingly we investigated which chemicals form rheomelanins in human plasma during incubation, since their formation very likely can occur only through an indole pathway. The following chemicals were incubated in heparinated plasma for 24 hours at 38°C.

L-epinephrine
epinephrine bitartarate
epinephrine·HCl
L-norepinephrine
L-norepinephrine bitartarate
L-norepinephrine·HCl
L-epinephrine-methyl-ether·HCl
L-dopa
dopamine
L-alphamethyldopa
adrenalone·HCl
L-tyrosine
tyramine·HCl
phenylephrine·HCl
DL-metanephrine·HCl
normetanephrine·HCl
phenylalanine
DL-5-hydroxytryptophan
N-acetylserotonin
5-hydroxy-3-indoleacetic acid
serotonin-creatinine-sulphate-monohydrate
5-methoxytryptamine
melatonin
5-methoxy-3-indoleacetic acid
adrenochromesemicarbazone
L-tryptophan
3-indoleacetic acid
isatin
N-acetylindole

After incubation for 24 hours L-epinephrine, L-norepinephrine, L-epinephrine-methyl-ether·HCL, L-dopa, dopamine, and L-alphamethyldopa produced plasma-soluble rheomelanins.[2] These solutions had brown colors, characteristic odors, and yellowish-green fluorescences in ultraviolet light of 366 nm, which was used in all these experiments. However, the rheomelanin plasma solutions all had somewhat different ultraviolet and visible spectra and excitation and fluorescence maxima, except that L-dopa and dopamine gave almost the same findings in several cases. The ultraviolet and visible spectra of all the rheomelanin plasma solutions were different from the spectra of the catecholamines, of L-dopa, and of their derivatives obtained in plasma immediately after the chemicals were dissolved in it. The paper chromatograms of each rheomelanin plasma solution produced elongated or pear-shaped spots with Rf values of 0.78 or close to it. In the same experiments, use of heparinated distilled water adjusted to *p*H 7.4 with sodium bicarbonate instead of human plasma resulted in completely different findings from those obtained with the plasma rheomelanin solutions (Hegedus and Altschule, 1970c).

It is evident that the indole pathway of catecholamine metabolism is available for all catecholamines in blood plasma, and it is probable that some enzyme systems act on all of them. At least in the mammalian brain, the same enzyme cyclizes dopamine and epinephrine (Van der Wende and Spoerlein, 1963). Dopa is evidently also cyclized in the same fashion, but the extent to which this might occur in tissues other than the skin is evidently very small (Van Woert et al., 1967). Whereas in other species blood plasma causes tyrosine to change to melanin (Evans, 1968), the only compounds studied that form rheomelanins in this way in human plasma are the catecholamines, dopa, and some of their derivatives in which the orthohydroxyl groups are free.

When epinephrine, adrenochrome, and adrenolutin were incubated separately in heparinated whole blood, the plasmas obtained after incubation all contained rheomelanins. They all yielded closely similar ultraviolet and visible spectra, which occurred as five types (Figures 6-5, 6-7, 6-8, 6-9, and 6-10). Ultimately they all became a single type, type C (Figure 6-8; Hegedus and Altschule, 1970a).

Plasma from each heparinated blood incubated with the three chemicals all showed excitation maxima at around 340 nm, fluorescence maxima at around 490 nm and identical curves only after approximately 48 hours of incubation (Figure 6-11). Plasma from each oxalated blood incubated with the three chemicals produced virtually identical maxima and curves earlier. These excitation and fluorescence spectra were different from those of the blanks. The intensities of fluorescence decreased not only with the duration of the exposure to ultraviolet light during the measurements but also with longer incubation (Hegedus and Altschule, 1970a).

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[2] The hydrochlorides and bitartarates of epinephrine and norepinephrine also formed rheomelanins.

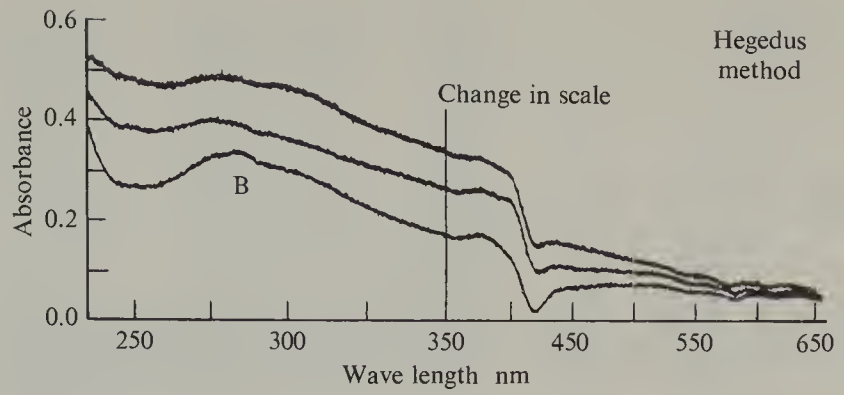


FIGURE 6-7.
Type B spectra obtained as in Figure 6-5.

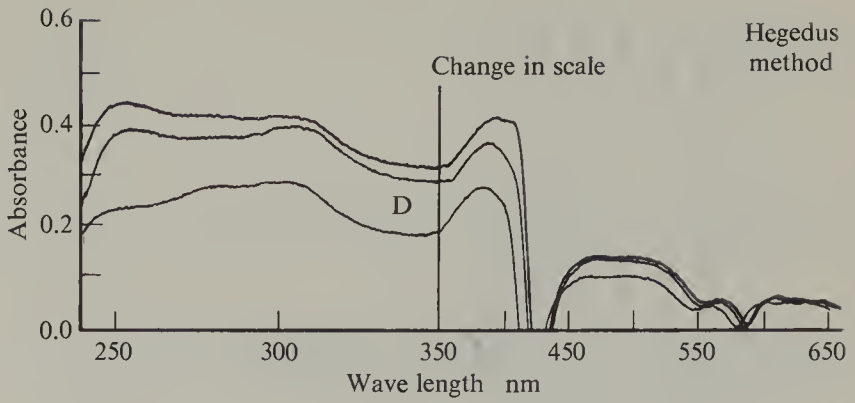


FIGURE 6-9.
Type D spectra obtained as in Figure 6-5, except that the samples and the reference were incubated for 32 hours.

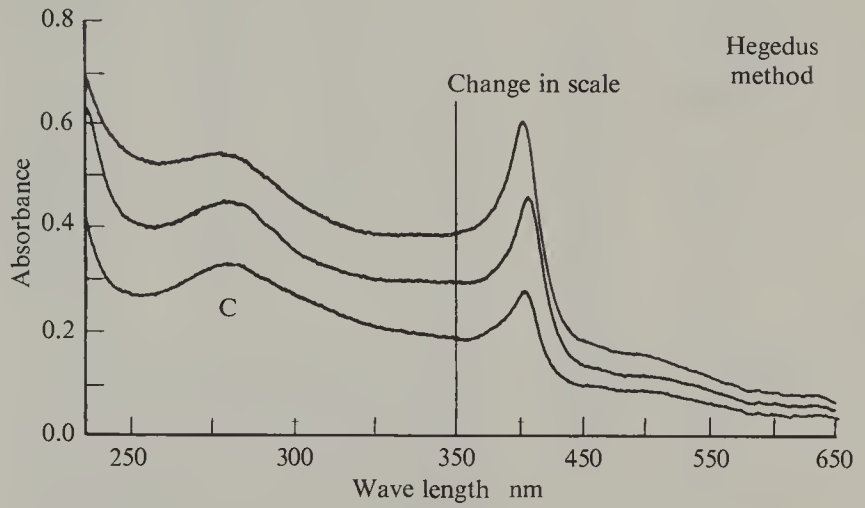


FIGURE 6-8.
Type C spectra obtained as in Figure 6-5, except that the samples and the reference were incubated for 35 hours.

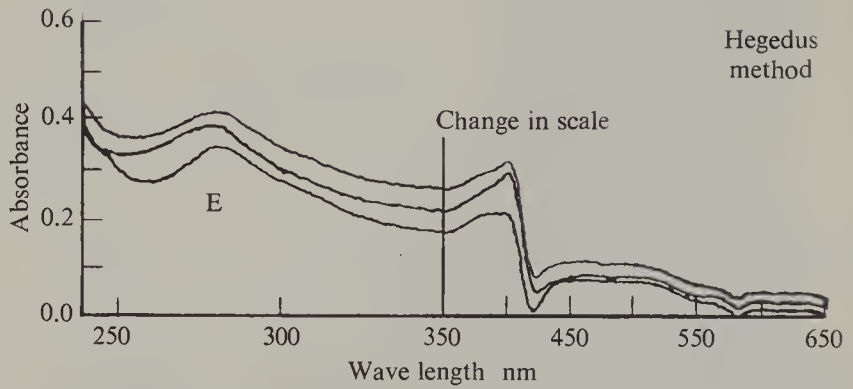


FIGURE 6-10.
Type E spectra obtained as in Figure 6-5, except that the samples and the reference were incubated for 33 hours.

The undiluted plasmas obtained from the bloods incubated with the three chemicals for 24, 32 to 36, and 48 to 51 hours yielded brown spots on the paper chromatograms. The upper elongated spots with an average Rf of 0.78 were almost identical with the elongated rheomelanin spots described previously (Hegedus and Altschule, 1968), and they also had yellowish-green fluorescence in ultraviolet light. In most cases, especially after longer incubations, running behind these spots were several partly overlapping reddish-brown spots and (less often) streaks, all of which had

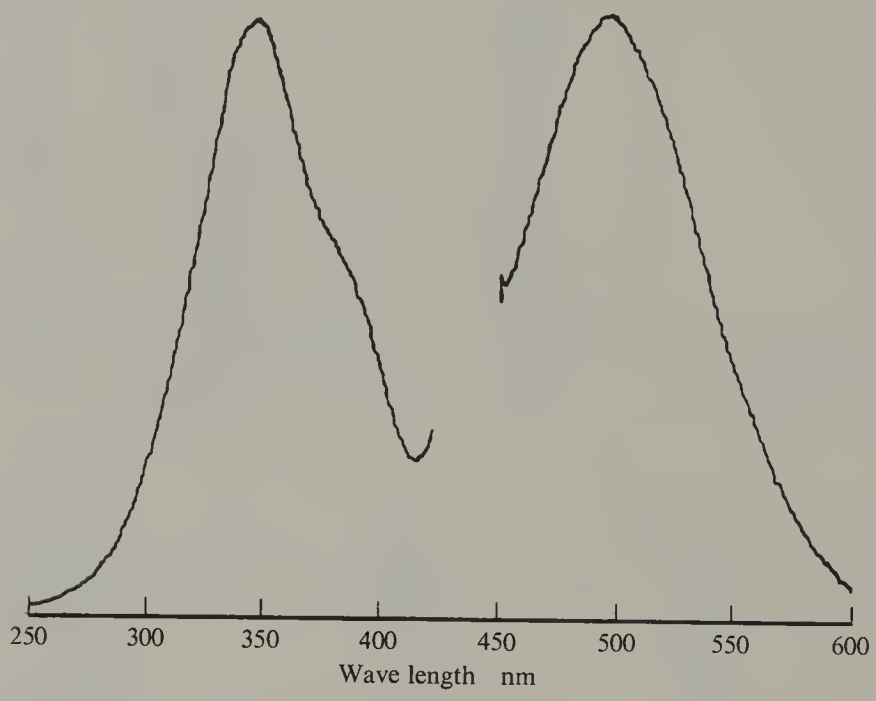


FIGURE 6-11.
Excitation and fluorescence spectra of plasma from a heparinated blood incubated with adrenochrome for 48 hours.

similar Rf values. These additional spots, owing to the products of hemolysis, had green fluorescence in ultraviolet light. The blanks showed closely similar Rf values but the spots were much lighter (Hegedus and Altschule, 1970a).

The incubation of norepinephrine, dopamine, and dopa in whole blood also yielded rheomelanins, and their ultraviolet and visible spectra were surprisingly closely similar to the rheomelanin spectra derived from epinephrine (Figures 6-12, 6-13, 6-14 and 6-15). This is another indication (beside rheomelanin formation itself) that these chemicals also follow an indole pathway in whole blood (Hegedus and Altschule, 1970d).

The undiluted plasmas obtained from the bloods incubated with any of the three chemicals for 24, 32, and 48 hours gave brown spots on the paper chromatograms. The average Rf value for the upper elongated rheomelanin spots was 0.76. The Rf

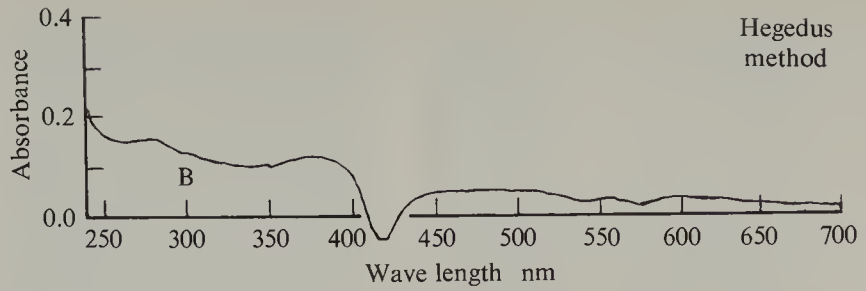


FIGURE 6-12.
Type B spectrum of plasmas obtained from some heparinated or oxalated bloods incubated with either norepinephrine, dopamine, or dopa for 24, 32, or 48 hours.

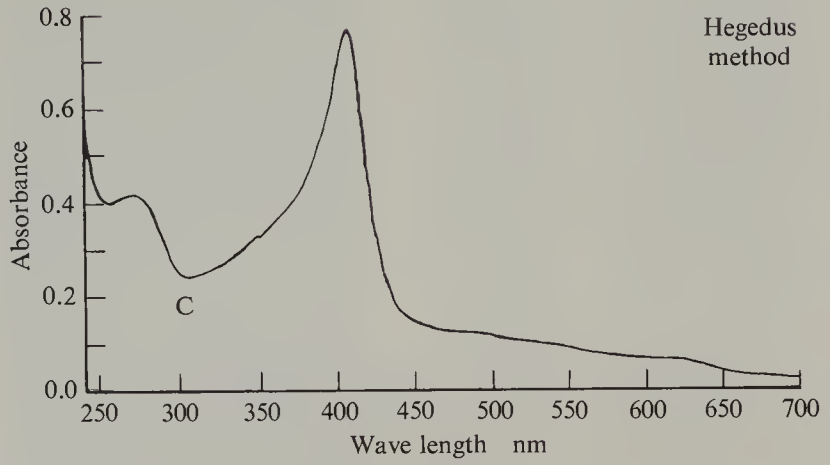


FIGURE 6-13.
Type C spectrum of plasmas obtained from some heparinated bloods after 48 hours and from some oxalated bloods after 32 hours of incubation with either norepinephrine, dopamine, or dopa.

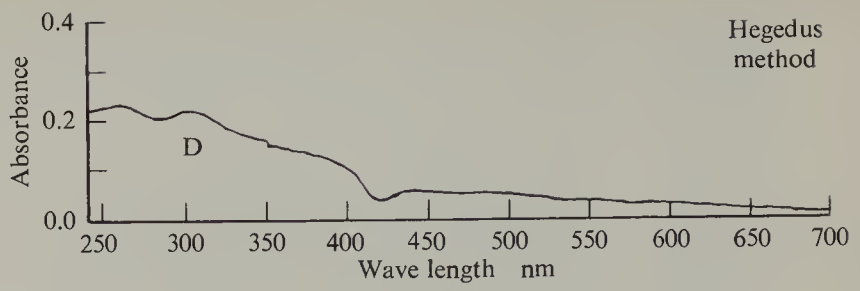


FIGURE 6-14.
Type D spectra of plasmas obtained from some heparinated blood incubated with norepinephrine, dopamine, or dopa, or from some oxalated blood incubated with dopamine or dopa for 24 and 32 hours.

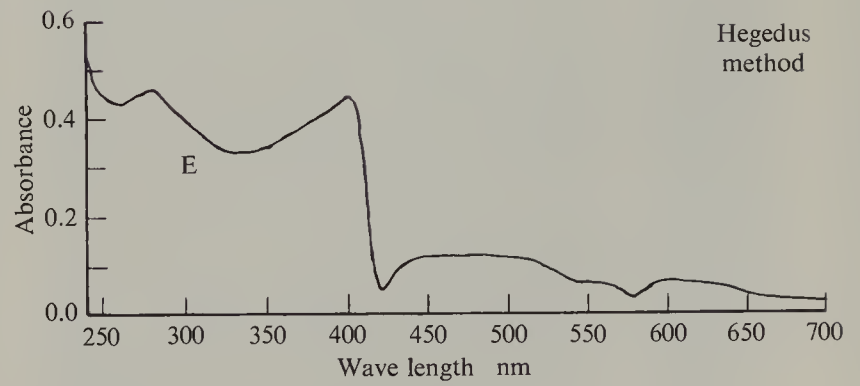


FIGURE 6-15.
Type E spectra of plasmas obtained from some heparinated bloods incubated with dopamine or dopa for 48 hours or from oxalated bloods incubated with dopamine or norepinephrine for 32 hours.

values decreased slightly with longer incubation. The rheomelanin spots from plasmas obtained from bloods incubated with L-dopa or dopamine gave a light green fluorescence, whereas that from L-norepinephrine was a more yellow-green in ultraviolet light.

After longer incubations, additional dark yellow-brown spots with similar Rf values were frequently seen running below the upper elongated spots of most rheomelanins. They had a dark green fluorescence in ultraviolet light. These darker spots were undoubtedly due to the products of hemolysis, because they were absent when the chemicals were incubated in plasma only. The spots were surrounded by other substances that were not visible in daylight, but had pale bluish-white fluorescence in ultraviolet light. Samples incubated with L-epinephrine, adrenochrome, or adrenolutin also showed this phenomenon. In addition, most of the oxalated and heparinated samples from bloods incubated with L-dopa showed in ultraviolet light a bright bluish-white fluorescence spot with an average Rf of 0.4 right under the spots of products of hemolysis. These spots were also not visible in daylight. They were evidently owing to some products of hemolysis for they occurred during incubation of dopa in blood and not in plasma (Hegedus and Altschule, 1970d).

Hemolysis Associated with Catecholamine Degradation via the Indole Pathway in Whole Blood

The amount of rheomelanins, as measured by the optical density at about 280 nm, found in the plasma of the whole blood after 24 hours of incubation with any of the chemicals was less than that which formed in isolated plasma. This suggested that some of the substrate entered the red blood cells. Catecholamines are known to do this (Schanker et al., 1961; Roston, 1964, 1966, 1967) and adrenochrome has also been reported to enter the erythrocytes (Hoffer, 1967). However, there may be other reasons for the discrepancy: it is possible, for example, that rheomelanins are adsorbed to the cell wall, as appears to be true of the polymer formed from alpha-methyldopa (Vyas et al., 1969), which we showed to be rheomelanin (Hegedus and Altschule, 1970c).

The incubation of catecholamines, dopa, and the aminochromes in human whole blood led to the appearance of a peak at about 400 nm characteristic of hemes and porphyrins (Hegedus and Altschule, 1970a, 1970d). In the studies done here the spectral curves obtained by differential spectroscopy initially took a variety of forms (Figures 6-5, 6-7, 6-8, 6-9, and 6-10), owing to the variety of changes that occurred. The change from catecholamines, dopa, or aminochromes to rheomelanins was moderately rapid, but the processes that occurred during hemolysis were less rapid and, at least at first, more varied. In the reference sample the lysis of erythrocytes led solely to the release of hemoglobin with its absorption maximum at 418 nm, and the

action of the catecholamines, dopa, and aminochromes incubated with whole blood led to the more or less delayed change of released hemoglobin to other hemes and to porphyrins. Accordingly, when the plasmas from bloods incubated with one of the chemicals was read against the reference sample, negative peaks might occur at about 418 nm (Figures 6-9 and 6-12). However, as the amount of changed hemoglobin and porphyrins increased, all the samples gave a sharp peak at about 400 nm.

With the progression of the hemolysis, the peak at about 400 nm increased in height, as also happened at about 280 nm, in contradistinction to the lack of increase when plasma alone was incubated with the chemicals. The peaks at about 400 nm increased more with longer incubations than did the peaks at about 280 nm. It is clear that certain products of hemolysis contributed to the increase in this peak. Some of these products were probably only red blood cell proteins but others presumably were rheomelanins that were probably derived from catecholamines that entered the cells (Schanker et al., 1961; Roston, 1964, 1966, 1967) and were released during the hemolysis. The same is apparently true of adrenochrome (Hoffer, 1967). Moreover, if the rheomelanins of catecholamines, dopa, and aminochromes behave like methyldopa-polymer, they might also be bound to red blood cell membranes but released after hemolysis.

The mechanism of the hemolysis is not established. All the rheomelanins prepared by us have free-radical activity (Polis, 1969, personal commun.) in common with other melanins (Mason et al., 1960; Van Woert et al., 1967). Free radicals not only hemolyze red blood cells but also can change the hemoglobin to other hemes and to porphyrins (Rowland et al., 1968). Adrenolutin has actually been shown to change hemoglobin to porphyrin (Veech, 1968, personal commun.). Aside from these facts little is known about the hemolysis that accompanies rheomelanin formation.

Excessive Hemolysis of Chronic Schizophrenic Blood During Incubation with Catecholamines, Aminochromes, or Dopa

When heparinated or oxalated chronic-schizophrenic blood is incubated with catecholamines, aminochromes, or dopa, excessive hemolysis frequently develops (Hegedus and Altschule, 1970b, 1970e). This hemolysis varied with different times of incubation, with different amounts of chemicals, and with different anticoagulants for the various chemicals tested (Figures 6-16 and 6-17). The excessive hemolysis noted with these chemicals was not affected by placebos. It did, however, disappear when two patients so studied improved. The excessive hemolysis is evidently a reflection of a relative lack of some protective substance in schizophrenic blood, because the differences between normal and schizophrenic bloods are not evident when

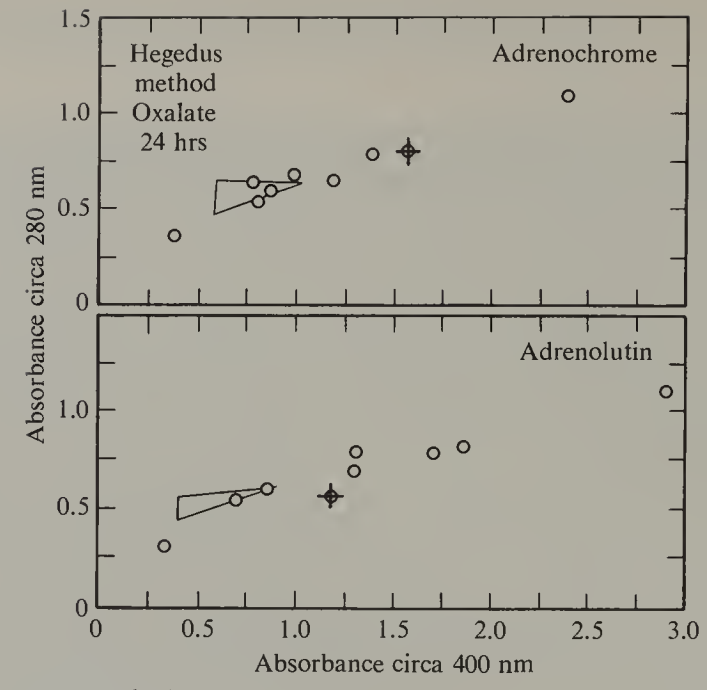


FIGURE 6-16.
Findings in plasma of patients' oxalated blood incubated with the two aminochromes. The triangular figures indicate the normal range. All the data are from venous blood except the crossed dot, which represents an arterial blood sample.

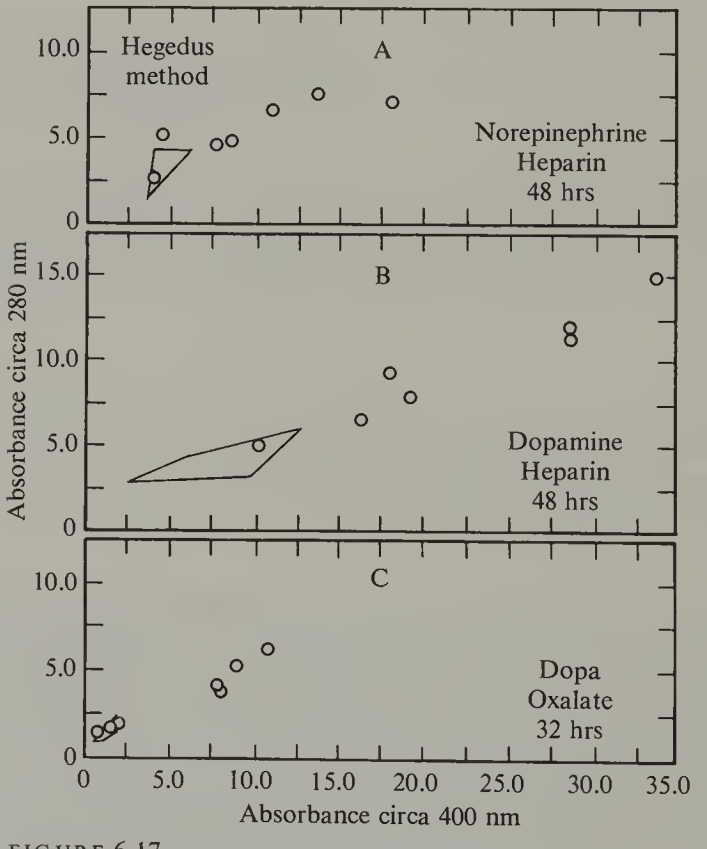


FIGURE 6-17.
Findings in plasma of patients' heparinated or oxalated blood incubated with (A) norepinephrine, (B) dopamine or (C) dopa. The triangular figures indicate the normal range. The absorbances are plotted in original concentrations.

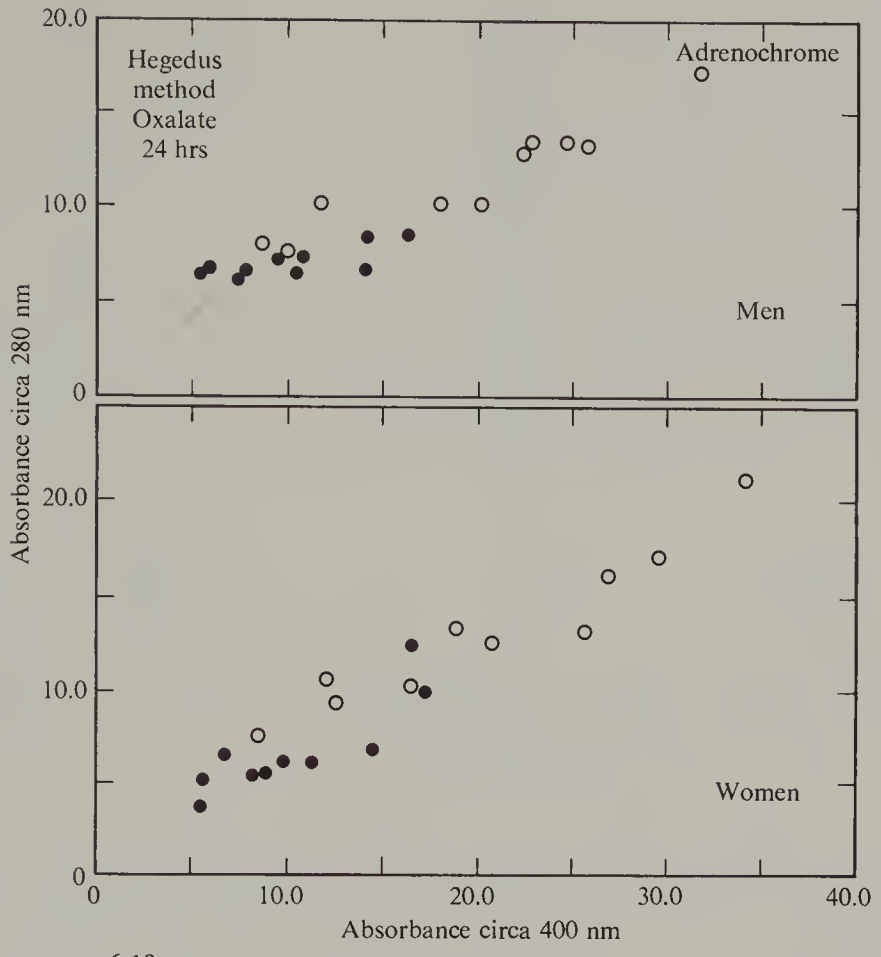


FIGURE 6-18.
Findings in plasma of patients' oxalated blood incubated with adrenochrome. The concentration was 2 mg/5 ml. The open circles show findings in plasma of patients' oxalated blood. Dots represent findings in plasma from oxalated normal blood treated the same way. The absorbances are plotted in original concentration.

smaller amounts of the aminochromes tested are used. The hypersensitivity of the blood to rheomelanins of aminochromes was not found in LSD psychosis. When oxalated or heparinated normal and chronic schizophrenic bloods were incubated without the chemicals no significant differences were evident. These observations on excessive hemolysis provided the basis of a recently developed method for the routine study of psychotic patients (Hegedus et al., 1970f). The rheomelanins or their precursors from adrenochrome, adrenolutin, and dopamine were found to cause the greatest differences in hemolysis between normal and chronic schizophrenic blood, and these chemicals were chosen for this test.

The following changes were made from the original method: 2 mg of adrenochrome, 3 mg of adrenolutin-monohydrate, and 4 mg of dopamine were each incubated in 5 ml of oxalated blood in a 50-ml sterile rubber-stoppered Erlenmeyer flask. Another 5 ml of the same oxalated blood was incubated without any chemical.

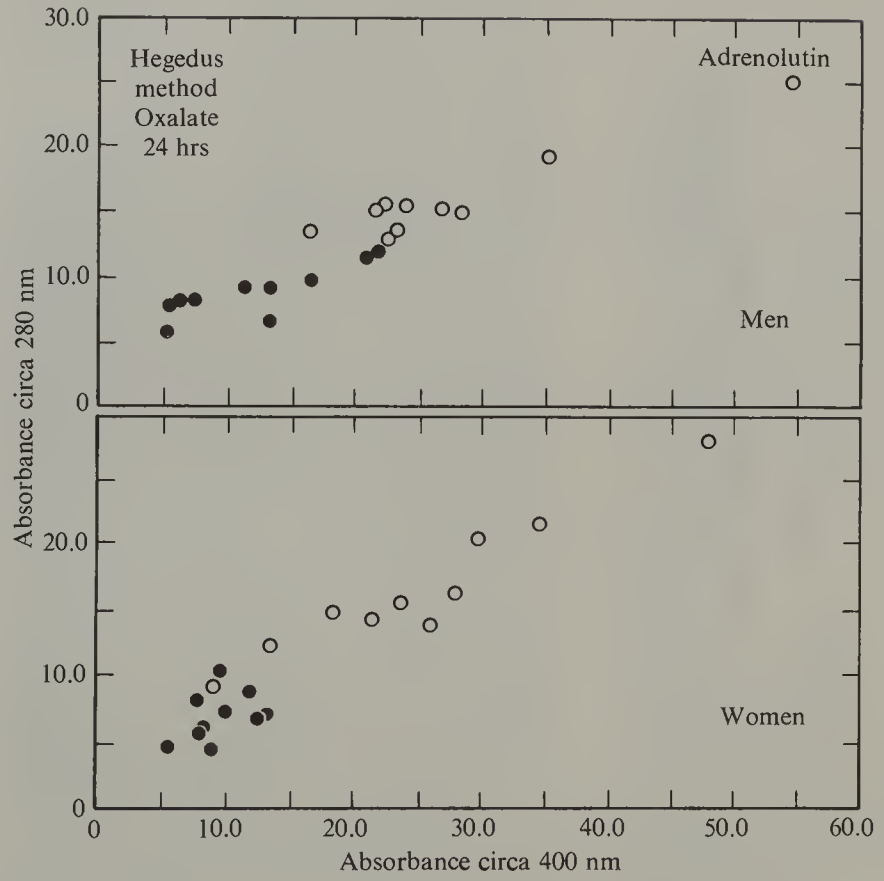


FIGURE 6-19.
Same as Figure 6-18 except that adrenolutin-monohydrate was used in 3 mg/5 ml concentration.

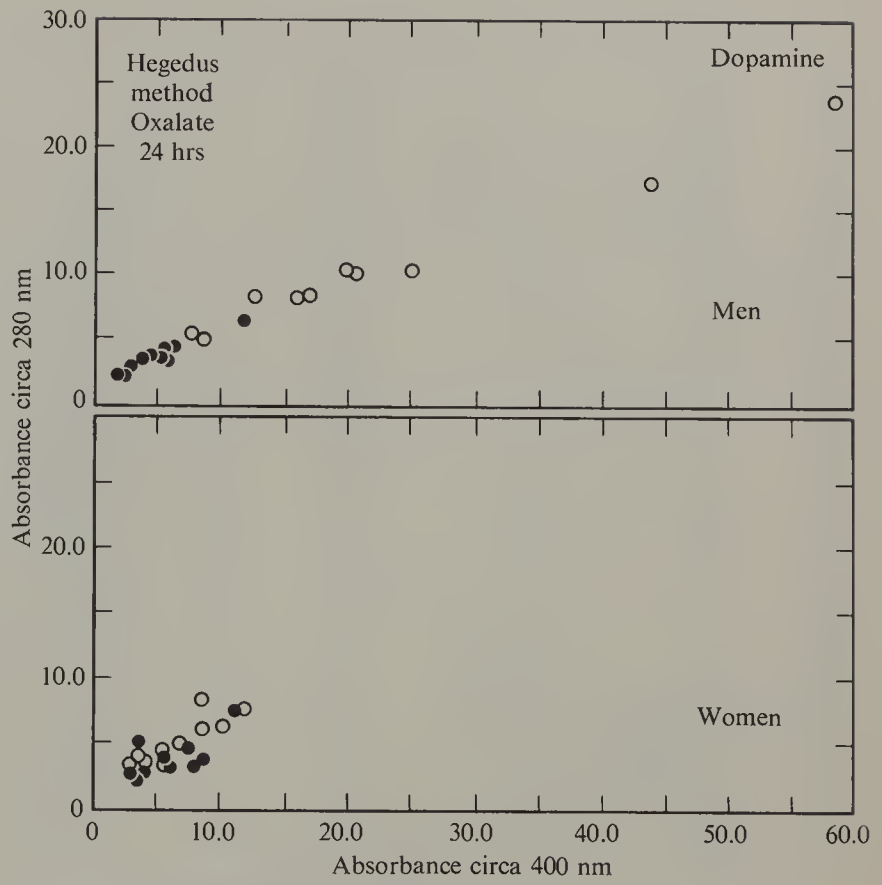


FIGURE 6-20.
Same as Figure 6-18 except that dopamine was used in 4 mg/5 ml concentration.

The samples and the reference were incubated for 24 hours under sterile conditions at 38 ± 0.1 °C in a Dubnoff type water-bath shaker incubator set at a frequency of 86 cycles per minute with a stroke of 1.5 inches. After incubation 3 ml of each sample and 3 ml of reference were removed for centrifugation. The separated plasmas were diluted with 29 volumes of distilled water and the ultraviolet and visible spectra were recorded.

With this test we studied four groups of ten subjects each: normal men, normal women, psychotic men, and psychotic women. The results are shown in original concentrations in Figures 6-18, 6-19, and 6-20. The differences are evident; however, there were no differences with dopamine between normal and psychotic women. These data were not corrected for the anemia that some patients had.

DISCUSSION

The adrenochrome hypothesis of the etiology of schizophrenia was introduced almost two decades ago. It aroused considerable interest and, because of the controversial field into which it was introduced, widespread adverse criticism. Today it is still neither proved nor disproved. However, the studies of the last five years have clarified a few points. It is not likely that the effective toxic principle evolved in the cyclizing of epinephrine is adrenochrome. Its period of existence is short, and the compound is soon isomerized to adrenolutin. This in turn is rapidly polymerized to rheomelanin, a substance with strong free-radical activity; hydrogen peroxide might be liberated during the polymerization and this would likewise be toxic, at least to some tissues, such as brain, which, unlike the blood, lacks enzymes for inactivating nascent oxygen (Cohen and Hochstein, 1963). Accordingly, instead of using the term *adrenochrome hypothesis* it would be more appropriate to call it the *aminochrome–rheomelanin hypothesis*.

Our studies suggest that aminochromes and rheomelanins are present in human blood (Hegedus and Altschule, 1970a, 1970c); they have not yet, however, been isolated and identified. Consequently, there is no method of measuring blood aminochrome (unless the recently proposed method of R. T. Houlihan proves itself) and blood rheomelanin concentrations. Hence no statement can be made about quantities in different subjects. Future work will perhaps eliminate these uncertainties.[3] What can be stated, however, is that one tissue (that is, the blood) of most schizophrenic patients is unusually susceptible to the toxic actions associated with rheomelanin formation from catecholamines, from their indole derivatives, and from

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[3] After exposure to hyperbaric oxygen, adrenochrome was reported to form in rat brain (Gershenovich et al., 1955) and rheomelanins have been demonstrated in rat blood and lungs (Houlihan et al., 1969a, 1969b).

dopa. Since the blood is perhaps the least susceptible of the tissues, the possibility that brain tissue is even more susceptible is a strong one. Since, except for small effects on dopamine, blood shows no ability to degrade catecholamines by the monoamine oxidase mechanism (Tryding et al., 1969), if epinephrine and norepinephrine are degraded in the blood stream they probably follow the indole pathway. In addition, the catecholamine and dopa cyclization that may occur in the solid tissues could be a potential source of aminochromes that might be delivered to the circulating blood.

The formation of rheomelanins deserves some comment. In our studies only the catecholamines, dopa, and a few of their derivatives polymerized to form rheomelanins. It appears that the two free 3,4-hydroxyl groups on the benzene ring are necessary for the formation of rheomelanins. Although melanins may form slowly from 5,6-dihydroxyindole after O-methylation at carbon 6 (Axelrod and Lerner, 1963), there is no indication that metanephrine or normetanephrine produce rheomelanins (Hegedus and Altschule, 1970c); this seems to be because of their inability to form indole derivatives.

The melanin formed during the incubation of catecholamines, aminochromes, or dopa is soluble in blood, and hence cannot be ordinary melanin. Accordingly it has been given the name rheomelanin, that is, flowing melanin. Although water-soluble melanins derived from catecholamines or from some indole derivatives are known, rheomelanins formed from catecholamines, from dopa, or from their indole derivatives differ from them chemically and constitute a previously undescribed class of compounds that can exist in blood. Naturally occurring tissue melanins are insoluble and are found combined with proteins; they are called melanoproteins (Mason, 1955; Dain et al., 1964; Mason and Peterson, 1965). Rheomelanins may be transport forms of melanin in mammals.

The chemical nature and pharmacologic properties of rheomelanins remain to be elucidated. However, it is known that they act as free radicals, a property they share with other melanins. Melanins catalyze the oxidation of NADH and hence influence many metabolic systems (Van Woert, 1968).

Hemolysis occurs during incubation with adrenolutin; not only are the cells lysed but also the hemoglobin is degraded via a porphyrin pathway (Veech, 1968). It is probable that the substances reported to have been detected in blood to which adrenochrome or adrenolutin had been added (Altschule, 1967) were porphyrin. Recent studies have shown that porphyrins can be formed more easily in schizophrenic than in normal blood solely with the addition of sodium bisulfite (Altschule and Hegedus, 1970). The finding of excessive amounts of pyrroles in schizophrenic urine (Irvine et al., 1969) may reflect activation of the porphyrin pathway of heme degradation. Mature erythrocytes are damaged during the incubations studied here. There is evidence that immature erythrocytes are even more susceptible to damage by melanins derived from dopamine (Prasad and Seale, 1969).

CONCLUSIONS

There is as yet no evidence of increased accumulation of aminochromes in schizophrenic patients. In any case, adrenochrome cannot accumulate, and hence the term *adrenochrome hypothesis* is a misnomer. On the other hand, the red blood cells of schizophrenic patients are unusually susceptible to hemolysis when incubated with catecholamines or dopa in the process of polymerizing to rheomelanins. Hence the theory of the origin of schizophrenia should be called the *aminochrome-rheomelanin* theory.

ACKNOWLEDGMENTS

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7

The Methylation Hypothesis in Relation to 'Pink Spot' and Other Investigations

A. PAULINE RIDGES

INTRODUCTION

During this century many scientists have sought an answer to the puzzle of schizophrenia. Researchers publish an estimated 600 papers a year (Bannister, 1968), yet the disease remains as much an enigma as ever. The lack of understanding concerning this and other psychiatric conditions is in sharp contrast with the remarkable and often dramatic developments which have taken place in other spheres of medicine. Although encouraging progress in the relieving of schizophrenic symptoms through drug therapy has been made, beneficial results have been largely fortuitous, and we are still without knowledge of how the drugs modify processes in the brain and nervous system.

In the study of mental disorders we are attempting to understand the functioning under pathological conditions of the most highly organized and complicated components of the body, whose normal processes are only beginning to be revealed.

It has become apparent that differences in local permeability of the blood-brain barrier and the blood-cerebrospinal fluid barrier are of prime importance in the

functioning of the brain and nervous system. For example, the hypothalamus and pineal gland show differential transfer of some metabolites, such as adrenalin, from the blood to the brain (Weil-Malherbe et al., 1959), and the structural differences in the subependymal layer have a tremendous influence on the exchange of materials between the ventricular system and the brain (Fleischauer, 1961).

There is an intimate relationship between the anatomical and functional attributes of the brain and the relative concentration of certain substances. For example, the highest concentrations of noradrenalin in the brain occur in the hypothalamus, in some mid-brain structures and, in particular, in the reticular formation (Hornykiewicz, 1964), whereas dopamine is present in the highest concentrations in the caudate nucleus, putamen, and substantia nigra (Bertler and Rosengren, 1959). Serotonin is present in both diencephalic and limbic structures, and melatonin is concentrated in the pineal gland (Lerner et al., 1959).

Histochemical techniques have provided information about the organization of cells into metabolic compartments whereby formation, storage, and inactivation can proceed simultaneously in the same cell, and the properties of the cell membrane determine which substances are able to pass from one cell to another. The blood-brain barrier is relatively impermeable to noradrenalin and dopamine. These catecholamines must be formed directly in the cells in order to function there, and the brain and nervous tissue are more dependent on the rate of chemical reactions for their functioning than are other organs and tissues.

It is not surprising, with our increased knowledge of the processes and mechanisms going on in the brain and nervous system, that much recent work has been done in fields which could be included under the heading "Orthomolecular Psychiatry." This term was first used by Pauling in 1968 to denote the study of the concentration of substances normally present in the human body, and Pauling suggested that provision of the optimum molecular environment for the mind could form the basis for the treatment of mental disease.

However, despite the complexities inherent in the study of so intricate and delicately balanced an organ as the human brain, the initial obstacle confronting the investigator is simply that of defining the term "schizophrenia." Bleuler (1950) recognized the heterogeneity of clinical material included in this category when he defined schizophrenia, or the schizophrenias, as a group of diseases having similar symptoms and prognoses, but the meaning of the term "schizophrenia" varies enormously. It is still necessary to emphasize this, just as Richter did in 1957 when he stated that it is doubtful if an agreed definition of schizophrenia is possible in our present state of knowledge. Perhaps one of the fundamental problems of psychiatric diagnosis is the establishment of consistent diagnostic criteria. The difficulty of establishing a diagnosis is illustrated by the findings of a survey made by Cooper (1967). He showed that there was a relationship between the number of times a schizophrenic patient is readmitted to a hospital and the likelihood of his diagnosis

changing. Only 37 percent of patients with four or more hospital admissions retained their original diagnosis. It would be valuable if schizophrenia could be characterized and differentiated from other conditions by biochemical tests. It seems likely that in due course increasing knowledge will enable this to be realized.

In the past, the search for biochemical differences between schizophrenics and mentally normal individuals has been carried on with such enthusiasm that it has been remarked that "if all the reports of abnormalities were true, then the schizophrenic would be a sorry physical specimen indeed; his liver, brain, kidney, and circulatory functions are impaired, he is deficient in practically every vitamin, his hormones are out of balance, and his enzymes are askew." Extreme caution must be exercised in relating any apparent biochemical abnormality to schizophrenia (Horwitt, 1956, 1963; Kety, 1965). Frequently, there are complicating factors present that are unrelated to the genesis of schizophrenia, such as adventitious disease, nutritional deficiencies, and changes brought about by the treatment of the disease and its management. Most of the reported differences between schizophrenics and other individuals have been readily shown to be unrelated to the disease.

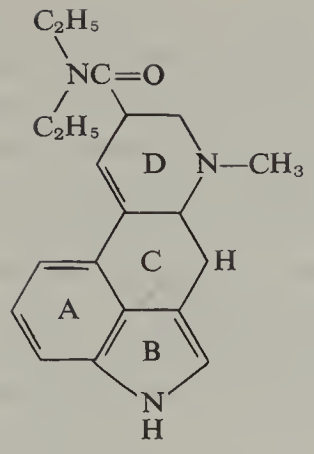
In 1956 Page wrote that "we are witnessing and participating in the rebirth of a new branch of knowledge dealing with the chemical substrates of thought, from a theme established long ago. Unless I exaggerate, a new era is indeed upon us."

Indeed, a new era in biochemical research on schizophrenia was begun in 1950 when investigators directed their efforts into specific channels designed to test the hypotheses which they had formulated. A hypothetical psychotogen was the center of these ideas. This is a substance which is formed by a pathological process and which produces the schizophrenic symptoms. Its action can be likened to that of the known psychotomimetic drugs. It would seem that the biochemical systems ultimately affected by this endogenously produced psychotogen are peculiar to the brain and nervous system, although the basic defect might conceivably be in any process going on in the body or brain.

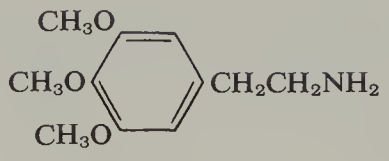
In the past decade or so, attention has been focused on methylated compounds as being of importance in the etiology of schizophrenia. Evidence has accumulated from diverse directions which would tend to support this, and this is considered in the following sections.

HALLUCINOGENS

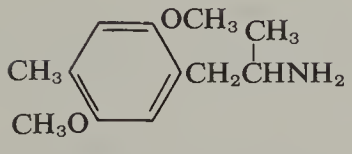
The possibility that the structures of known hallucinogenic compounds (Figure 7-1) could provide a clue as to the type of compound which is a psychotogen in schizophrenia is one of the reasons for these substances to have been intensively investigated. Although as yet we know very little about their modes of action, a number of



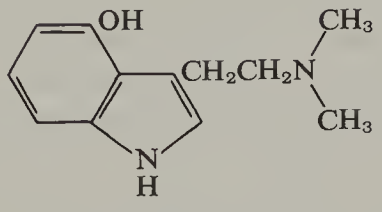
LSD



Mescaline



STP



Psilocin

FIGURE 7-1.
Structural formulae of some hallucinogens.

interesting observations have been made; for example, that LSD increases the level of brain serotonin (Freedman and Giarman, 1962).

They all produce, to a varying degree, similar symptoms, yet they include chemically dissimilar classes of compounds—derivatives of the tryptamines, phenylethylamines, and phenylisopropylamines. If one could find what chemical or physical properties are unique to the hallucinogenic compounds then it would be possible to predict the activity of compounds from their structure.

On the basis of studies of structure-activity relationships, Snyder and Richelson (1968) suggested that the modes of action of LSD and the hallucinogenic tryptamines and phenylisopropylamines (amphetamines) are similar, and indicated possible similarities of molecular structure based on hydrogen bonded rings. Snyder and Richelson's proposed structures were criticized by Chothia and Pauling (1969), who proposed other molecular structures for these classes of compounds and suggested somewhat different similarities between them. The structures of several of these compounds are now known, but no definite conclusions have yet been reached relating hallucinogenic activity with molecular structure.

A survey of catecholamine excretion in various psychiatric disorders has provided some evidence that urinary catecholamine levels are increased in acute but not

chronic schizophrenia (Bergsman, 1959), and there are indications that in schizophrenia dopamine is produced normally but is metabolized to give abnormally high levels of noradrenalin and adrenalin (Mattok et al., 1967). On the other hand a good deal of evidence suggests that while the excretion of catecholamines may be modified by emotional and physical factors in schizophrenia the overall metabolism of catecholamines is normal (Brune and Pscheidt, 1961; Brune et al., 1963; Pscheidt et al., 1964; Berlet et al., 1965). Work relating catecholamines and schizophrenia has been reviewed elsewhere (Bourdillon and Ridges, 1970).

Aberrant methylation by the schizophrenic could lead to the formation of metabolites having the necessary groupings to meet the structural requirements of a psychotogen.

In view of the structure of the known hallucinogens, attention has focused on indoleamines and catecholamine derivatives as possible endogenous psychotogens. The N-methylated and N,N-dimethylated derivatives of serotonin and tryptamine are known to have considerable psychotogenic activity. Whether bufotenin is excreted by schizophrenics has been disputed, although it has been identified in their urine following administration of methionine and a monoamine oxidase inhibitor (Tanimukai et al., 1971).

Mescaline (trimethoxyphenylethylamine) has formed the basis of one hypothesis concerning the etiology of schizophrenia upon which much subsequent research has been based. Osmond and Smythies had been studying this substance for several years when, in 1952, impressed by the similarity between mescaline and adrenalin, they postulated that in schizophrenia a compound might be formed which had a structure resembling both adrenalin and mescaline, and with properties like mescaline. They suggested that dimethoxyphenylethanolamine could be this compound and that it might arise by a disturbance in the final stage in the formation of adrenalin. This is a transmethylation reaction. The general idea behind this hypothesis is particularly attractive because we know that, just as physical stress affects the secretion of adrenalin and noradrenalin (Cannon, 1931; Euler and Hellner, 1952; Euler, 1964), so does psychological stress affect these compounds (Elmadjian et al., 1957; Levi, 1965; Hamburg, 1962; Breggin, 1964), and it is logical to study them in relation to the normal functioning of the brain and to the functioning of the brain in mental illness.

THE METABOLISM OF CATECHOLAMINES AND THE ROLE OF METHYLATING ENZYMES

We now have a far better understanding of the metabolism of catecholamines than at the time Osmond and Smythies put forward their hypothesis that schizophrenia is the result of a disturbance in the methylation of noradrenalin to adrenalin. Not only

is methylation involved in the biogenesis of adrenalin, but it also plays a vital role in the metabolism of the catecholamines. In the process of methylation, a methyl group is donated by an active form of the compound methionine (S-adenosylmethionine), and transferred to the oxygen atom of the catecholamine. The presence of magnesium and other bivalent ions is necessary for this reaction (Cantoni, 1953; Greenberg, 1963).

A number of enzymes concerned with methylation have now been described. They include a soluble catecholamine-O-methyltransferase (Axelrod and Tomchick, 1958), hydroxyindole-O-methyltransferase (Axelrod and Weissbach, 1961), indophenol-O-methyltransferase (Tomita et al., 1964), microsomal catechol-O-methyltransferase (Inscoe et al., 1965), phenol-O-methyltransferase (Axelrod and Daly, 1968), a non-specific N-methyltransferase (Axelrod, 1965), and indole (ethyl) amine-N-methyltransferase (Morgan and Mandell, 1969).

The metabolic pathway whereby catecholamines are formed in the body is well established (Blaschko, 1959), and details have been worked out concerning the enzymes and cofactors involved in the individual steps (Figure 7-2) in the pathway (Axelrod, 1966; Sourkes, 1966; Udenfriend, 1966; Kirshner and Goodall, 1957).

For many years it was thought that the main pathway of catecholamine metabolism was by oxidative deamination involving monoamine oxidase (MAO), but then it was found that inhibition of MAO activity did not prolong the physiological effects of administered adrenalin and noradrenalin (Griesemer et al., 1953). It is now known that two enzymes are involved in the metabolism of the catecholamines. These are MAO, which is particularly involved in the metabolism of stored amines, and catechol-O-methyltransferase (COMT), which is the major enzyme concerned in the metabolism of circulating catecholamines (Axelrod et al., 1958a, 1958b; see Figure 7-3).

While metabolites O-methylated in position 3 have been shown to predominate, there is now considerable evidence that position 4 can also be O-methylated (Axelrod and Tomchick, 1959).

A pilot study of the effect of catechol-O-methyl transferase on schizophrenics (Hall and Hartridge, 1969) resulted in exacerbation of the clinical symptoms, indicating that abnormal transmethylation may be a feature of schizophrenia.

The body is also known to be able to N- and O-demethylate compounds (Franklin, 1965; Ackerman and Heinrick, 1970), but the importance of these demethylases is still to be established. It may, in fact, be more strictly correct to represent the metabolism of dopamine as shown in Figure 7-4. In this sequence of reactions, the compound dimethoxyphenylethylamine (DMPE) is produced and subsequently demethylated in position 4. Harley-Mason had predicted in 1952, in connection with Osmond and Smythies' hypothesis, that this would be an interesting compound to investigate and, in 1962, Friedhoff and Van Winkle reported that they had found this compound in the urine of schizophrenics but not in that of normal individuals.

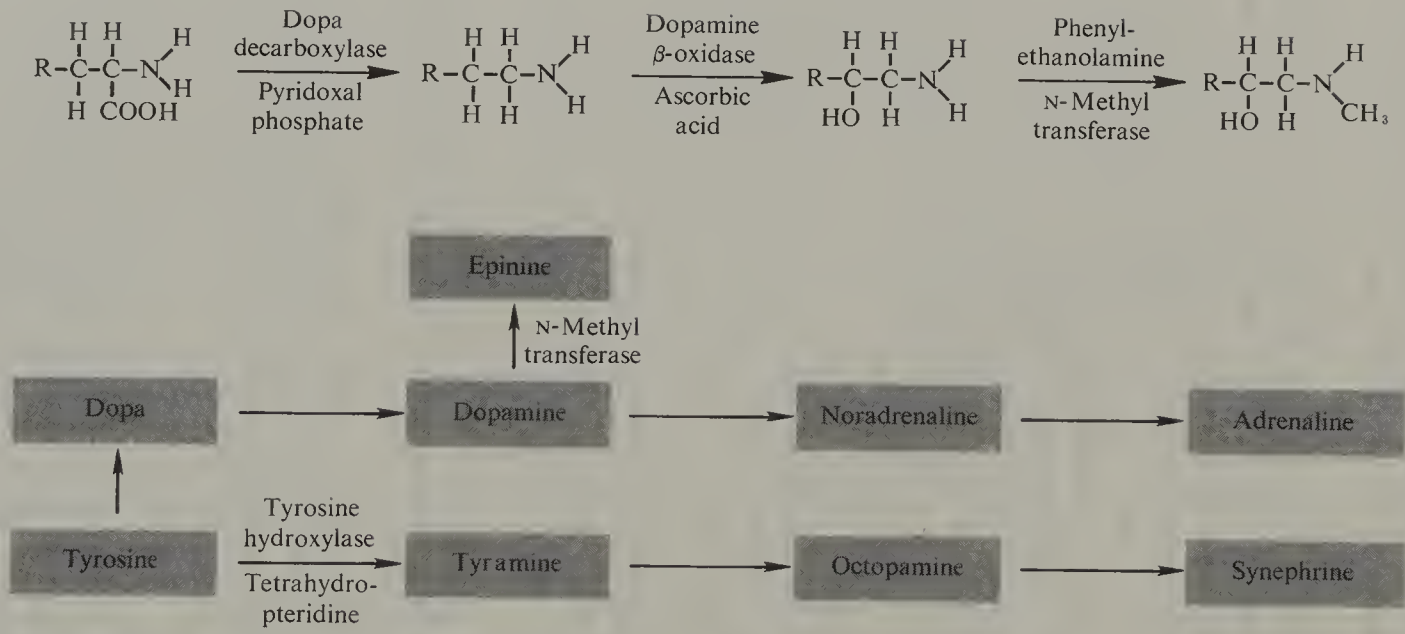
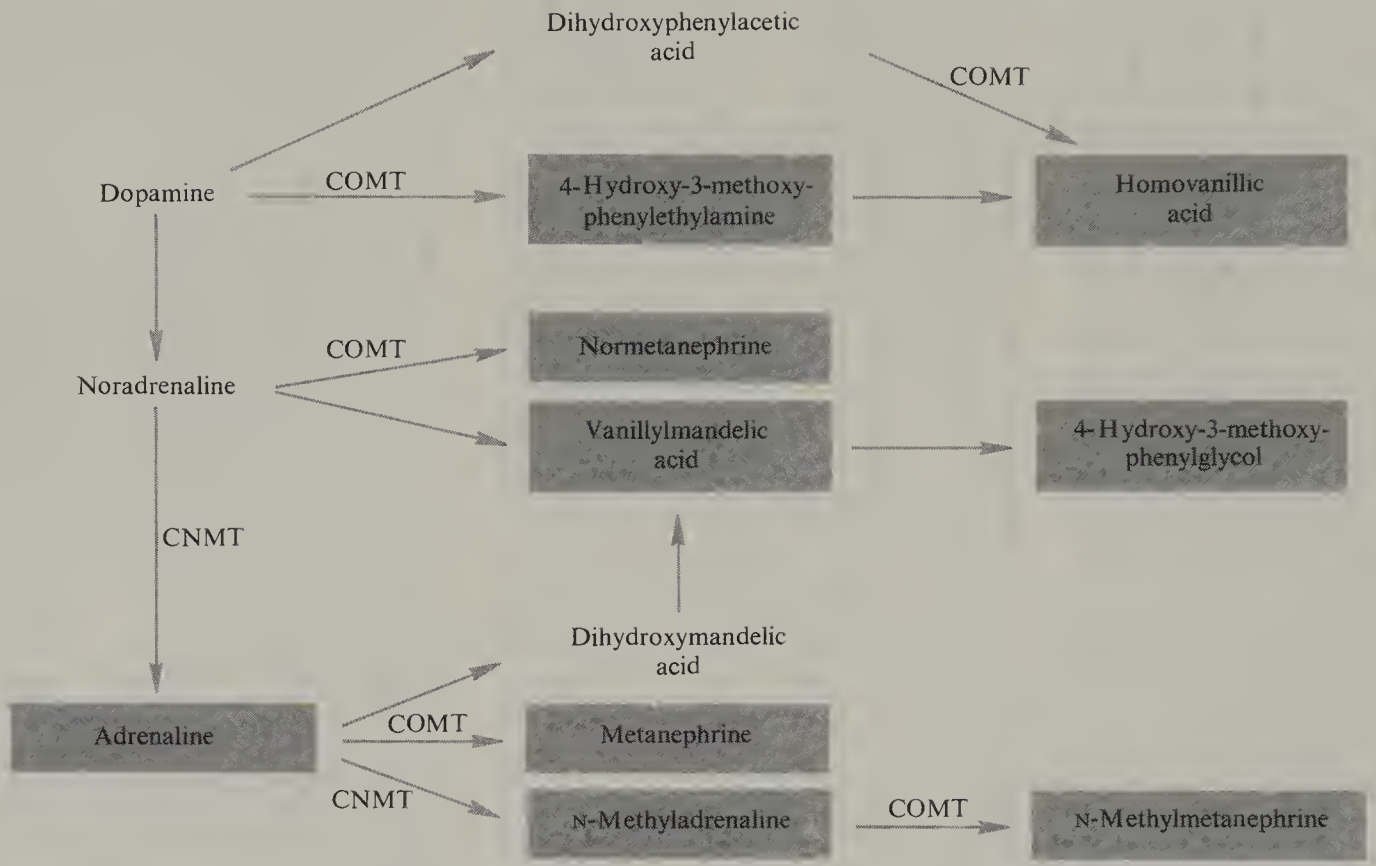


FIGURE 7-2.
Some pathways in the formation of the catecholamines.



COMT = Catecholamine O-methyltransferase

CNMT = Catecholamine N-methyltransferase

FIGURE 7-3.
Methylated metabolites of the catecholamines.

EXCRETION OF DIMETHOXYPHENYLETHYLAMINE AND 'PINK SPOT'

Investigations in our laboratory into the excretion of dimethoxyphenylethylamine (DMPE) by schizophrenics were initially intended to determine if DMPE might be a genetic marker of schizophrenia, and our first experiments were designed to see if Friedhoff and Van Winkle's report could be confirmed. Using similar methods, we were able to find material in the urine of schizophrenics which corresponded to DMPE. However, we did not have sufficient evidence to conclude that the material we detected was, in fact, DMPE, and thus we termed the samples in which it was found "pink spot positive," because of its color when reacted with ninhydrin and modified Ehrlich's reagent.

By definition, "pink spot" is a substance which behaves in a manner indistinguishable from DMPE in the solvent extraction, paper chromatography, and staining procedures we used in our investigations.

Having established that there is a substance present in schizophrenic urine, a survey was designed to find whether its excretion was confined to schizophrenics (Bourdillon et al., 1965). This was done under double-blind conditions, and individuals were included who would be most likely to produce pink spot.

The subjects selected could be divided into three groups. One consisted of mentally normal people, the second was mainly schizophrenics, all of whom were rated and referred by the same psychiatrist; and the third group (nearly three times as large as the second) consisted entirely of patients from psychiatric hospitals. Details of this survey are described elsewhere (Ridges et al., 1968). The methods described by Friedhoff were modified and extended. The results are shown in Table 7-1.

This survey showed that there is an association between the excretion of material behaving like DMPE and the diagnosis of schizophrenia. In group 2 there was compelling evidence that pink-spot excretion is associated with Schneider-positive (Schneider, 1959) individuals (Table 7-2). It is much rarer in those who are Schneider-negative and rarer still (if present at all) in other forms of mental disorder and in nonschizophrenics. In both groups 2 and 3, pink spot was most likely to be found in schizophrenics who were not, by our definition, paranoid schizophrenics. Individuals in the subgroup Schneider-positive nonparanoid had the highest incidence of pink spot (83.3 ± 5.75 percent).

Several factors may be responsible for the lower incidence of pink spot in group 3 as compared with group 2. The method of case selection was different and there was a much larger proportion of chronic and less acutely disturbed patients in group 3 than group 2. Also in group 3 a much larger proportion of individuals were on drug therapy, which we now know suppresses pink-spot production.

From these experiments it is concluded that pink-spot excretion is associated with

TABLE 7-1.
Survey of Individuals for Excretion of Pink Spot

Groups	Pink Spot Status			
	Present	Absent	Impossible to assess	Total
Group I: Mentally normal individuals				
Apparently healthy volunteers	1	264	0	265
Hospital inpatients	0	126	0	126
Unaffected relatives of schizophrenics	0	20	0	20
Total	1	410	0	411
Group II: Mainly schizophrenics (individually selected by interview)				
Schizophrenics (excluding paranoid)	44	12	11	67
Paranoid schizophrenics	2	15	0	17
Nonschizophrenics	0	16	1	17
Total	46	43	12	101
Group III: Mental hospital patients (selected by Case Sheet diagnosis)				
Schizophrenics (excluding paranoid schizophrenics)	20	30	19	69
Paranoid schizophrenics	2	54	6	62
Schizophreniform syndromes	5	58	25	88
Nonschizophrenics	1	68	8	77
Total	28	210	58	296

TABLE 7-2.
The Association Between Pink Spot Status and the Schneider Rating of Schizophrenics

Schneider rating	Pink Spot Status			
	Positive	Negative	Impossible to assess	Total
Positive	35	11	6	52
Negative	7	16	4	27
Impossible to assess	4	0	1	5
Total	46	27	11	84

the schizophrenic group of individuals; however, until other factors are ruled out, this does not necessarily mean that it is associated with the disease.

Starting in 1962, a number of research teams investigated the excretion of DMPE or a DMPE-like substance in the urine, and by 1967 there were innumerable discrepancies in the literature. Questions were raised as to whether such material was excreted at all, or excreted by normal individuals, if it was associated with schizophrenia, or if it was present in other conditions, such as Parkinson's disease. Table 7-3 summarizes the conclusions drawn by the various investigators.

Many factors could contribute to these apparent discrepancies, but the most important have been due to differences in case selection, the methods used for investigating the urine samples, and differences in the use of the term pink spot (Ridges and Bourdillon, 1967).

In the published reports the criteria used for the selection of schizophrenics have not always been stated. The effect of different methods of case selection is seen in the altered incidence of pink-spot excretion in our groups 2 and 3. It is not surprising that pink spot has not been found by workers who have investigated chronic schizophrenics (Perry et al., 1966b). Also, the previous history of the patient and if he has recently been receiving drug therapy undoubtedly influences the likelihood of finding pink spot in the urine. It is well known that lipid-soluble compounds such as anesthetics and drugs can persist for long periods of time in the body and make a considerable contribution to the unsaponifiable fraction of depot fat which acts as an appreciable reservoir for drugs. For example, phenothiazines have been detected in patients who have not received drug therapy for more than six months (Horwitt, 1965; Laster, 1965, personal commun.). Because of this it is essential to study the processes whereby pink spot is produced in individuals who have never previously had any drug therapy.

The methods used in our survey were essentially the same as those used by Friedhoff and Van Winkle (1962). Other workers who have used these techniques (Bell and Somerville, 1966; Predescu et al., 1968) have agreed that pink spot is not found in normal individuals. Takesada et al. (1963) who used column chromatography for the initial separation of urinary constituents, separated pink spot in the urine of normal individuals. Using column chromatography we have found that material isographic with DMPE on paper chromatograms can be recovered from normal urine. However, if the eluate is fractionated this material comes off the column much earlier than the pink spot found in schizophrenics, and in samples which were positive by our routine methods it was present in addition to the DMPE-like pink spot. It seems likely that this pink-staining material found in normal urine is of dietary origin, since it disappears from the urine of normal individuals maintained under metabolic ward conditions on a milk diet.

Much attention has been focused on whether or not pink spot is excreted in Parkinson's disease, but in our laboratory we have not found any substance that

TABLE 7-3.

Investigations into the Excretion of DMPE or a DMPE-like Material

Workers	Individuals investigated	Number with DMPE or DMPE-like material	Methods used
	No such material excreted		
Faurbye and Pind, 1964	10 normal	0	Column and thin-layer chromatography
	16 chronic schizophrenics	0	
Perry et al., 1964	10 acute schizophrenics	0	Column chromatography
Williams et al., 1966	22 schizophrenics	0	Thin-layer chromatography
Perry et al., 1966	12 chronic schizophrenics	0	Column and paper chromatography
	7 nonschizophrenics	0	
	Material excreted in normal urine		
Takesada et al., 1963	46 normal	21	Column and paper chromatography
	21 psychoneurotics	14	
	78 schizophrenics	70	
Von Studnitz and Nyman, 1965	3 normal	2	Paper chromatography
	6 schizophrenics	4	
	Material present in schizophrenic urine and in patients with Parkinson's disease		
Barbeau et al., 1963	16 Parkinson's disease	14	Solvent extraction and paper chromatography
	33 hospital patients (controls)	7	
	7 normals		
Boulton, 1966	20 Parkinson's disease	16	Solvent extraction and paper chromatography
Kuehl et al., 1967	17 Parkinson's disease	7	Solvent extraction and paper chromatography
Rinne and Sonninen, 1967	20 Parkinson's disease	17	
	9 neurological conditions (without extra pyramidal symptoms)	7	
	Material associated with schizophrenics' urine		
Friedhoff and Van Winkle, 1962	14 normal	0	Solvent extraction
	19 schizophrenics	15	Paper chromatography
Kuehl et al., 1964	10 normal	0	Column and thin layer chromatography
	12 acute schizophrenics	5	
	10 less acute schizophrenics	2	
Sen and McGeer, 1964	1 normal	0	Paper and gas chromatography
	15 acute schizophrenics	1	Paper chromatography
	7 acute schizophrenics	4	Paper and gas chromatography
Bourdillon and Ridges, 1965	370 normal	1	Solvent extraction and paper chromatography
	20 unaffected relatives of schizophrenics	0	
	84 acute schizophrenics	46	
	131 less acute schizophrenics	22	
	88 schizophreniform syndrome	5	
	94 other psychiatric disorders	1	
Bell and Somerville, 1966	27 schizophrenics	3	Paper and fluorimetric techniques
Predescu et al., 1968	115 normal		Solvent extraction and paper chromatography
	51 schizophrenics	23	
	55 other psychiatric disorders		

fulfills the criteria for our definition of pink spot, although pink-staining material which appears to be related to therapy has been detected (Ridges and Harper, 1969). Boulton et al. (1967) maintained that pink spot is excreted in Parkinson's disease and is *p*-tyramine, but this cannot be so, since *p*-tyramine can be readily distinguished from DMPE in the procedures used (Takesada et al., 1963; Vogel et al., 1967). Other suggestions have been made for the identity of the pink-staining material in Parkinson's disease. Kuehl et al. (1968) are of the opinion that it is tryptamine, whereas Barbeau et al. (1963), who originally reported on the excretion of DMPE, now believe that it is a drug metabolite (Bartlett et al., 1967).

The question of whether the association which we have consistently found between pink-spot excretion and schizophrenia is due to something other than the disease process has been given much consideration. Factors such as diet, bacterial flora, drugs, and activity level are generally regarded as being of greatest importance in causing biochemical differences between individuals. However, investigations of pink-spot excretion in schizophrenics with these conditions strictly controlled have never been done.

A number of urinary constituents have their origin in the diet, and exclusion diets have frequently been used to ascertain whether a constituent is of exogenous origin, but the ensuing complexities which dietary restrictions can have on intermediary metabolism, as reflected by the concentration of metabolites in the urine, is sometimes ignored. Von Studnitz and Nyman (1965) showed that pink spot disappeared when the patients were maintained on glucose, water, and citric acid, and concluded that pink spot was, therefore, of dietary origin. However, it has also been demonstrated that glucose feeding causes a marked reduction in excretion of the dopamine metabolite homovanillic acid (Friedhoff and Coupet, 1967), and withdrawal of food causes a decrease in the excretion of a metabolite of noradrenalin, vanillylmandelic acid (Goodman, 1967).

It seems likely that if some foodstuff or group of foodstuffs were responsible for the presence of pink spot in the urine, then in the course of our survey of normal individuals we would have found people who were excreting it. We attempted to exclude as far as possible the effect of diet by including nonschizophrenics from the same wards and on the same diet as the schizophrenics we investigated, but under double-blind conditions pink spot was not found in the other psychiatric patients. If pink spot is of dietary origin, then the question arises as to what differences exist between the metabolism of schizophrenics and normal individuals so that only the schizophrenics excrete it unchanged.

We have found (Ridges and Bourdillon, 1966) that modifications of the intestinal flora by a 5-day course of neomycin did not alter the pink spot status of schizophrenics. Perry et al. (1966a) believe that, among the amines excreted in the urine, tryptamine, *p*-tyramine, and octopamine are of intestinal bacterial origin.

Careful consideration has been given to the question of whether pink spot might

be a drug artifact, and this is a very real possibility since the diagnosis of schizophrenia is frequently associated with particular medication (Steinberg and Robinson, 1968; Ridges and Harper, 1970). However, there is no evidence to suggest that drugs and their metabolites are responsible for this phenomenon. Pink spot has been found in patients who are known with certainty not to have received any therapy, and we have no evidence from the mass-spectral data of the components of pink spot to suggest that they are products of therapy.

The incidence of pink spot is markedly reduced when patients are receiving therapy. In part, this is explained by the increased difficulty in assessing chromatograms when drugs are present. We have noted, however, that there appears to be a relationship between the disappearance of pink spot from the urine and the response of the patient to therapy. The period during which pink spot is excreted seems to be variable, but generally it can be detected for 5 to 14 days following therapy in a patient who has had a severe attack.

Some of our data have also been analyzed by multiple regression analysis to ascertain whether a number of factors which taken separately might not appear to be related to pink-spot excretion could, when summated, account for this phenomenon. Such factors as urine volume, *p*H, duration of illness, age, sex, and duration of hospitalization, in addition to diet, bacterial flora, and drugs, have been included in this study, but there were no indications that these could account for the association we found.

So, in the light of the available evidence, it seems reasonable to assume that pink spot exists as an entity associated with schizophrenia. No satisfactory explanation of pink spot has been made in terms other than of schizophrenia, and when the criteria laid down in the definition of pink spot are followed there is no convincing evidence of its existence in other conditions.

The question of the identity of pink spot has not been settled. Friedhoff and Van Winkle's initial identification as DMPE was based on the behavior of the unknown compound during solvent extraction, paper chromatography, and staining. These workers also obtained an ultraviolet spectrum and melting point of the purified material and carried out gas chromatography of the free material and the N-acetyl derivative. The finding of dimethoxyphenylacetic acid in the urine has also been regarded as evidence that DMPE is its precursor. However, if metabolic pathways such as those shown in Figure 7-4 are operative, then quantitative measurements of dimethoxyphenylacetic acid are not directly related to the amount of amine produced, and this may explain the findings of Kuehl et al. (1966), who showed that there were no differences between the levels of the acid in normal and schizophrenic urine. It has become evident that the clinical material found to be pink-spot positive by ourselves and by Friedhoff is essentially similar. Our initial attempts to characterize pink spot by isolation of sufficient material for a mass spectrum showed that our material was impure, but the spectrum obtained had none of the characteristics of the mass

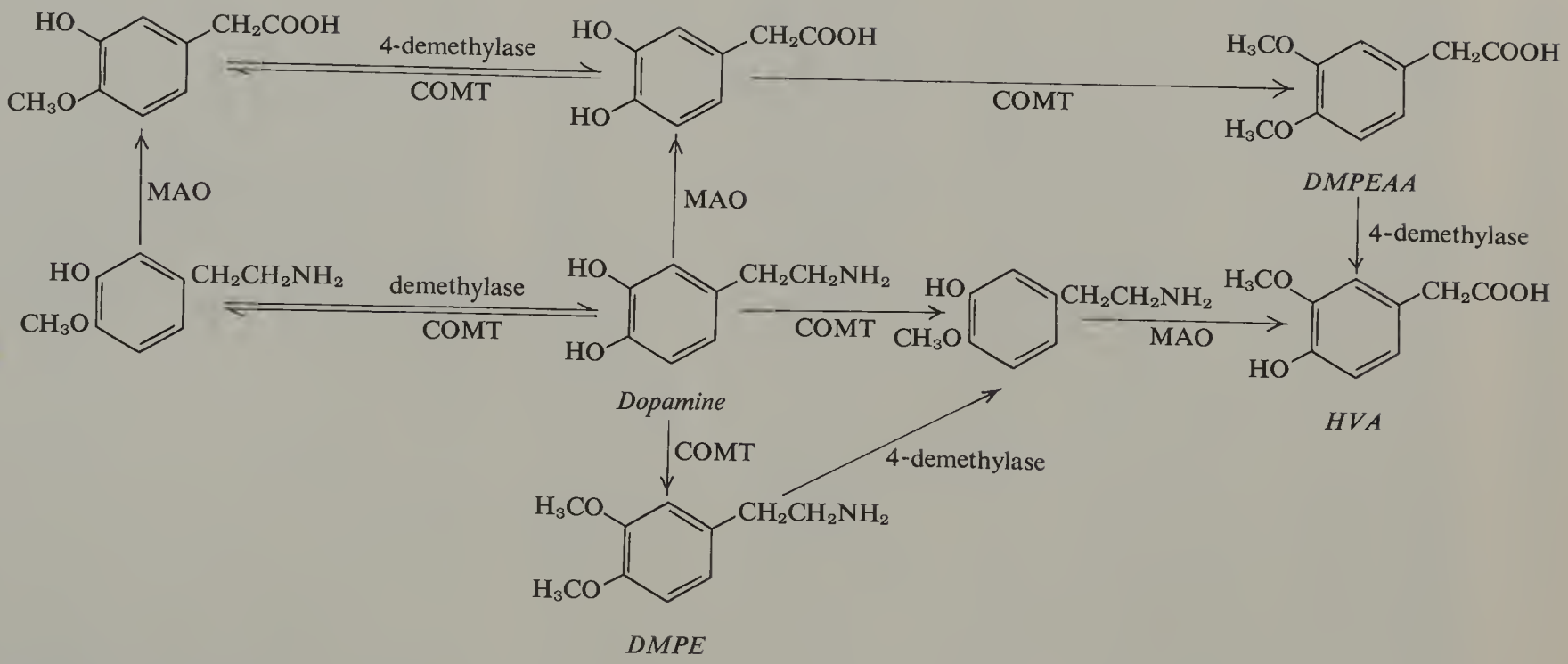


FIGURE 7-4.
Metabolism of dopamine.

spectrum of DMPE. Bell and Somerville (1966), using samples provided by us and investigated blind, confirmed which samples were pink-spot positive, but were unable to demonstrate by spectrophotofluorimetric methods that pink spot was DMPE. It was also shown that the partition characteristics of DMPE were such that negligible amounts would be extracted at *p*H 9.0, which was used by Friedhoff and Van Winkle in 1962. We further purified our material using mass spectrometry with gas chromatography, and showed that pink spot consisted of a number of components, some of which were common to all pink-spot positive samples and others which were not common to all. None of the mass spectral data corresponded to DMPE, although DMPE added to the urine in microgram amounts and subjected to the same procedures could be readily identified.

Pink spot cannot be solely DMPE, but the converse, that DMPE is present in pink spot, might be true. DMPE would, by definition, give a pink spot on chromatograms (Bourdillon and Ridges, 1966). Creveling and Daly (1967), using mass spectral data of the dansyl derivative, have identified DMPE as a minor component of pink spot. Recently, these workers showed that DMPE is present in tea in small amounts and can be recovered from the urine of normal individuals who have drunk 1 to 2 liters of tea in less than 4 hours (Stabenau et al., 1970). In view of our findings that 1 out of 411 mentally normal, and 1 in 77 nonschizophrenic psychiatric patients were pink-spot positive, it must follow that DMPE from tea is not frequently responsible for pink spot.

Our work suggests that the components of pink spot are present in a variety of combinations in different patients and they appear to be methylated compounds related to the catecholamines.

SERUM FACTORS IN SCHIZOPHRENIA

Bergen (1965) demonstrated that a small molecule associated with a serum factor which he had found in schizophrenics had properties resembling a catecholamine. It is possible that this factor is related to pink spot, as may be the urine heteropeptide with a catecholamine residue reported by Barrass et al. (1970). More recently, Bergen has investigated taraxein, the serum factor factor which Heath (1963) isolated from schizophrenic serum. Heath found that this factor produced abnormal spiking on the EEG's of normal people, which resembled spiking that occurred with psychotic behavior, and it caused behavioral symptoms similar to schizophrenia, suggesting a link between taraxein and the clinical manifestations of schizophrenia. When given to monkeys it produced catatonia.

Because of the comparative crudeness of the techniques used in the isolation of taraxein its activity can readily be lost, and other workers have failed to confirm Heath's findings. However, in 1969 Bergen confirmed the part of Heath's work that

involves the separation of taraxein and the demonstration of its influence on EEG's and catatonia in monkeys. His findings are in agreement with Heath's suggestion that activity is due to a specific gamma globulin, but as yet Heath's finding (as reported in 1967) that the globulin attaches itself to neural cell nuclei in the septal region of the brain has not been confirmed.

THE EFFECTS OF METHYL DONOR COMPOUNDS ON SCHIZOPHRENICS

Since pink spot is most likely to be found in acutely disturbed schizophrenics and appears to contain methylated substances, and since administration of methyl donor compounds is known to cause exacerbation of the symptoms of schizophrenia (Pollin et al., 1961; Brune and Himwich, 1962a; Park et al., 1965), it is of obvious interest to see whether pink-spot excretion is initiated by administration of a methyl donor and monoamine oxidase inhibitor. The worsening of symptoms by methionine and an MAOI has also been described in patients with psychoneuroses (Sprince et al., 1963). Park et al. (1965) emphasized that many of the symptoms could be the result of toxicity. Pollin et al. (1961) found that alterations in behavior were associated with administration of L-methionine and of L-tryptophan, and Axelrod (1961) speculated that this might occur because these amino acids can serve as methyl donor and precursor for the psychotomimetic compounds bufotenin and N,N-dimethyltryptamine.

Sprince et al. (1963), attempting to correlate urinary indoles with behavior changes brought about by methionine, tryptophan, and MAOI, failed to demonstrate the presence of these N,N-dimethyl derivatives of serotonin and tryptamine, although their results indicated a relationship between increased urinary levels of tryptamine and indoleacetyl glucuronide in both schizophrenics and psychoneurotics and the onset of mental symptoms. Brune and Himwich (1960, 1961, 1962b; Berlet et al., 1965a) found a correlation between elevated levels of urinary tryptamine, indole-3-acetic acid, and 5-hydroxy-indole-acetic acid and the exacerbation of psychotic symptoms. Urinary levels of these substances became normal with improvement of the mental state.

On the other hand, total catecholamines in the urine appeared to reflect the level of sympathetic activity in schizophrenic patients, and the evidence suggested that the overall metabolism of catecholamines is normal in schizophrenics (Brune and Pscheidt, 1961, 1963; Pscheidt et al., 1964; Berlet et al., 1965b). Kakimoto et al. (1967) found that after methionine loading they failed to detect 4-DMPE, N-methyl-tryptamine, N-methylserotonin, or the corresponding dimethylated derivatives, suggesting that methionine exerts its action through some other mechanism than methylation.

Only recently has the effect of a monoamine oxidase inhibitor and cysteine on controls and schizophrenics been investigated at the same time (Narasimhachari et al., 1970). In this study no controls showed any schizophrenic-like symptoms; bufotenin was found only in the urine of the schizophrenics.

In our investigations using chronic schizophrenics (Abensen et al., in prep.), although three patients showed worsening of symptoms, pink spot was not detected in the urine at any time. There are several reasons why this was so, including the chronicity of the patients available for the investigation and the possibility that the worsening of symptoms is, in fact, due to a toxic psychosis. However, at another time a schizophrenic who had on earlier occasions been found to be pink-spot positive became acutely disturbed when given MAOI therapy and recommenced to excrete pink spot.

In the past the exacerbation of schizophrenic symptoms by methionine and MAOI has been cited as providing support for the methylation hypothesis, and it is interesting to consider the effects of methionine sulphoximine in connection with this work. In animals, methionine sulphoximine produces convulsions similar to epileptic seizures in humans. One of the properties of methionine sulphoximine is that it is an antimetabolite of methionine (see Figure 7-5), and schizophrenics can

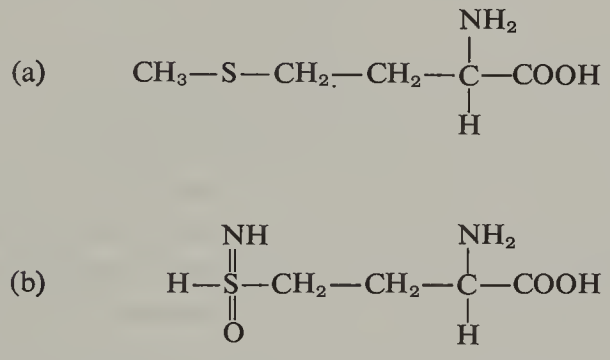


FIGURE 7-5.
Methionine (A) and its antimetabolite methionine sulphoximine (B).

tolerate much larger doses of it than can normal individuals (Heath et al., 1966). This fact can be interpreted as further supporting the methylation hypothesis and the suggestion that schizophrenics have an overactive methylating system.

Other work on methionine sulphoximine (De Robertis et al., 1967) has indicated that there is a definite concentration of methionine sulphoximine in the nerve endings and that it produces striking ultrastructural changes in synaptic endings. This indicates that the drug has a profound action in synaptic transmission. It has been postulated that the methionine sulphoximine probably acts on nerve endings related to glutamic acid-glutamine-GABA metabolism. It was also observed that when it is injected intraperitoneally methionine sulphoximine has practically no effect on

cholineacetylase, acetylcholinesterase, and monoamine oxidase. Some increase in the activity of catechol-O-methyltransferase was observed, the noradrenalin-5-hydroxytryptamine content of the whole brain was slightly lowered, and the dopamine remained unchanged, although the free-bound ratio altered.

The use of nicotinic acid in the prevention and treatment of methionine-induced exacerbation of symptoms in schizophrenics has been investigated (Ananth et al., 1969) and is discussed later.

THE EFFECT OF METHYL ACCEPTOR COMPOUNDS ON SCHIZOPHRENIA

Complementary to the findings that methyl donor compounds cause an exacerbation of schizophrenic symptoms are the reports that methyl acceptor compounds effect an alleviation of symptoms. One such methyl acceptor is nicotinic acid. An interest in this compound in the treatment of schizophrenia arose from investigations of adrenochrome (a compound which can be formed by decomposition of adrenalin), which has been implicated as a possible hallucinogen in schizophrenia (Hoffer, 1957; Osmond, 1955). Although there has been doubt expressed that adrenochrome is present in human beings and has hallucinogenic properties (Hoffer, 1958; Szara et al., 1958; Rinkel and Solomon, 1957), it now seems almost certain that aminochromes can be formed in vivo, and all the enzyme systems needed for this formation are known to exist. Hoffer and Osmond (1964) believed that by giving a methyl acceptor the production of adrenalin would be reduced, which would result in less adrenochrome being formed. Nicotinic acid is converted to nicotinamide in the body in a number of stages (see Figure 7-6). Nicotinamide adenine dinucleotide (NAD), which is an intermediary compound in this pathway, is also reported to cause remarkable improvements in the condition of patients, although other workers (Kline et al., 1967) have been unable to confirm this. There are several explanations, but the fact that only chronic and considerably deteriorated schizophrenics were investigated and that NAD was given for only 20 days may account for these findings. Numerous workers report that schizophrenic symptoms can be alleviated by nicotinic acid, particularly if it is given with a diet high in fat and protein (Osmond and Hoffer, 1962; Hoffer and Osmond, 1964; Ward, 1971; Hawkins, 1971). Mosher (1970) on reviewing earlier literature concluded that massive doses of nicotinic acid appear to be relatively harmless.

Considerable evidence is accumulating that the use of vitamins at much larger levels than required for the treatment of deficiency diseases can cause an improvement in schizophrenic symptoms, particularly if used in conjunction with drug therapy. These include vitamin B3 (which may be given as nicotinic acid or nicotinamide), and pyridoxine (vitamin B6).

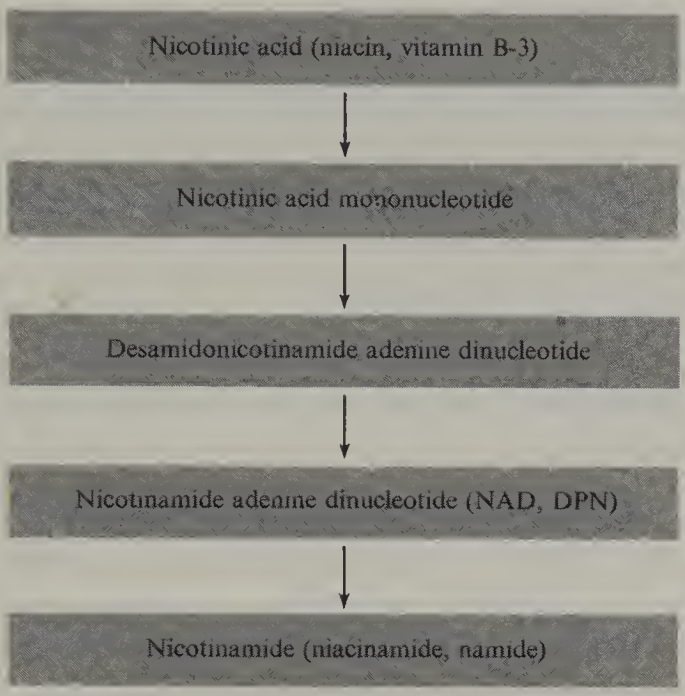


FIGURE 7-6.
The conversion of nicotinic acid to nicotinamide.

However, if we accept that nicotinic acid can cause an improvement in schizophrenic symptoms there is no proof that methylation is the underlying mechanism responsible for this improvement and that nicotinic acid is effective because of its action as a methyl acceptor. Ananth and his colleagues (1969) have investigated the effect of nicotinic acid on schizophrenics whose symptoms have been exacerbated by methionine. These investigations were done with chronic schizophrenics and it was found that nicotinic acid produced significant improvement ($P < 0.02$) prior to administration of methionine, although exacerbation of symptoms still resulted from administrations of a methionine MAOI combination. It should be noted that the latter is probably a quantitative effect, since the amount of methyl donor (20 g of methionine per day) given far exceeded that of the methyl acceptor (3 g of nicotinic acid per day).

MELANIN PRODUCTION IN SCHIZOPHRENICS

An increased pigmentation (the result of increased melanin production) which is not merely the effect of phenothiazine therapy has been observed in schizophrenics. This again links a faulty methylation mechanism with schizophrenia. Melanin is formed from dihydroxyphenylalamine (DOPA) and its production is governed by a number of factors, some of which (for example, copper ions and dopa oxidase) stimulate

melanin production, whereas others (for example, melatonin and catecholamines) reduce it.

Melatonin is formed in the pineal gland by O-methylation of N-acetylserotonin (Figure 7-7). In theory, if a copper chelating agent is given in the presence of defective melatonin production the balance of melatonin production might be expected

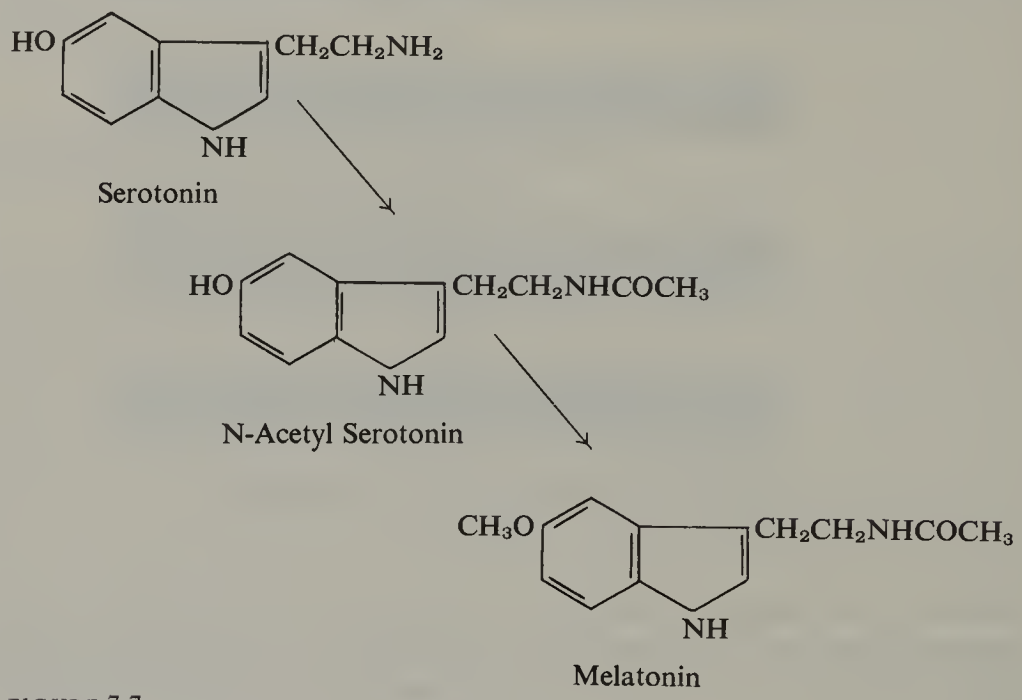


FIGURE 7-7.
The formation of melatonin from serotonin.

to be restored. It is, therefore, of considerable interest that penicillamine (which is a chelating agent) given with a low-copper diet has been found not only to reduce pigmentation, but also to cause an improvement in schizophrenic symptoms (Greiner and Nicolson, 1965; Helmchen et al., 1967; Nicolson et al., 1966).

Chelating agents have been shown to inhibit tyrosine hydroxylase activity (Taylor et al., 1969), so that penicillamine might also reduce the amount of DOPA available for conversion to melanin. Development of tremor in rats, noted by these workers, suggests that chelating agents cause a lowering of brain dopamine, resulting in a disturbance of the extrapyramidal system. One wonders if penicillamine is alleviating the schizophrenic symptoms by such a mechanism.

SUMMARY

At the present time there is considerable uncertainty in areas where there appears to be an association between methylation and schizophrenia. However, the methylation

hypothesis is a plausible one and has served the purpose of providing a foundation for experimentation. It has been capable of modification as fresh evidence has come to light and has provided a link between a number of observations which are apparently related to schizophrenia. These include the observations and reports that hallucinogens are methylated compounds, that methylation reactions are intimately involved in the metabolism of a variety of compounds, including normal body constituents and also antipsychotic drugs, that methyl donor compounds can exacerbate schizophrenic symptoms and a methionine antimetabolite is better tolerated by schizophrenics than by normal individuals, that there is an association between the excretion of methylated compounds such as pink spot and DMPE and schizophrenia, and that there exists a serum factor in schizophrenia which may be associated with a smaller methylated molecule.

The methylation hypothesis of schizophrenia has developed from a hypothesis which referred to a defect in a specific chemical reaction. This has coincided with the accumulation of a considerable amount of information concerning the methylation of compounds by the body and the appreciation of their widespread distribution and the diversity of reactions in which they play a part. If a generalized disturbance of methylation is postulated this would surely lead to a variety of physical defects. The repercussions of such a disturbance in the metabolism of compounds are so diverse as to make such a general hypothesis difficult to reconcile with a specific disorder. On the other hand, it is reasonable to consider that the brain and nervous system are tissues that are particularly sensitive to the concentration of methylated compounds, and that the maintenance of these compounds within close limits is necessary for the normal functioning of the brain. It seems that a disturbance of methylation could contribute to the symptoms of other psychiatric conditions besides schizophrenia.

The methylation hypothesis goes farther than any previous hypothesis toward providing a unified explanation of the etiology of schizophrenia. It has stimulated research which has been of undoubted value in progressing toward this goal, but it seems that its relevance to schizophrenia must of necessity be considered in terms of a specific hypothesis rather than in general terms.

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8

Kryptopyrrole in Molecular Psychiatry

D. G. IRVINE

INTRODUCTION

The first steps toward the discovery of the relationship between kryptopyrrole excretion and psychoses were taken by Dr. A. N. Payza, who noted a new substance in the urine of several persons experiencing experimental LSD model psychoses (Payza, 1958, personal commun.). Their urine had been monitored for Ehrlich-positive substance on the supposition that indoles would be the most pertinent substances to check, and with the hope that the LSD experience would provide not only a valuable clinical model of psychotic mental illnesses but also a useful biochemical model (Payza, 1957, personal commun.) of these conditions. The abnormal material discovered in this way was subsequently found in the urine of many psychiatric patients who had never been exposed to LSD.

I became associated with Dr. Payza in October 1958, in time to give the name "mauve factor" to the then unknown chromatographic spot which appeared in the urine of these individuals. Research on this substance has proceeded along often parallel but rather different lines, as Dr. A. Hoffer, initially carrying on his research

in the Psychiatric Research Unit, and later in private practice at Saskatoon, has emphasized the clinical and therapeutic application of mauve factor determinations, while we at North Battleford have concentrated upon the interdisciplinary correlates of this substance and upon its chemistry and identification, almost to the exclusion (thus far) of any etiological or therapeutic implications.

Our preoccupation with the basic research aspects of the mauve factor has led to its identification as 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole), but precludes our use of the term "ortho" molecular psychiatry, as this implies clinical application (adjustment) of the biochemical parameter. Hence our topic is "Krytopyrrole in Molecular Psychiatry," rather than "Mauve Factor in Orthomolecular Psychiatry."

For more than twelve years, then, the Research Laboratory of the Saskatchewan Hospital in North Battleford has pursued an interdisciplinary research program in molecular psychiatry. Molecular psychiatry would seem to possess several advantages over "biochemical psychiatry." It enjoys these advantages because:

1. It includes and integrates neuroanatomical chemistry and genetic psychiatry with biochemical psychiatry.
2. It avoids stereotyped thinking solely in terms of the currently familiar approaches and methods of biochemistry (for example, "normal levels"; solution rather than microarchitectural and solid-state biochemistry; abnormal metabolites, and the like).
3. It suggests additional avenues of approach to the relationships between chemistry and psychiatry.
4. It facilitates a redevelopment of the subject from a statement of the new concepts of molecular biology.
5. It suggests the use of selected molecular differences as the basic criteria for primary differentiation of clinical groups. treating clinical measures as dependent variables.
6. It envisages the serious application of individual differences at the molecular level, to establish the optimum biochemical substratum for the best medical-psychosocial functioning of each patient.

The purpose of this chapter is to illustrate one approach in molecular psychiatry, using the story of mauve factor (kryptopyrrole) as an example. Some goals, strategies, steps, and results are presented, followed by a synopsis of our current knowledge of kryptopyrrole in psychiatry, its relation to other compounds in biology and medicine, and prospects for the future.

AIMS AND STRATEGIES

Most studies in the biochemistry of mental disease have sought a biochemical difference between some clinically diagnosed group and normal controls. Several centers have added the refinement that other patient groups are used for comparison. Such studies would appear to involve the implicit assumption that a single biochemical abnormality causes or associates with a *specific* diagnostic category. The validity of this assumption is questionable, particularly if one takes into account the variety of clinical pictures associated with each of such biochemical states as "model psychoses," acute intermittent porphyria, and myxedematous madness. Moreover, this widely used approach is certainly not strengthened by pertinent considerations of the real complexity of the system studied, or of the long-acknowledged heterogeneity and low shareability of psychiatric diagnostic categories.

It appeared to us that such difficulties might be largely overcome by *first* assuming that the molecular abnormalities concentrated in mental patient populations would be more likely to be psychiatrically relevant; *second*, grouping patients on the basis of the presence, absence, or degree of such molecular abnormalities, rather than on the basis of clinical diagnosis; *third*, searching for specific, operationally defined, shareable, clinically relevant measures which might associate significantly with the molecular abnormalities; and *fourth*, cross-validating the observed molecular/clinical relationships in "blind" studies, to eliminate chance associations.

Based on these premises, then, our Research Laboratory has pursued an interdisciplinary research program with the following basic aims and strategies:

1. To integrate in a single conceptual framework, investigations on the biochemistry, genetics, and drug responses of persons with psychiatric disorders (Irvine, 1965, 1966a, 1966b, 1968).
2. To stress the individual differences (Williams, 1951, 1959; Irvine, 1961, 1963, 1965) in molecular constitutions which may influence the development, onset, severity, duration, treatment response, prognosis, or recovery from a psychiatric disorder.
3. To invert the classical approach of looking for molecular differences between clinically defined groups (Irvine, 1961, 1963, 1965, 1966b) and thus to use selected molecular tests to *define* the groups, and *then* look for clinical differences related to these molecules.
4. To establish one or more molecular tests of value in the prediction of clinically relevant parameters concerning groups of patients or individual patients (Irvine, 1963).
5. To nevertheless avoid premature or undue emphasis on molecular intervention as a primary means of treating mental illness. We consider that mental

functioning is a product of repeated interaction between the total environment and the total molecular substratum of the individual.

6. To avoid simplistic use of "cause," and to apply the concept of "necessary and sufficient conditions" instead.

A series of investigational steps is readily developed from the aims and strategies of molecular psychiatry. Some general steps appropriate to a long-term research project in molecular psychiatry may be expressed in the form of the following questions:

Is there a molecular anomaly associated with a mental illness?

Is this association due to an artifact?

What is the molecule involved?

What is the general causal mechanism underlying the association between this molecule and this illness?

What is the detailed or exact mechanism underlying this association?

How can this information best be used in therapy?

How can this information best be used in rehabilitation?

How can this information best be used in prevention?

These questions belong to three phases: the first three relate to phase I (correlation and validity); the next two to phase II (causal mechanism); and the last three to phase III (clinical applications). Let us now look at the history of mauve factor (kryptopyrrole) in terms of these three phases, and their specific steps.

PHASE I—CORRELATION AND VALIDITY

Is there a Molecular Anomaly Associated with a Mental Disorder?

PSYCHOSIS AND MAUVE FACTOR

To determine if there is a molecular anomaly associated with a selected mental disorder[1], it is necessary (1) to select the class of compounds to be investigated, (2) to conduct a pilot clinical experiment or survey to select the promising compounds (if any) in this class, then (3) to demonstrate the reproducibility of the associations

[1] It is at least equally valid to replace the initial criterion (mental disorder/disease) by "symptom," "behavior," "ward rating," "psychological test score," or "EEG measure," in order to gain new knowledge in molecular psychiatry.

between the chemical and the disease. It may also be necessary to establish experimentally the selectivity of the chemical measure, if this is a "new" compound which has to be measured. Further clinical understanding of the "syndrome" in which this chemical/clinical association exists can be gained at this stage by relating symptoms, ward behaviors, and psychological and EEG measures to the chemical measure.

Historically, when originally searching for a molecular anomaly associated with psychosis we chose to study the indolic class of compounds. There was a long history of their tentative association with mental illnesses stretching back to the early work of Bouchard (1894), Herter and Kendall (1909), and Bianchi (1906). These compounds were measured in urine because no other body fluid could be examined in quantity without disturbing the patients.

To further narrow the search for metabolites related to psychosis, the drug-induced model psychosis was used as a biochemical model in a pilot probe about thirteen years ago. In this work LSD (Figure 8-3) was administered to normal persons and alcoholics and their urines were monitored by paper chromatography, using the Erhlich stain to reveal the indoles and related substances (Payza, 1957, personal commun.). During the course of this work we noticed a new spot isographic with bufotenin in a one-dimensional chromatographic system (Payza, 1958, personal commun.; Irvine, 1961). We then monitored various clinical conditions without the use of LSD and found that the same "spot" or substance was present in many psychiatric patients (Irvine, 1961), and that it was rare in normal controls.

We named this substance "mauve factor," and pointed out its statistical association with psychosis (not specifically schizophrenia) in 1961. Hoffer (who had made similar observations in the same year) went further than this and suggested that persons excreting the mauve factor could be described as suffering from a disease called "malvaria" (Hoffer and Osmond, 1963).

Once this "chromatographic spot" had been found to associate with a type of mental disorder (psychosis) in the first study, it was necessary to determine if the same association could be found on repeating the studies; to ensure proper replication, it was prerequisite either to identify the compound or to operationally define it. If it could be identified as some known compound, this could serve as a basis for standardization, and established analytical methods could be used. Otherwise, special attention would have to be paid to the extraction and chromatographic procedures, to the description of the "spot," and to its quantitation.

Since mauve factor proved different from all known compounds available in the early 1960s, the procedures for its extraction from urine, for its chromatographic detection, and for its differentiation from other "spots" were all presented in detail as part of the first description of this material (Irvine, 1961). Since then the procedures have remained unchanged, except that methanol is now used in place of any acetone in the original method, the Ehrlich reagent is sprayed, not dipped, and there

TABLE 8-1.

Prerequisite Steps of Demonstrating Analytical Reliability. Operationally Defined Chromatographically Rated Mauve Factor

Results	Subjects		Statistic	P value
	Number	Type[b]		
I. Inter-rate reliability adequate.				
Blind study 1[ac]	35	MCP	Three-rater unanimity in 80% of cases	
Blind study 2[ad]	4	MCP	Kendall's coefficient of concordance, W	$<0.10>0.05$ 0.001 <0.005 <0.01
II. Inter-method reliability adequate.[e]				
Study 1	n = 11	MCP	Inter-method agreement = 73%	
Study 2	n = 42	MCP	Inter-method agreement = 74% Chi-square	0·005

[a] With 3 independent raters.
[b] M = male, CP = chronic psychotics, chronically hospitalized.
[c] Single tests; cross sectional.
[d] Each with many repeat tests; longitudinal. Results from individual subjects statistically analyzed ($W \rightarrow X^2$ 2-tailed).
[e] Method NB (adsorption) and Method S (extraction) were applied to different urine specimens from each subject, using staggered series and complex coding; lab personnel blind as to design (1-tailed).

is a more selective confirmatory chromatographic procedure available (Irvine and Anderson, 1965; Irvine et al., 1967; Irvine and Bayne, 1969). What have not been reported heretofore, however, are our experiments to establish the reliability of the 1961 procedure in terms of inter-rater agreement in detecting mauve factor and in rating the amount (spot intensity) on a 9-point scale. The results of these multiple-blind studies showed that the method is in fact highly reliable and shareable. The results are summarized in Table 8-1.

Similarly, interlaboratory tests of the methods have been carried out successfully. Dr. E. Fischer of Buenos Aires confirmed the effectiveness of our methods for distinguishing mauve factor from bufotenine (Fischer et al., 1961). Dr. R. A. Heacock quite early found that at least three components of mauve factor extracted in his laboratory using a different method (Hoffer and Mahon, 1961) were apparently identical with three components extracted by our technique from North Battleford specimens. Sohler et al. (1967) found that our 1961 technique, used in their Princeton laboratory, yielded the same type of chemical and the same diagnostic correlates as

found in Saskatchewan. These tests of validity established the safety of proceeding to clinical correlative studies, even though the compound responsible for mauve factor could not yet be identified.

While experiments designed to identify the mauve factor were underway, simultaneous studies of its diagnostic or clinical correlates progressed in a number of research units, including our own. Consequently, our reported statistical association between mauve factor and psychosis (not specifically schizophrenia) was confirmed by Sohler et al. (1967), and O'Reilly et al. (1965a, 1965b). At least the same trends were observed by Yuwiler and Good (1962) and Ellman et al. (1968), although these two groups were uncertain as to the significance of these observations. Despite their reservations, Yuwiler and Good (1962) have commented concerning mauve factor that "this substance was found in 66 percent of the schizophrenic and 38 percent of the nonschizophrenic populations—the greatest difference encountered [among all the psychochemical tests used]". They were measuring the Reigelhaupt reaction, sulfatoxyskatole, mauve factor, depression factor, and tryptophan. These and additional confirmations (Hoffer and Mahon, 1961; Hoffer and Osmond, 1963) of the association between mauve factor excretion and psychosis were made despite the fact that four different procedures were employed to extract it. While much more could be said about the work of Hoffer and his colleagues, and of the other studies referred to, this chapter will present instead a statistical summary of the results the North Battleford Research Unit has obtained in trying to plot out the dimensions of a syndrome associated with kryptopyrrole (mauve factor) excretion.

The biochemical/clinical associations presented are derived from one or more of several studies. The first involved a series of 62 consecutive female psychiatric admissions, and served to establish the psychiatric relevance of mauve factor. More recent studies were conducted on 90 newly admitted male alcoholics, 42 chronically hospitalized male psychotics, and 68 unselected psychiatric and alcoholic admissions of both sexes.

The measures employed always included our routine estimates of mauve factor and various other biochemical determinations. These were always carried out blind on coded specimens. The clinical measures varied from study to study, and only those yielding statistically significant results can be mentioned in the space available. My colleagues made clinical measures (on a blind basis) in the fields of psychiatry, psychology, ward nursing, electroencephalography, and haematology (Table 8-2).

CLINICAL MEASURES

The excretion of mauve factor (kryptopyrrole) was found to be related to:

Psychosis as routinely diagnosed by senior clinical psychiatrists.

Perceptual disorder as measured by the Hoffer-Osmond diagnostic card-sorting test.

Increased perceptual disorder was associated with mauve factor whether we used our chemical method or the Mahon method.

"*Dissimulating*" *and psychotic personality profile*: dissimulating in the sense of having a high F and low K score on the Minnesota Multiphasic Personality Inventory: psychotic in the sense of having elevated scores for Paranoia and Social Introversion on the same test.

Psychological organicity as measured by Tien's Organic Integrity Test.

Partial disorientation as measured by the Orientation, and Personal and Current Information subscales of the Wechsler Memory scale.

Cooperative behavior observed in mauvuric male chronic psychotics being subjected to EEG procedures including photic stimulation.

In addition to these results, Irvine et al. (1965, unpub. rept.) have derived Minnesota Multiphasic Personality Inventory scales based upon the presence or absence and amount of kryptopyrrole (mauve factor) in a large group of psychiatric inpatients.

The late Dr. O'Reilly, from his very extensive studies of mauve factor excretion by various psychiatric groups and control populations, concluded that mauve factor was certainly associated with psychiatric disturbances, particularly with schizophrenia and "thought changes." Terming the excretion of this compound malvaria following the suggestion of Dr. Hoffer, he wrote (O'Reilly et al., 1965b):

> There is no doubt that malvaria exists, but what is its significance? Our results show that the incidence of malvaria rises with the severity of the disturbance, i.e., from 10.5 percent to 24 percent in disturbed children, 41.8 percent in psychiatric cases to 52.3 percent in schizophrenics. Does malvaria-positive (normal) indicate a latent psychotism? Or just a reaction to stress by a specific group of individuals? Are we indeed dealing with a specific disease entity as predicated by Hoffer and Osmond?

Some of the highly pertinent questions raised by Dr. O'Reilly are still unanswered. Meanwhile, however, certain prognostic and electrophysiological differences between kryptopyrrole-excreting patients and their "same ward" controls have been brought to light.

PROGNOSTIC MEASURES

Within a group of chronic psychotic subjects the prognosis seemed to be related to mauve-factor status. Of 42 patients studied, nine have left the hospital. Only one of these was consistently mauve-factor positive, while two were positive in only one testing, and the other six were completely negative (that is 1 : 2 : 6). The corresponding distribution of mauve factor among those remaining in the hospital was 11 : 8 : 14. Some additional prognostic correlates of mauve factor (kryptopyrrole) excretion may be found in Table 8-3.

TABLE 8-2.

Clinical Measures Relating to Kryptopyrrole (Mauve Factor) Excretion

Results	Subjects		Statistics	P Value
	Number	Type[a]		
I. Kryptopyrrole associated with psychotic diagnosis[b]	56	FAD	Chi-square Yates' corrected	<0.06
II. Detectable excretion of kryptopyrrole (Method NB) associated with personality measures on the Minnesota Multiphasic Personality Inventory[c]				
Elevated *Pa* score	90	MAL	Student's t	0.04
Elevated *F* score	90	MAL	Student's t	0.03
Lowered *K* score	90	MAL	Student's t	0.04
III. Specific MMPI Mauve Factor Excretion subscales, statistically derived from item analysis of MMPI using the LGP-30 and IBM 1620-II computers.				
IV. Kryptopyrrole associated with partial disorientation as measured by two subscales of the Wechsler Memory Scale.				
Orientation subscale				
Method NB first day[d]	42	MCP	Student's t	0.021
Method S second day	42	MCP	Student's t	0.041
Personal and current information subscale				
Method NB first day	42	MCP	Student's t	0.012
Method S second day	42	MCP	Student's t	0.100
V. Kryptopyrrole associated with organicity as measured by Tien's Organic Integrity Test				
Method NB first day[e]	42	MCP	Chi-square	0.040
Method S second day	42	MCP	Chi-square	0.047
VI. Excretion of kryptopyrrole associated with 3 measures of perceptual disorder from the H.O.D. Diagnostic Test				
HOD Total Weighted Score				
Chemical Method NB	81	MAL	t-Test[f]	0.013
Chemical Method NB	42	MCP	Chi-square[f]	0.021
Chemical Method S	42	MCP	Chi-square[f]	0.019
HOD Paranoid Score				
Chemical Method NB	81	MAL	t-Test[f]	0.052
Chemical Method NB	42	MCP	Chi-square[f]	0.033
Chemical Method S	42	MCP	Chi-square[f]	0.038

TABLE 8-2—*continued.*

HOD Malvaria (Mauvuria) Score				
Chemical Method NB	81	MAL	t-Test[f]	0.042
Chemical Method NB	42	MCP	Chi-square[f]	0.057
Chemical Method S	42	MCP	Chi-square[f]	0.037

[a] F = female; M = male; CP = chronic psychotic, chronically hospitalized; AD = consecutive admissions of any age, and including readmissions; AL = alcoholic admissions.
[b] Moderate to marked excretion *US* lesser excretion by method NB; 1-tailed (predicted from mauve factor excretion in LSD model psychosis).
[c] Detectable vs. negative excretion by method NB; all 2-tailed; all consistent in split-half analysis.
[d] Moderate to marked excretion vs. lesser excretion, by two methods: all 1-tailed; kryptopyrrole-positive S's performed worse, as expected
[e] Detectable vs. negative excretion, by two methods; 1-tailed tests.
[f] 1-tailed tests; direction predicted from Saskatoon studies.

TABLE 8-3.

Prognostic Measures Relating to Kryptopyrrole (Mauve Factor) Excretion

Results	Subjects			P Value (Fisher exact P)
	Number	Type[a]		
I. Continuous hospitalization for at least 2½ years post chemistry-test-date				
Chemical Method NB	42	MCP		$< 0.076^b$
Chemical Method S	42	MCP		$< 0.103^b$
II. Spending less than 45% of time out of hospital in the 4 years following chemical testing				
Chemical Method S	42	MCP		$< 0.038^b$
III. Condition on leaving hospital			*Kryptopyrrole negative*	*Kryptopyrrole positive*
Much improved or improved	36	FAD	75%	25%
Recovered but prognosis "guarded", guarded, or poor	18	FAD	56%	44%
IV. Type of separation from hospital	54	FAD	*Kryptopyrrole negative*	*Kryptopyrrole positive*
Discharged			50%	21%
Probated			41%	64%
Not separated in 2½ years			6%	14%
V. Number of days in hospital until first separation			*Negative (means)*	*Positive (means)*
	54	FAD	79 days	87 days
	90	MAL	41 days	54 days

[a] F = female; M = male; CP = chronic psychotics, chronically hospitalized; AD = consecutive admissions of any age, and including readmissions; AL = alcoholic admissions.
[b] 1-tailed; poorer prognosis with excretion of "mauve".

These results are preliminary but further work on prognosis and follow-up measures in relation to biochemical variables seems highly desirable. Other groups are convinced of the prognostic value of kryptopyrrole determinations, but the prognostic impression on discharge may not always reflect the level of this chemical (O'Reilly et al., 1965b).

ELECTROPHYSIOLOGICAL MEASURES

In the course of the interdisciplinary studies outlined earlier, diagnostically (and chemically) blind EEGs were analyzed clinically and by multiple-factor forced-choice card completion. Several EEG anomalies were found associated significantly with kryptopyrrole (mauve-factor) excretion. The EEGs of kryptopyrrole excretors

TABLE 8.4.

Electrophysiological Measures Relating to Kryptopyrrole (Mauve Factor) Excretion

Results	Subject		P Value[b]
	Number	Type[a]	
I. Kryptopyrrole excretion associated with "borderline abnormal to abnormal" EEG			
Chemical Method NB	42	MCP	0.027
Chemical Method S	42	MCP	0.12
II. Moderate to marked excretion of kryptopyrrole associated with certain specific EEG features			
Dominant frequency *not* alpha	40	MCP	< 0.005[c]
	68	MAL	
Dominant frequency is beta	108	MT	< 0.01
Alpha content low or nil	108	MT	0.012
Negative association with paroxysmal response to photic stimulation[d]	187	M&FT	
Delta activity[e]	187	M&FT	

[a] F = female; M = male; CP = chronic psychotics, chronically hospitalized; AL = alcoholic admissions; T = all psychiatric inpatients tested.

[b] Chi-square, 2-tailed.

[c] 2-tailed; but direction obvious and same in both subgroups.

[d] Thus far, all psychiatric patients showing EEG paroxysms in response to photic stimulation are non-excretors of kryptopyrrole.

[e] Thus far, all psychiatric patients manifesting delta activity are kryptopyrrole excretors.

were more frequently abnormal or borderline abnormal, and had low alpha content, high beta content, and sometimes delta activity, but no paroxysmal response to photic stimulation. For details, the reader is referred to Table 8-4, to a report by Irvine and Keogh (1962, unpub.), and the Monty Wyand Memorial Award address by R. P. Keogh (1964). While we are intrigued by the large excess of beta waves associated with kryptopyrrole in our patients, no other laboratory seems to have studied the EEG in relation to this biochemical abnormality.

The electrophysiological *effects* of kryptopyrrole in animals will be covered in a later section.

With convincing evidence of the clinical significance of this biochemical sign (mauve-factor excretion) at hand, it became crucial to determine whether the phenomenon might be due to some artifact. Simultaneously, efforts to chemically identify the factor were redoubled.

Is the Molecular-Clinical Association Due to an Artifact?

MAUVE FACTOR AND DIET, HABITS, AND DRUGS

An association between a metabolite and a psychiatric disorder can arise as a *statistical* artifact (but then it won't be cross-validated), as a *dietary or treatment* artifact (frequent sources of promising "abnormal" compounds in the past), or as a *chemical* artifact (when several substances cannot be distinguished, or when the substance is misidentified).

We have already seen that the association between psychosis and kryptopyrrole (mauve factor) is reproducible. And we have been unable to obtain any evidence that it might be a chemical artifact—it does not arise through ammonolysis, is not produced by the processing procedures, and it is readily distinguished chemically from other urine constituents. Let us therefore turn our attention then to its *source:* can it be from the diet or drugs?

Kryptopyrrole (the mauve factor) either is taken preformed into the body, or is produced there from some precursor. While it is known that tobacco smoke and the aroma of coffee both contain simple pyrroles, trialkylpyrroles (like kryptopyrrole and porphobilinogen, which are associated with mental disorder) have never been reported from these sources (Gianturco et al., 1966). Further evidence for the non-involvement of tobacco and coffee is our demonstration of kryptopyrrole in the urine of subjects who never drink coffee and never smoke. Of course, some other dietary constituents might be implicated as the source of the kryptopyrrole excreted, but we have grossly modified the diet without any effect on the level of this compound. Addition or removal of tea, coffee, or cola drinks, the addition of extra tyrosine or tryptophan, addition of vitamin B complex or vitamin B_{12}, and switching to a Metrecal-and-cream (chlorophyll-free) diet were all tried. In addition, in all our clinical-correlative projects, all the subjects were patients who were provided with the identical diets in the same hospital wards.

Even other manipulations, such as the consumption of several bananas, or the use of effective laxatives, enemas, or enemas plus laxatives, either had no effect, or altered the excretion rate of kryptopyrrole in the direction opposite to that expected if the source were artifactual. The results of manipulating diet and bowel function are presented in Table 8-5.

TABLE 8-5.

Effects of Bowel Function and Dietary Manipulation on Kryptopyrrole (Mauve Factor) Excretion

Results	Subjects[a]	Statistic	P Value[b]
I. "Mauve factor" was significantly decreased or eliminated, by oral administration of broad spectrum antibiotics			
Study 1, easily absorbed antibiotic, "Declomycin"	4 specially selected subjects, studied *longitudinally*	In all four subjects Declomycin reversibly abolished mauve factor excretion	
Study 2, essentially non-absorbable antibiotic "Kantrex"	4 specially selected subjects, studied *longitudinally*	Mann-Whitney U	0.037 0.022 0.0062 0.0037[c]
Study 3, essentially non-absorbable antibiotic "Kantrex"	5 specially selected subjects, studied *longitudinally*	Friedman (overall) Rank Sums Test	< 0.01[d] < 0.025 < 0.05 < 0.025 0.005 < 0.025
II. "Mauve factor" was not decreased by repeated administration of laxatives and/or enemas.[e]	Same individuals as above, but at different times: mineral oil; enema; mineral oil + enema; 3 enema	Rank Sums Test	Not significant
III. Not all indoles were decreased by treatment with oral "Kantrex" with or without enemas etc. Such treatments had no effect on excretion of 5-hydroxy-indole-3-acetic acid or indole-3-acetic acid	5, same individuals as above, simultaneous measurements	Friedman (overall) (a) 5-hydroxy-indole-3-acetic acid (b) indole-3-acetic acid	Not significant < 0.76 Not significant 0.95
IV. Mauve factor levels were relatively little influenced by marked modifications of diet.	1, studied longitudinally and intensively, with daily chemical and clinical observations, over a 13 month period		

DIET SUMMARY TABLE

Treatment	*Effect on mauve factor level*
L-Tryptophan (oral) 2-4-6-10-10-10 grams per successive day	Somewhat lowered
L-Tyrosine (oral) 7 days at 2 grams per day and 7 days at 6 grams per day	Maintained high baseline level
Low protein Diet 21 days	Maintained high baseline level
Folic Acid (oral) 10 mg per day	Lowered
Ascorbic Acid (oral) 600 mg per day	No effect

TABLE 8-5—*continued.*

Vitamin B_{12} (injections) 14 days at 1 mg. 3 times per week, followed by one-half mg. 3 times per week	No effect
"B-Plex" Vitamin B complex preparations (Wyeth) (injections) 2 cc 3 times per week.	No effect

[a] All subjects were male, chronic psychotics, chronically hospitalized, who were known to excrete mauve factor.
[b] Each individual statistically analyzed separately; 1-tailed test.
[c] Inversion.
[d] 2-tailed test.
[e] All treatments aimed at speeding bowel movements tend to increase mauve levels.

The question of whether mauve factor might be phenothiazine metabolites was recently raised by Ellman et al. (1968), and merits special discussion. In their paper, Ellman's group concluded that their results "all point to the likelihood that the mauve spot material noted in the urine of many schizophrenics is a phenothiazine metabolite." In spite of the fact that we had examined this question earlier and had come to the conclusion that mauve factor was not a phenothiazine metabolite (Irvine, 1961), we thoroughly re-examined the question in view of Ellman's rather startling results. I am very grateful to him for his assistance in clarifying the discrepancy between our findings and his, and for arranging the exchange of samples between our laboratories. This work has now been completed and the findings (to be published in detail elsewhere) are as follows:

1. Mauve-factor excretion was not associated statistically with phenothiazine administration when adequate experimental design and correct analytical procedures were used.
2. Ellman's simplified method for mauve factor in urine does extract mauve factor (among other things) and does suffer from interference from phenothiazine metabolites.
3. Split-sample extraction of urine by the two methods (Ellman's and Irvine's), followed by routine one-dimensional chromatography, showed that the addition of chlorpromazine or thioridazine grossly interfered with the routine chromatographic determination of mauve factor when using Ellman's extraction technique, but did not interfere when using ours.
4. Two-dimensional autotransfer chromatography (Irvine and Anderson, 1965; Irvine et al., 1967) of the corresponding urine extracts from the same urines demonstrated some mauve factor *and* considerable amounts of phenothiazine metabolites when Ellman's extraction was used, but at least equal amounts of mauve factor, and *no phenothiazines* when our procedure was used.
5. A pretested "mauve-factor positive" urine extract from Ellman's laboratory revealed no mauve factor, but did show considerable amounts of phenothiazines when tested by autotransfer chromatography.

6. In a joint work with Dr. M. Galambos, a blind study of continuously institutionalized mentally retarded individuals revealed that four out of the five "strong producers" of mauve factor had never had even a single dose of any phenothiazine.
7. We have extracted, purified, and identified mauve factor from urine of chronic psychotic patients who have not had any phenothiazines for at least one year.
8. We have identified mauve factor (Irvine et al., 1969b; Irvine et al., 1970) as kryptopyrrole (2,4-dimethyl-3-ethylpyrrole), and it is exceedingly difficult to see how this molecular structure could arise from the phenothiazines.

On the basis of this evidence we may conclude that if adequate chromatographic procedures or selective extraction techniques are applied, highly specific tests for mauve factor (kryptopyrrole) will result, and there will not be confusion with phenothiazine metabolites. Kryptopyrrole (mauve factor) is *not* a phenothiazine metabolite.

As we have just seen, particularly powerful independent evidence regarding the source of a metabolite may be forthcoming from *identification of its molecular structure*. Some structures simply cannot arise from specified drugs or normal food. Several other advantages also attach to the identification of any molecular anomaly relevant to psychiatric disorder, and some of these will be indicated in the next section on the identification of mauve factor as kryptopyrrole.

What is the Molecule Involved?

WHAT IS THE MOLECULAR STRUCTURE OF MAUVE FACTOR?

Early attempts to identify the factor were hampered by its extreme sensitivity to mild procedures but, on the basis of the chromatographic properties and an extensive battery of color reactions with unsaturated aldehydes (*with* D. E. Smith, 1960, unpub. rept.), it was concluded (Irvine, 1960) that mauve factor was most probably a mixture of "pyrroles . . . probably alkylated on one of the α-carbon atoms." Further studies showed that it was heterogeneous, though difficult to resolve (Irvine, 1961). It was not until autotransfer chromatography was developed (Irvine and Anderson, 1965) that it was possible to clearly and routinely separate mauve factor into its five components. The autotransfer chromatograms of the factor yielded a *characteristic pattern* of five spots which stained identically. This pattern was reported (Irvine et al., 1967; Irvine et al., 1969a), but it proved impossible to match any or all of its components until we investigated the urinary metabolites of rats given intraperitoneal injections of synthetic pyrroles. Detailed analysis of the resultant autotransfer chromatograms led to the testing of kryptopyrrole, and the "metabolites" of this compound uniquely and completely matched the pattern or

"fingerprint" established by the natural mauve factor. It soon became clear that passage through the animal was not essential, and that a solvent effect (particularly the influence of water) was the critical element. Many experiments, to be reported elsewhere, revealed that all five components of the mauve factor were spontaneously interconverting forms of kryptopyrrole (2,4-dimethyl-3-ethylpyrrole). Finally, in collaboration with Dr. J. R. Majer of Birmingham, Great Britain, we established by high-resolution mass spectrometry that (1) mass peaks due to kryptopyrrole were present in urine extracts from mauve factor positive urines, but absent from negative urine extracts, and (2) the mass spectrum of "mauve factor component 1" was identical with that of an aqueous solution of pure synthetic kryptopyrrole (Irvine et al., 1969b; Irvine et al., 1970).

Mauve factor is, then 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole). Identification of such a previously unknown compound should not only rule out some sources, but also suggest its origin, allow studies of its metabolism, and make it possible to test it

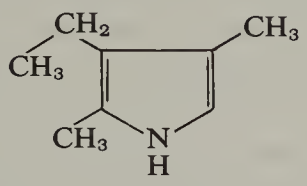


FIGURE 8-1.
The kryptopyrrole molecule ("mauve factor").

for pharmacological and behavioral activity. The identification should also materially help clear up any previously puzzling chemical behavior of the "unknown," while facilitating rigorous inter-method, inter-laboratory, inter-project and inter-period comparisons of extracts and results.

While most of the new work recently made possible by the chemical identification of mauve factor has yet to be done, some preliminary work and prospects for the future will be outlined in a later section. Extensive work utilizing our new knowledge of the molecular structure of mauve factor has already been completed, however, in the areas of establishing the broad comparability of mauve factor as studied at different times, places, and with different methods, and in explaining the sometimes puzzling chemical and chromatographic behavior of mauve factor.

By 1969 there was no doubt about the identification of mauve factor as currently studied in our particular laboratory, but it was necessary to establish that the mauve factor extracted by other methods in other laboratories was also kryptopyrrole, and that we had not strayed from the operationally defined mauve factor of our original work (Irvine, 1961).

Thus, in order to determine whether mauve factor extracted from urine using different procedures in other laboratories might yield a pattern different from that observed with kryptopyrrole, an extract from many mauve factor-positive subjects was obtained from an independent laboratory using the Hoffer and Mahon method

of extraction. This pool, prepared mainly from mentally disturbed individuals, showed precisely the same pattern of five spots on autotransfer chromatograms as did kryptopyrrole. A second extract prepared by the same method but from mauve-factor-positive mental retardates was obtained from a third laboratory, and this concentrate, too, did not yield any mauve-factor components outside the well-established pattern. To be certain that the components of mauve factor recently described on autotransfer chromatograms were actually due to mauve factor as defined in early work, samples of mauve factor extracted and purified by us in 1959 and 1960 and continuously deep-frozen since then were subjected to autotransfer chromatography (ATC). All five components were evident; those samples considered "cleanest" in 1959–1960 proved now to be those with the greatest relative enrichment of the typical mauve-factor-component spots, as compared with other metabolites. Finally, Ellman's method (Ellman, 1968, personal commun.; Ellman et al., 1968), was applied in our own laboratory to urines from mauve-positive individuals, and these extracts too yielded *inter alia* the characteristic spots on ATC. Clearly, the pattern of spots described is characteristic of mauve factor extracted by a variety of procedures and corresponds in all known instances to that obtained when kryptopyrrole is processed.

While the various procedures designed to extract mauve factor from urine *do* in fact extract kryptopyrrole, monitoring these extracts has sometimes given puzzling results. The availability of pure synthetic mauve factor, following its positive identification, has allowed the exploration of anomalous chemical and chromatographic behaviors previously noted.

The early reports suggesting that mauve factor was heterogeneous or a mixture of closely related compounds were based on slight differences in paper chromatographic behavior in early solvent systems. It is now known that several forms of kryptopyrrole can chromatograph to the same position, while some other forms travel slightly farther in the routine isopropanol-ammonia-water system. These forms are more readily separated in Reio's system D (Reio, 1958), by thin-layer systems, or by autotransfer chromatography. Nevertheless, work with synthetic kryptopyrrole shows that all of the heterogeneity is due to a rather unique interconverting set of "forms" of this *one compound.* The chemical details of this phenomenon will appear in other publications.

Correspondence with other laboratories engaged in the chemical characterization of mauve factor and the exchange of samples with these laboratories has repeatedly demonstrated peculiarities in the behavior of mauve factor. One of the most confusing and disturbing properties of mauve-factor concentrate has been the apparently spontaneous disappearance and reappearance of the mauve factor. This peculiarity was especially prominent in early thin-layer chromatography work on mauve factor, both in our North Battleford laboratory and in Dr. R. A. Heacock's laboratory. We have now demonstrated that this odd behavior is due to the ready interconversion of

components of extracted kryptopyrrole. In early work on thin layer chromatography, a particular component of mauve factor was (mistakenly) considered to be *the* mauve factor. On storage in deep freeze or in shipping, this component was sometimes converted into another form (component), but since we had assumed that the first spot was *the* mauve factor, it had, to any worker at that time, "disappeared." Since such mild procedures as adding distilled water are sufficient to cause components to convert or revert to another form (component), and since one of these was thought to be *the* mauve factor, mauve factor would at times "spontaneously reappear."

All of this behavior of mauve factor is exactly duplicated by synthetic 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole) subjected to the same conditions (Irvine et al., 1970).

Another important early difficulty was the virtual impossibility of demonstrating that mauve factor was a simple pyrrole. This was due to (1) the alteration of kryptopyrrole's chromatographic properties by extremely mild pretreatments, and (2) the movement of *kryptopyrrole exposed to water* to a chromatographic position in Reio's systems that was characteristic of highly polar amides, glycols, and enols. This position was distant from that occupied by the simple neutral indoles, aromatic hydrocarbons, and expected for simple pyrroles. The reasons for this highly anomalous position of kryptopyrrole "component 1" are still conjectural, but it is now known that this component is the ether formed by a reversible reaction between two molecules of kryptopyrrole and water.

This brings us to the end of Phase I, the correlative and validity-checking phase of the work. Perhaps a summary of the current status of our knowledge of kryptopyrrole is in order before proceeding to consider causality, broader contexts, and the future of kryptopyrrole.

End of Phase I—Current Status of Our Knowledge Regarding Kryptopyrrole (Mauve Factor)

In Phase I, we addressed ourselves to three general questions: Is there a molecular anomaly associated with a mental illness? Is the association due to an artifact? What is the molecule involved?

We saw that psychotic patients differ from nonpsychotic psychiatric patients and normal controls in the incidence of what has been called mauve factor. This metabolite, discovered by chemically monitoring experimental LSD model psychoses, and subsequently found in psychotic patients who had never had psychedelic drugs, possessed a number of clinical correlates which have been presented and summarized. In brief, it may be seen that kryptopyrrole excretion is associated not only with a psychotic diagnosis, but also with measures relating to perceptual disturbances and

bizarre experiences, as well as to electrophysiological peculiarities, and a poorer prognosis. The biochemical abnormality has been explored not only in terms of clinical and paraclinical correlates but also in terms of factors influencing its excretion, possible artifactual origins, and chemical structure. Diet, activity, constipation, smoking, and psychotherapeutic drugs seem to have very little bearing on excretion levels.

The validity of the association between psychosis and mauve factor and of the methods used to extract and detect it have been confirmed, especially by Sohler's group in New Jersey. The conjecture that mauve factor might be due to phenothiazines was based on oversimplification of procedures, and has been refuted.

Finally, mauve factor was found to be 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole).

Now that a specific compound is associated reliably with psychotic disorder, and its molecular structure is determined, what is the next step? Do we immediately seek to eliminate the compound from the body, or search for an antidote? That logically depends on the causal mechanism underlying the molecular/clinical association.

PHASE II—CAUSAL MECHANISMS UNDERLYING THE ASSOCIATION

Kryptopyrrole and Psychotic Disorder

Not only the detailed, but even the general mechanism responsible for the association between kryptopyrrole and psychotic disorder remains unknown to-day. Figure 8-2 illustrates the four basic causal pathways which can explain a given, stable association of this type. They are:

1. The chemical produces the clinical abnormality.
2. The clinical abnormality produces the specific chemical.
3. It's a vicious circle.
4. Some unknown "third factor" produces both the clinical abnormality and the chemical one.

Such mechanisms are themselves gross oversimplifications, but they do suggest graphically the profoundly different therapeutic approaches appropriate to the different causal paths which may produce an observed association between a chemical abnormality and a corresponding clinical disorder.

Specifically, for kryptopyrrole's association with psychosis we have so far no clear evidence favoring any one of these four mechanisms over the others. It is just as likely that psychosis produces kryptopyrrole as that the converse is true. Obviously this is

an unsatisfactory situation which clearly indicates the priorities for future research on kryptopyrrole in molecular psychiatry. We must concern ourselves with uncovering the mechanism which causes kryptopyrrole and psychosis to co-occur. We must also keep in mind the whole man—not just the disease process he presents. Even if the abnormal mental functioning or behavior were to cause the production of kryptopyrrole, this compound might still have important effects on the functioning of other organ systems, and might impair physical health (see Figure 8-2, causal pathway A).

In many ways, this work on causal mechanisms is more difficult than the correlative and validity studies. A number of approaches are available but none is sufficient alone. Longitudinal blind studies of excretion levels and mental functioning (both

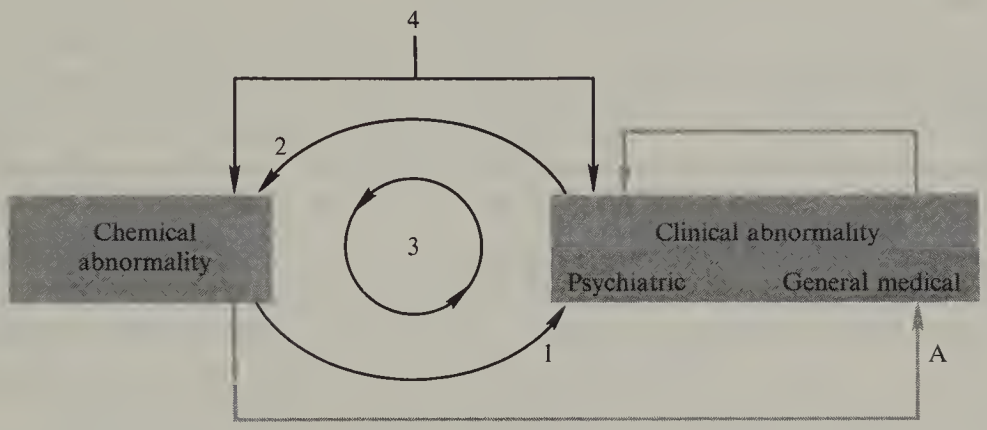


FIGURE 8-2.
Causal mechanisms which may underlie clinical/chemical associations in psychiatry.

within the acute illness, and prospectively in the community) with careful analysis of time relationships will be useful. So would therapeutic trials of agents selected to eliminate kryptopyrrole, and trials of kryptopyrrole or its precursors in volunteers when more data become available on its toxicity and behavioral effects in animals. Trials of kryptopyrrole should be monitored not only from a clinical psychiatric and perceptual point of view, but also electrophysiologically. Further, it will be necessary to properly quantitate kryptopyrrole in these studies, to determine chemically whether it crosses the blood-brain barrier, and to establish where it may occur in the brain. However, antecedent occurrence of one element in a correlated pair of parameters does not prove it is causal; successful therapy based on a causal theory does not prove that theory; animal results may not generalize to human disease; acute administration of kryptopyrrole to volunteers may not mimic the possible effects of its long-term presence in those who have become psychotic; dosage effects or local accumulation may be critical; and presence of the compound in brain structures does not prove it acts there. Nevertheless, a *combination* of these approaches should

produce a fairly adequate understanding of the causal mechanism underlying the association between kryptopyrrole and psychosis. These approaches to general causal and molecular mechanisms should be most productive if kryptopyrrole is first placed in as broad a biochemical context as possible.

Relationships of Kryptopyrrole to Other Molecules in Psychiatry, Medicine, and Biology

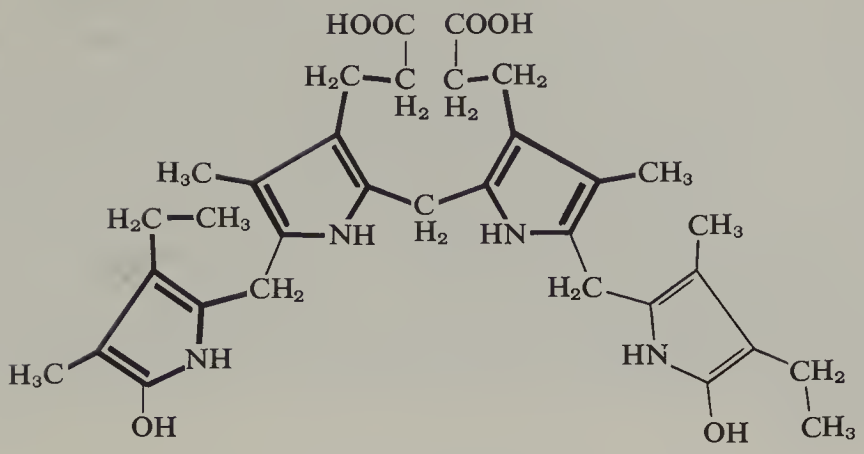
Naturally the first question which arises is, What connection is there between kryptopyrrole and the other compounds now associated with schizophrenia or psychotic disorder, or between kryptopyrrole and various theories in biochemical psychiatry? In a word, there is apparently very little connection. There are, however, some exceptions. First, one can *on paper* expel C_6 from 6-hydroxyskatole or its sulfate ester (a well-known correlate of psychotic disorder) and get kryptopyrrole. Second, the diffusible micromolecule bound to protein and responsible for the various biological activities noted for taraxein-like substances might conceivably be kryptopyrrole. While the kryptopyrrole molecule does bear two methyl groups, it appears unlikely that these have much to do with the excessive or abnormal methylation postulated as a factor in psychotic disorders. Similarly we have no definite evidence to relate kryptopyrrole to the metabolism of adrenalin, dimethoxyphenylethylamine, *p*-tyramine, bufotenine, or creatine phosphokinase. There is just as much evidence to relate this pyrrole to the old view of "auto-intoxication" from intestinal compounds.

But much more striking is the molecular resemblance of kryptopyrrole to all the psychoactive indoles and to various pyrroles already implicated in mental disorder or mental retardation. These *formal* relationships are depicted in Figure 8-3.

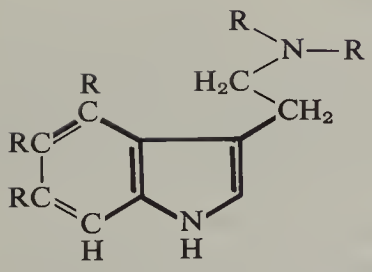
OTHER PYRROLE ABNORMALITIES RELATED TO MENTAL FUNCTIONING

The kryptopyrrole nucleus, being present in hydroxyskatoles, psychotomimetic tryptamine derivatives, LSD, bilirubin, porphyrins (and, modified, in vitamin B_{12}), places this compound in an area of biochemistry singularly rich in established psychiatric correlates.

There is little doubt now that the excretion of kryptopyrrole is associated significantly with psychotic disorder, and in this connection it is interesting to ponder the known psychiatric correlates of metabolic insults involving various compounds containing the kryptopyrrole moiety (Figure 8-3). Thus a high level of bilirubin (one source of synthetic kryptopyrrole) is thought to cause kernicterus in the neonate and resultant mental retardation. Hematoporphyrin is an active antidepressant excitant (Angus, 1936; Huhnerfeld, 1936; Steinberg, 1936) but, like bilirubin, it has an affinity for neurones and may cause extensive damage to them. In acute intermittent

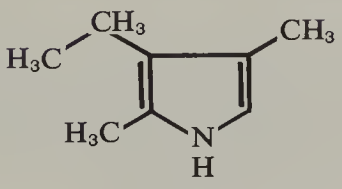


Mesobilirubinogen

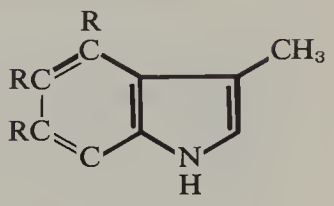


Psychotomimetic Tryptamines

R = H, OH, or OCH_3

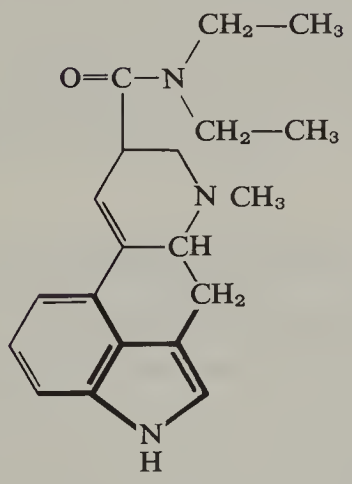


Kryptopyrrole



Hydroxyskatoles

R = H or OH



L.S.D.

FIGURE 8-3.
The kryptopyrrole structure within molecules related to brain dysfunction.

porphyria, excessive excretion of porphyrins, particularly those which consist basically of kryptopyrrole tetramers, is related to psychiatric disorder (Sourkes, 1962, pp. 188–197). Other disturbances of porphyrin metabolism have been reported in schizophrenics (Huszák and Durkó, 1968). Interestingly, a deficiency of the related

structure, cyanocobalamin or vitamin B_{12}, is likewise frequently associated with psychiatric difficulties (Sourkes, 1962, pp. 225–234; Douglas-Wilson, 1965).

In more general terms, pyrrole has been called a nerve poison (Corwin et al., 1960), and a relationship between the bile pigments and mood disorders was suggested by Polybus as early as 380 B.C. Finally, Heinrich Klüver has described regional differences in the distribution of porphyrins within the human brain (Klüver, 1944a, 1955) and has suggested (1944b) that ". . . certain neurological and psychiatric disorders may be due to or associated with a 'cerebral porphyria' or a disturbance of the metabolism of certain pyrrole compounds in the nervous system."

Work on the mechanism linking kryptopyrrole to psychotic disorder is strongly indicated.

OTHER SIMPLE PYRROLES RELATED TO HUMAN DISEASE

We have already noted that porphobilinogen, a key compound in the psychiatric disorder Acute Intermittent Porphyria, contains the pyrrole nucleus. However, this substance bears an even closer molecular similarity to kryptopyrrole, in that both compounds are 2,3,4-trialkylmonopyrroles.

Recently, the Wakayama group has identified two compounds (Yamaguchi et al., 1966) which they previously showed to associate primarily with collagen diseases (Nishimura et al., 1966, 1967). The compounds are pyrrole-1,2-dicarboimide and pyrrole-1,2-dicarbamide. The association of these monopyrroles with this group of connective tissue disorders is not yet understood.

In sum, then, four different oligo-alkylmonopyrroles are known to be associated with human diseases.

OTHER NATURALLY OCCURRING MONOPYRROLES

Apart from porphobilinogen (which is extremely widely distributed in living organisms) and perhaps pyrrole-2-carboxylic acid (Radhakrishnan and Meister, 1957), the occurrence of monopyrroles seems to be very sporadic. We have been unable to find kryptopyrrole in any species other than man tested thus far, and our series has included a number of primates. The only other animal species well known to produce monopyrroles are certain of the butterflies (Meinwald and Meinwald, 1966; Meinwald et al., 1969). Like kryptopyrrole, the butterfly compound is tri-substituted, but at positions 1, 2, and 3, rather than at 2, 3, and 4. Unlike kryptopyrrole, two of the side-chains unite to form a secondary ring. This interesting compound plays a definite role in chemical communication between individuals during courtship, and thus Pliske and Eisner (1969) with Schneider and Seibt (1969) have established that this monopyrrole is the pheromone of such butterflies as *Lycorea ceres ceres*.

Another biologically occurring monopyrrole is the substance pyrrolnitrin, studied

by Gorman et al. (1968). This pyrrole is an active antifungal substance produced by several species of *Pseudomonas*. Finally, it may be recalled that some other monopyrroles exist either preformed or in the processed material from tobacco and coffee (Morton, 1946; Schofield, 1967; Gianturco et al., 1966), but these have not been demonstrated in human urine and do not belong to the class of compounds (trialkylmonopyrroles) which are related to human psychiatric disorder.

Curiously, virtually all the known natural monopyrroles are associated with human disease, or are present in a psychoactive preparation used by man, or are involved in chemical communication between individuals. Such is the broad biomedical context of kryptopyrrole; this, combined with the results presented earlier, can form a basis for new work.

The Next Steps

Assignment of the specific kryptopyrrole molecular structure to the so-called mauve factor and its synthesis in the laboratory open the door to a comprehensive evaluation of its involvement in clinical psychiatry. Some questions which followed immediately on its identification were

1. Does it resemble other chemicals with known relevance for brain function?
2. What is its source?
3. Is it pharmacologically active, behaviorally active, or psychoactive?
4. Does it affect brain electrical activity?
5. What happens when it is blocked or eliminated?

The first question has been answered (Figure 8-3); the remaining four form the bases for the next segment of the work on kryptopyrrole. One prerequisite, however, is the availability of quantitative analytical methods and a more complete understanding of the complex chemistry of this pyrrole.

CHEMISTRY

While refinements are still being made to the analytical methods for the determination of kryptopyrrole (mauve factor), there already exists a highly reliable semiquantitative selective procedure, which has been documented extensively (Irvine, 1961, 1965; Irvine et al., 1967; Irvine and Bayne, 1969). Although the best method available at this time differs but little from the one originally published (Irvine, 1961), several important points should be re-emphasized. First, because of the sensitivity of pyrroles to acetone, we now avoid the use of this solvent and replace it with methanol throughout our procedures. Second, simplification of the procedure can

easily lead to invalid results (Ellman et al., 1968). Third, the general clinical correlates, the pyrrolic nature of the material extracted, and the freedom from interference by phenothiazines have all been confirmed by Sohler et al. (1967) using our method in their New Jersey laboratory. Fourth, the general statistical adequacy of this semi-quantitative method for kryptopyrrole was demonstrated in Table 8-1.

Fifth, because autotransfer chromatography (Irvine and Anderson, 1965; Irvine and Bayne, 1969; Irvine et al., 1967, 1970) is so much more selective than the classical isopropanol-ammonia-water system, we routinely check urine extracts using this newer method in addition to the original chromatographic procedure. Finally, it is our intention to develop fully quantitative procedures for this compound in biological samples utilizing the extraordinary simplicity, selectivity, and sensitivity of the high-resolution mass spectrometric integrated ion current (IIC) technique of Majer and Boulton (Jenkins and Majer, 1967; Boulton and Majer, 1970; Majer et al., 1970). Such improvement to, and the automation of, the measurement of kryptopyrrole will facilitate its application in mental health screening programs, prospective community surveys, family studies, and psychiatric inpatient and outpatient investigations to further determine its distribution, predictive value, and therapeutic applications.

Other chemical work will be directed toward measurement of kryptopyrrole and related compounds in tissues, and toward a better understanding of this substance from the point of view of physical chemistry and molecular architecture (Pauling and Hayward, 1964).

BIOCHEMISTRY, AND THE SOURCE OF KRYPTOPYRROLE

The extraordinary reactivity of the kryptopyrrole molecule, coupled with its lack of functional groups, makes it unusually difficult to study "truly biochemical" reactions which might utilize this compound as substrate. By the same token, however, this unusual reactivity of the free alpha position suggests that kryptopyrrole may react even nonenzymatically with various sensitive chemical groups of macromolecules and intermediary metabolites.

Only a few clues exist concerning the biosynthetic pathways involved in the production of kryptopyrrole. The main clues are (1) the highly characteristic molecular structure itself, and (2) our observations that nonabsorbable oral antibiotics sharply decrease or eliminate the excretion of kryptopyrrole in the urine of patients producing this compound.

If kryptopyrrole is produced in the body, it is either via catabolism of pre-existing pyrrole compounds, or through anabolism from simpler, nonpyrrolic substances. If the source is catabolic, it is plausibly from bile pigments (including the dipyrroles, "probilifuscins," "bilifuscins," and "propentdyopents"), or from the porphyrins and heme-type prosthetic groups of hemoglobin, myoglobin, catalase, or cyto-

chromes. Because there would have to be considerable rearrangement or modification in order to yield kryptopyrrole, we believe that both porphobilinogen and vitamin B_{12} are less likely precursors. Alternatively, kryptopyrrole may be built up from simpler fragments, possibly from an acyl CoA plus glycine, or from aminoacetone plus pentanone-2 (decarboxylated β-ketocaproic acid), or even from a substituted levulinic aldehyde and ammonia. Other conceivable sources might be hexosamine residues, sialic acid, tryptophan (via the integral pyrrole ring or by a Gorman cyclization), proline, and hydroxyproline, but all of these would require very extensive biochemical alteration before they would yield kryptopyrrole. Finally, the loss of C_6 from skatole, followed by reduction, is a remote but interesting possibility, particularly since 6-hydroxyskatole has already been implicated in psychosis.

One phase of this biochemical work on the source of kryptopyrrole will be based on our observation (Irvine, 1963) that its excretion can be abolished or greatly lessened by oral administration of nonabsorbable antibiotics. Hence, considerable energy will be devoted to the microbiological aspects of the kryptopyrrole problem. It seems that one of the necessary (but probably not sufficient) conditions for the excretion of kryptopyrrole is some antecedent or precursor step involving the intestinal tract; this might be either a reductive splitting and decarboxylation of existing tetrapyrroles, or a biosynthesis from simpler nonpyrrolic substances.

Since we have been unable to find any animal which produces kryptopyrrole, we are somewhat limited in the biochemical experiments which can be performed. Yet much can probably still be deduced from monitoring kryptopyrrole in patients administered selected enzyme inhibitors, cofactors, and presumed precursors. Such studies are under way, and will be supplemented with isotopic tracer procedures. Tracer experiments should rapidly answer such questions as the origin of kryptopyrrole, its distribution in the various organs and in substructures of the brain, its subcellular distribution, and its protein binding patterns.

PHARMACOLOGY

Toxicology. The simple monopyrroles have long been known as toxic substances (Saccardi, 1922; Rabbeno, 1929, 1930; Rezek, 1937). These early authors emphasized that the predominant effects were upon the lungs and central nervous system, and Corwin et al. (1950) have called pyrrole a "nerve poison." Yet it was not until very recently that the toxicology of trialkylpyrroles was investigated. Thus, Moffett (1968) was the first to report a quantitative estimate of kryptopyrrole's toxicity; he found a screening LD_{50} of 77 mg/kg in the mouse. More recently, using the method of Weil (1952), we determined the MLD_{50} for this compound in rats of the Wistar strain; it approximated 60 mg/kg. Both in our own work and in that of Williamina Himwich (1969, personal commun.) a delayed as well as an acute toxicity was obvious, and the predominant involvement of the lungs and central

nervous system was confirmed. An important "next step" will be to determine the exact mechanisms of kryptopyrrole's toxicity.

PSYCHOPHARMACOLOGY

Early work on simple pyrroles, including that of Rabbeno (1929) and Rezek (1937), showed that a prime target of these substances was the central nervous system, and the latter author produced both histological and behavioral evidence of neurotoxicity for the parent compound *pyrrole*, bringing us clearly into the area of psychopharmacology.

Behavioral activity of kryptopyrrole was apparently first described by Moffett (1968), who reported it to be a depressant and anticonvulsant. Moffett's gross observation that it "depresses" rodent behavior has been amply confirmed by our own findings. Our controlled studies showed that injection of this compound produced a huddling, inactive rat, with narrowed palpebral fissures. Nevertheless, the animals were very easily alerted. Subsequently, we have found that kryptopyrrole can reduce exploratory behavior in an open field situation, can reduce activity as measured in a simple activity wheel, but may not interfere significantly with the performance of an overlearned maze task. Further work with G. Zdanivsky (1969, unpub. rept.; Irvine and Zdanivsky, 1971), using various operant conditioning schedules, shows that kryptopyrrole is indeed behaviorally active at nontoxic dose levels.

PHARMACOLOGY OF SENSORY ORGANS

In our studies with Dr. N. P. V. Nair on the pharmacology of sensory organs, we have been checking the effects of kryptopyrrole on the eye. Confirming Himwich's observation of unilateral effects of unilateral carotid injections of kryptopyrrole, we have found in rats an enophthalmos and pupilary paralysis strongly predominant on the same side as the injection, although we did not find the edema which was the characteristic unilateral response observed in Himwich's dogs. The mechanisms of this eye effect may prove a rewarding facet of future work with kryptopyrrole in molecular psychiatry.

ELECTROPHYSIOLOGY AND ELECTROENCEPHALOGRAPHY

The fact that kryptopyrrole excretion in psychiatric patients is related to abnormalities of their EEG prompted us to start investigations of the effects of this compound on the brain electrical activity in experimental animals. The pilot work was done in

collaboration with Dr. Williamina Himwich[2] of the Galesburg State Research Hospital (telemetered EEG in dogs), and with Dr. Ewart Davies of the Neurocommunications Research Unit, Birmingham, England (neurone studies using the microtap of Whitfield and Comis, 1966, and Comis and Davies, 1969). The work in dogs has been impeded by their marked toxic reaction to kryptopyrrole, but in spite of this, Himwich (1969, personal commun.) has been able to show in preliminary experiments that a very early slowing of the EEG is produced, commencing about 15 minutes after injection and continuing for about 4 hours.

The microelectrode work at Birmingham has already shown that kryptopyrrole lowers the neural activity of some brain-stem structures when applied topically, and also inhibits single neurones of the cat cochlear nucleus in quite low concentrations.

More recently, in collaboration with R. P. Keogh of this unit, we have initiated electroencephalographic studies of rats given kryptopyrrole. Preliminary observations suggest that this compound may produce generalized slowing, increased amplitude, and an increase in frank beta activity in occipital areas. To maximize the information obtainable from the EEG measures, we are collaborating with Dr. G. Marjerrison in the application of a Drohocki (1948) type integrator (Goldstein et al., 1963a, 1963b), and anticipate A/D signal conversion followed by analysis on digital computers. Much further work is indicated to extend these experimental findings, and to determine their precise relationship with the EEG features characteristic of kryptopyrrole-excreting patients.

EXPERIMENTAL THERAPY

One technique for lowering or eliminating the excretion of kryptopyrrole is already known (Irvine, 1963). It has been tried (without producing any marked clinical change) in chronically ill schizophrenic patients, but needs repeating with acute cases, and using detailed blind ratings of these patients behaviors and psychiatric symptoms, paired daily with coded urine specimens for quantitative kryptopyrrole determinations.

Therapeutic responses to megavitamin therapy (Hoffer and Osmond, 1963; Pauling, 1968) and to drugs structurally analogous to kryptopyrrole should also be assessed as a function of the patient's initial kryptopyrrole status.

The five immediate steps just summarized should shed new light upon the mechanism linking kryptopyrrole excretion with psychotic disorder. Logically, they lead directly to Phase III in our molecular psychiatry schema, that is, to the clinical applications of this research.

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[2] I am indebted to Williamina Himwich and Ewart Davies for conducting the electrophysiological experiments using kryptopyrrole in their laboratories.

PHASE III—CLINICAL APPLICATIONS

Mauve factor has many significant psychiatric correlates; it is not an artifact, and it has the specific molecular structure of 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole). Although the causal matrix underlying its relevance to psychiatry is still under active study, we can already look forward to clinical applications. In this third phase of the work, we are concerned with how the information about kryptopyrrole can best be used, whether in therapy, in rehabilitation, or in prevention.

How Can the Information About Kryptopyrrole Best be Used in Therapy?

Owing to our basic research orientation we are probably not a group best qualified to answer this question. But from this viewpoint, I would say that kryptopyrrole, although perhaps not pathognomonic of a specific disease, is certainly a *sign* statistically associated with psychotic disorders. Kryptopyrrole determinations in psychiatry may be analogous with clinical thermometer readings in physical medicine; they do not diagnose the disease, but are very useful in the differential diagnosis and in following the clinical course of many cases.

Once we know the type of causal relationship between kryptopyrrole and psychotic disorder, we should be in a position to make more discerning therapeutic use of this specific chemical measure.

How Can the Information About Kryptopyrrole Best be Used in Rehabilitation?

It appears fairly clear that kryptopyrrole is associated with a poorer psychiatric prognosis. Nevertheless, it would be unfortunate indeed if this measure, in our present state of ignorance concerning mechanisms, were to be used prematurely in clinical settings to select patients "with an unfavorable prognosis."

How Can the Information About Kryptopyrrole Best be Used in Prevention?

At the present, we simply do not have nearly enough information. We must know which is cause and which is effect—what conditions are necessary, and what sets of conditions are sufficient—for kryptopyrroluria and psychotic disorder. We must

also conduct long-term prospective studies to determine differential risk. Integrated genetic/biochemical family studies, along with a careful assessment of possible *beneficial* effects or correlates (individual or societal), will have to guide any decisions relating to kryptopyrrole in primary prevention.

SYNOPSIS

The purpose of this chapter was to illustrate one approach in molecular psychiatry, using the story of mauve factor (kryptopyrrole) as an example. Some goals, strategies, steps, and results were presented, followed by a review of our current knowledge of kryptopyrrole in psychiatry, its relation to other compounds in biology and medicine, and prospects for the future. Some of the aims and strategies of the program described are:

1. To unify in a single conceptual framework, investigations on the biochemistry, genetics, and drug responses of persons with psychiatric disorders.
2. To stress the individual differences in molecular constitution (Williams, 1951, 1959) which may influence the development, onset, severity, duration, treatment response, prognosis, and recovery from a psychiatric disorder.
3. To invert the classical approach of looking for molecular differences between clinically defined groups, and thus to use selected molecular tests to *define* the groups, and *then* look for clinical differences related to these molecules.
4. To establish one or more molecular tests of value in the prediction of clinically relevant parameters for groups of patients or individual patients.
5. To avoid simplistic use of "cause," and to apply the concept of "necessary and sufficient conditions" instead, thus avoiding any premature or undue emphasis on molecular intervention as the only means of treatment for mental illness.

From the results of this program and related studies we know that mauve factor is kryptopyrrole and that excretion of kryptopyrrole is significantly associated with psychosis, unusual EEG, and a poor prognosis. We know that this pyrrole bears formal structural similarities to several series of biochemicals already implicated in mental dysfunction. And its source is not the phenothiazines. Additionally, current *experimental* indications are that kryptopyrrole is, in fact, toxic, behaviorally active, and effective in altering neuroelectrical activity. To the question, "What is its etiological significance?" the answer must still be, "We do not know." When we consider the complex biology of psychotic disorder, we must admit that despite the emphasis on the physicochemical substratum inferred from "molecular psychiatry,"

there is surely a very valid place for environmental and sociological factors in this field. Indeed, the question of interaction between the individual's social environment and the molecular substratum of his brain may open up a whole new field of clinical investigation.

Only further study will determine whether kryptopyrrole measurements can contribute substantially to the ultimate goal of orthomolecular psychiatry, which is the serious application of individual differences at the molecular level in order to establish the optimum biochemical substratum for the best medical-psychosocial functioning of each patient.

ACKNOWLEDGMENTS

I am particularly indebted to Dr. A. N. Payza for introducing me to this fascinating topic, and for teaching me all that was known about this subject in the earliest phase of this work, even before the "unknown spot" had been named "mauve factor."

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9

Biogenic Amines in Schizophrenia

EDMUNDO FISCHER

The discovery of the biogenic amines present in the central nervous system opened a new chapter in neurophysiology and pathology. The relationships of the most important amines, such as catecholamines and serotonin, to normal and pathological functions of this system have been studied with different biochemical and pharmacological methods. The selective localization of these amines in cerebral structures related to vegetative regulations and emotive responses gave some clues to the character of their activity. Additional pharmacological studies demonstrated interactions of cerebral amines in the psychopharmacological effects of reserpine, the phenothiazines, aminooxidase inhibitors, and other antidepressive and neuroleptic drugs.

New bases for research work on biogenic amines and behavior were created by the working hypothesis of Brodie and Shore (1957), which postulated that the ergotropic and trophotropic systems of the diencephalon governing basic behavior (Hess, 1949) depend on catecholamines and serotonin, respectively, as neurohumoral agents (chemical mediators). We shall not discuss this hypothesis here and mention it only

because it retains its basic significance, even though some corrections seem to be necessary (Fischer et al., 1967; Dewhurst, 1968).

Quantitative or qualitative changes, material or functional, of cerebral biogenic amines may also play an important role in the pathogenesis of certain mental and nervous diseases, or at least in the production of some of their symptoms. Arguments for such a postulate are based on the fact that antipsychotic drugs act through biogenic amines, and also on the important circumstance—considered first by Osmond

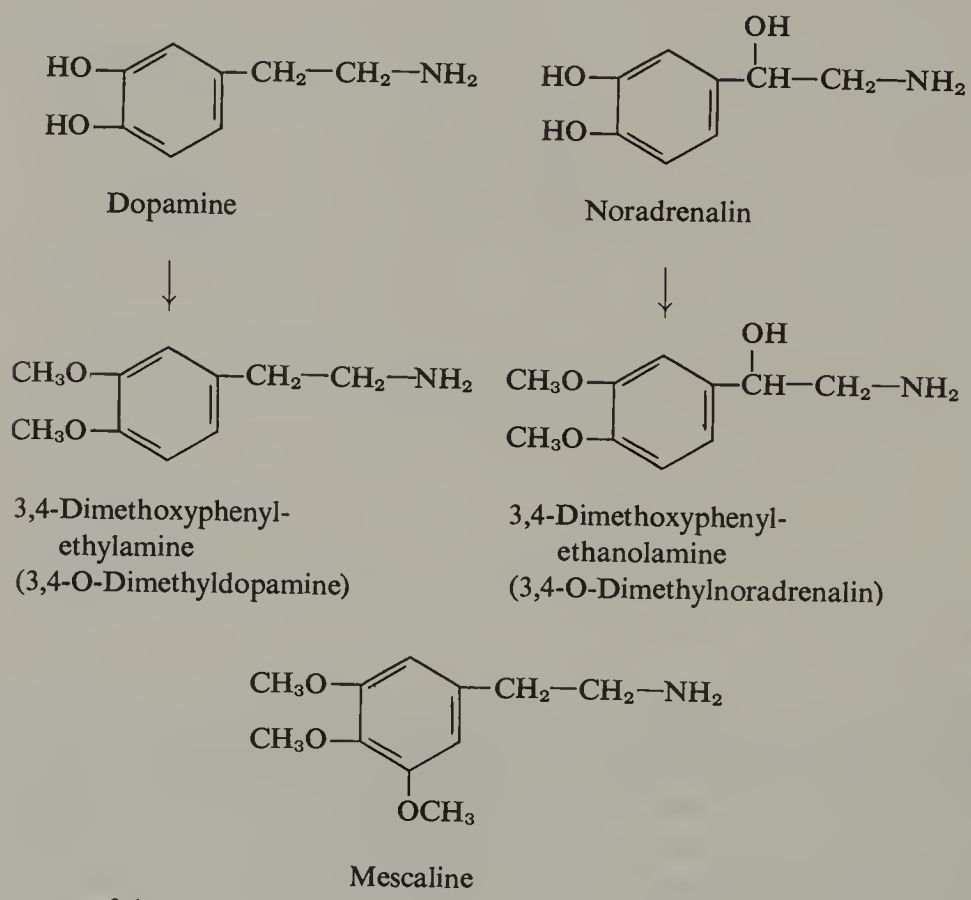


FIGURE 9-1.

and Smythies (1952) as well as by Hoffer et al. (1954)—that close chemical relations exist between brain amines and hallucinogenic drugs. Osmond and Smythies (1952) pointed to the similarity between catecholamines and mescaline. They suggested that by a faulty metabolic mechanism 3,4-dimethoxyphenylethanolamine and/or 3,4-dimethoxyphenylethylamine could be produced by a double O-methylation of noradrenalin and/or dopamine, leading to compounds very similar to mescaline (Figure 9-1). The production of schizophrenic symptoms by an endogenic substance similar to mescaline had been considered earlier by Stockings (1940), because of the

observed resemblances between the clinical picture of mescaline intoxication and of schizophrenia.

Osmond and Smythies (1952) thus offered the first hypothesis concerning pathological O-methylation in consequence of an inborn metabolic error as a pathogenetic factor in schizophrenia. The possibility of such an O-methylation of catecholamines received support from the discovery by Axelrod (1957, 1959) concerning the normal catabolism of catecholamines through the methylation of one of their phenolic hydroxy groups in position 3, catalyzed by a catechol-O-methyltransferase (COMT), with the aid of S-adenosylmethylmethionine as methyl donor. Taking into account the ideas of Osmond and Smythies (1952), we may suppose that a pathological variation of this process could lead to a methylation of more than one hydroxy group or of the specific hydroxy group in position 4 instead of that in position 3. We shall refer to this hypothesis as that of excessive or abnormal O-methylation.

Fischer (1960) approached the problem from a somewhat different point of view, postulating that the psychotoxic metabolic factor in schizophrenia may be represented by a double N-methylation of serotonin leading to the formation of bufotenin, another psychotomimetic substance. This hypothesis is based, similarly, on a supposed excessive methylation of one of the normal neurohumoral agents of the brain, but in this case, instead of an abnormal O-methylation of phenolic amines, a faulty N methylation of an indolamine was postulated. Fischer (1960) thought that "the key to the mystery of the schizophrenic pathogenesis is to be found in relation with serotonin in the form of an N-methylation, transforming it to N-methylserotonin in the first instance and to bufotenin in the second, both hallucinogenic substances."

The first experimental results about the selective presence of bufotenin in schizophrenic urine were published in 1961 (Fischer et al., 1961a, 1961b). At about the same time Axelrod (1961, 1962) discovered the existence of a special N-methyltransferase in mammalian organism, able to transform serotonin into bufotenin and tryptamine into N-dimethyltryptamine (Figure 9-2). Brune et al. (1963) confirmed the findings of Fischer and his co-workers. Himwich and his co-workers showed later that not only bufotenin but also its O-methyl derivative, as well as N-dimethyltryptamine, are selectively present in schizophrenic urine and blood (Tanimukai et al., 1967; Heller et al., 1970).

The two theories, one of excessive O-methylation and the other of excessive N-methylation (Figure 9-3), do not necessarily contradict each other. It is possible that both O-methylation and N-methylation are abnormal in the schizophrenic. The presence of excessively N-methylated indolethylamines other than bufotenin was also to be expected after the discovery by Axelrod of N-methyltransferase.

We should consider these two working hypotheses separately. There are three main points concerning each: (1) the psychotomimetic action of the corresponding derivative, (2) the possibility of its production in human metabolism, and (3) the

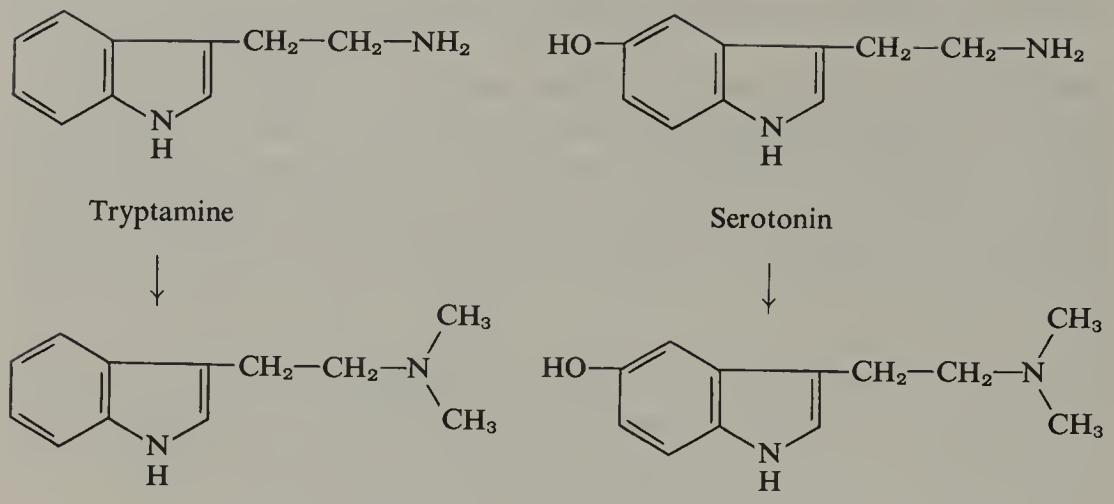


FIGURE 9-2.

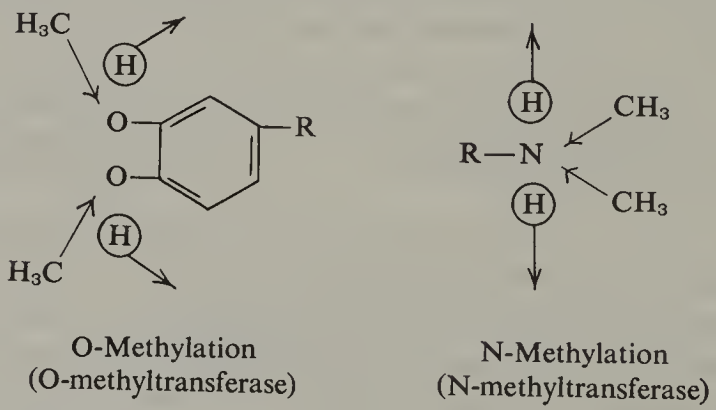


FIGURE 9-3.
Theories of O-methylation and N-methylation.

qualitatively or quantitatively selective presence of the psychotomimetic derivatives in the schizophrenic organism.

As to the psychotomimetic action, the basic question concerning the relationship between the psychotomimetic symptoms of a given drug and the symptoms of clinical schizophrenia have received no final answer as yet, despite its ample discussion. We shall deal with this problem later; for the moment we shall simply consider the practically undisputed hallucinogenic effect of the different abnormally O- or N-methylated derivatives of neurohumoral agents in the brain.

I. O-METHYLATED COMPOUNDS

A. Hallucinogenic Action of Excessively or Abnormally O-Methylated Catecholamines

There is no doubt about the hallucinogenic effects of mescaline, which is the starting point of the hypothesis of Osmond and Smythies (1952). Mescaline is, however, not a catecholamine derivative, but an O,O′,O″-trimethylated pyrogallolethylamine (3,4,5-trimethoxyphenylethylamine). Osmond and Smythies (1952) suggested that 3,5-dimethoxyphenylethylamine (O,O′-dimethyldopamine) or 3,4-dimethoxyphenylethanolamine (O,O′-dimethylnoradrenalin) may be produced by a faulty metabolism and that these substances could be hallucinogenic (Figure 9-1). It was shown, however, that 3,4-dimethoxyphenylethylamine has no hallucinogenic effect (Smythies

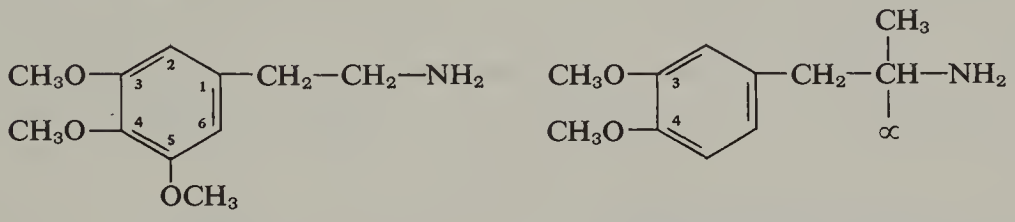


FIGURE 9-4.
Structural formula of 3,4-dimethoxyamphetamine.

and Levy, 1960; Hollister and Friedhoff, 1966; Shulgin et al., 1966, 1969). The studies of Johnston and Bradley (1968) on a series of mescaline derivatives have proved that the presence of at least three methoxy groups on the benzene ring is a necessary condition for the hallucinogenic effect and that these must be in the positions 3, 4, 5. If the number of methoxy groups is greater than three the hallucinogenic potency is increased. Shulgin (1964) found, however, that an alpha-methyl group on the ethylamine side chain can replace one methoxy group. Such a derivative of 3,4-dimethoxyphenylethylamine is represented by 3,4-dimethoxyamphetamine, which produces hallucinogenic effects (Figure 9-4). Further studies on alpha-methylated dimethoxy and trimethoxyamphetamines were carried out by Shulgin (1964) and by Johnston and Bradley (1968). Shulgin et al. (1969) think that 2-hydroxy-3,5-dimethoxyphenylethylamine could also represent a possible endogenous psychotogenic substance.

Summarizing the results of these experiments, we can say that there is no proof of the hallucinogenic activity of O,O′-dimethylated dopamine or noradrenalin. It seems, however, that the corresponding amphetamine derivative, which has an alpha-methyl radical on the side chain, is hallucinogenic. Thus, there remains the possibility that an O,O′-dimethylated and alpha-methylated catecholamine with hallucinogenic effect may be formed in the schizophrenic organism. Furthermore, it is possible that

some other structural change could also give a hallucinogenic character to the O,O′-dimethylated catecholamines (Shulgin et al., 1969). Notwithstanding, we still have no proof of the existence of such compounds in the human organism, sane or psychotic.

B. The Possibility of the Production of Abnormally O-Methylated Compounds in the Schizophrenic Organism

It was shown by Axelrod (1957, 1959) that the normal catabolism of catecholamines includes an O-methylation at position 3. It is supposed that this normal pathway could give place to an abnormal O-methylation in schizophrenic organisms. Friedhoff and von Winkle (1962) found a substance in schizophrenic urines, claimed to be O,O′-dimethoxyphenylethylamine (DMPEA). The identity of the substance is, however, still under discussion. It seems certain that a great number of schizophrenics eliminate selectively a substance or substances that appear as a pink spot in the urine chromatogram. This is an important finding but we must wait until the chemical nature of the substance has been cleared. (This is discussed in detail in Chapter 6.)

It should be mentioned that Kemali and Romano (1956) and Kemali et al. (1957) have reported the selective presence of different abnormal methoxy-derivatives of indolethylamines in schizophrenic urines.

C. Quantitatively or Qualitatively Selective Presence of Hallucinogenic Abnormally O-Methylated Substances in the Schizophrenic Organism

DMPEA is not a hallucinogenic agent and the real chemical nature of other substances present in pink spot is not known, nor is it known whether they have a hallucinogenic action; hence this question cannot be answered as yet.

II. N-METHYLATED COMPOUNDS

A. Hallucinogenic Action of N-Dimethylated Indolamine Derivatives

Turning to the excessive N-methylation of indoles, proposed first as a working hypothesis in 1960, we must consider the same questions as for the hypothesis of O-methylation.

Correctly, we should speak of N-alkylated indolamine derivatives, for it seems

that N-diethylated indolamines also have hallucinogenic effects, and there are even some statements that N-monomethylated derivatives show such an activity. We shall restrict ourselves to the discussion of N-dimethylated compounds, whose effects and metabolsim are better known. The most important hallucinogenic N-dimetyhl-indolethylamines are 5-hydroxy-N-dimethyltryptamine (N-dimethylserotonin, bufotenin), its O-methylderivative (5-methoxy-N-dimethyltryptamine or O-methyl-bufotenin), 4-hydroxy-N-dimethyltryptamine (psilocine), and N-dimethyltrypt-amine (Figure 9-5).

The hallucinogenic action of bufotenin was shown by Evarts (1956) in monkeys

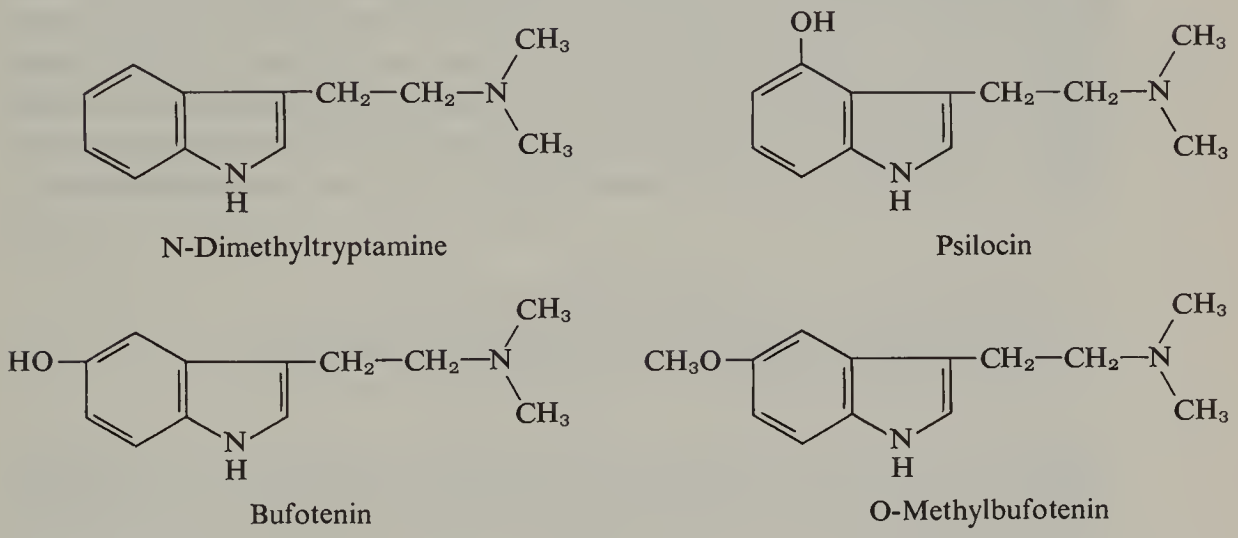


FIGURE 9-5.
The most important hallucinogenic N-dimethylindolethylamines.

and by Fabing and Hawkins (1956) in human beings. These results have been confirmed and extended to other animals by Costa et al. (1959), Gessner et al. (1960), Mahler and Humoller (1959), Melgar (1964), and Bonhour et al. (1963, 1967). It seems that the O-methylation of bufotenin potentiates its psychotomimetic action (Bennington et al., 1965; Holmstedt, 1967; Johnston and Bradley, 1968; Gessner and Page, 1965; Sanders and Busch, 1967). This is, however, not necessarily a measure of the intrinsic psychotoxic activity of these substances, for that depends also on secondary factors, such as diffusion across the blood-brain barrier. Bufotenin, like its parent substance serotonin, passes this barrier only with difficulty, because of its free phenolic group (Gessner and Page, 1965; Sanders and Busch, 1967). This means that bufotenin and serotonin need a much higher blood concentration for passing into the brain than do their O-methyl derivatives. This circumstance causes difficulties in human and animal experimentation, especially in view of the alarming peripheric symptoms produced by high endogenous doses of bufotenin

(Fabing and Hawkins, 1956; Melgar, 1964; Bonhour et al., 1963). This is the possible cause of some negative results obtained in human beings with bufotenin. Nevertheless, the hallucinogenic effect of bufotenin is assured. Such an action of dimethyltryptamine is also known (Szára, 1956, 1957; Sai-Halász et al., 1958; Rosenberg et al., 1963; Böszörményi et al., 1959; Johnston and Bradley, 1968).

B. Possibility of Production of Abnormally N-Methylated Substances in a Schizophrenic Organism

Such a possibility is clearly given by the discovery by Axelrod (1961) of an enzyme in the mammalian organism that transforms tryptamine into N-dimethyltryptamine and serotonin into bufotenin (Figure 9-3). Morgan and Mandell (1969) found a similar enzyme in brain tissues of different animal species and in human beings. Buscaino et al. (1966, 1967) reported that the blood of a schizophrenic has a much higher capacity to methylate nicotinamide than blood from a nonschizophrenic.

C. Quantitatively or Qualitatively Selective Presence of Hallucinogenic Abnormally N-Methylated Substances in Schizophrenic Urine

Bufotenin was first found in human urine by Bumpus and Page (1955). It seems that a relatively large volume of normal human urine was assayed in this work. Fischer et al. (1961a, 1961b), using a paper-chromatographic technique, found bufotenin only in schizophrenic urines, a result confirmed by Brune et al. (1963). Fischer and Spatz (1967) reported the results obtained on a larger number of cases (95 acute untreated schizophrenics, 43 chronic or treated schizophrenics, and 102 nonschizophrenic control subjects). In the control group no bufotenin was found. It was present in 75 percent of the acute untreated cases and in 37 percent of the chronic or treated group.

Several authors (for references see Fischer and Spatz, 1968) could not confirm these results or have not accepted their significance. Some investigators found that bufotenin was not present regularly in urines of either schizophrenics or controls, or they found bufotenin in both. Authors who did not accept the significance of the positive results argued that the presence of abnormal substances in the urine could be a result of diet or of staying in psychiatric hospitals.

Such arguments do not seem to be valid. Negative results may be due to technical difficulties of the paper-chromatographic method; to the lability of bufotenin, especially if ion-exchange columns are used; or to a faulty selection of cases, such as testing mostly chronic or treated schizophrenics (see Fischer and Spatz, 1968). As to the effects of staying in a psychiatric hospital, Poch et al. (1967) could show that

positive results are obtained with identical frequency in hospitalized and unhospitalized acute schizophrenics. The influence of diet was excluded later by quantitative experiments (Sireix and Marini, 1969).

Spatz (1967) worked out a highly sensitive quantitative method to assay bufotenin in human urine. The results (Fischer and Spatz, 1968, 1970) showed that nonschizophrenic subjects eliminate very small amounts of bufotenin, between 1.2 and 8.9 μg percent (μg per 100 ml), with a mean of 3.5, whereas 80 percent of acute untreated schizophrenics eliminate more than 10 μg percent, with a mean value of 17.5 μg percent. The situation is different in chronic and/or treated cases, where only 26.6 percent showed high values and the mean corresponded to 6.9 μg percent.

The results of Fischer and Spatz (1968, 1970) have been confirmed by Sireix and Marini (1969). In 20 normal subjects they found bufotenin values between 0 and 3.5 μg percent, with a mean of 2.1 μg percent, whereas 20 acute untreated schizophrenics eliminated amounts between 0 and 34 μg percent, with a mean of 15.5 μg percent. Excepting two cases (10 percent), every acute schizophrenic subject eliminated more bufotenin than any of the normal subjects. Twenty cases of other psychiatric diseases gave values between 0 and 5.1 μg percent, with a mean of 2.9 μg percent.

Saavedra and Ucha Udabe (1970) studied psychiatric outpatients with the same method. Their results show that hospitalization has no effect on bufotenin elimination. In four normal persons, values between 1.4 and 2.6 μg percent (mean 1.7 μg percent) were found; in 25 nonschizophrenic subjects with different psychiatric symptoms amounts between 0.6 and 5.0 μg percent were eliminated with a mean of 2.4 μg percent. In ten untreated acute schizophrenic cases the values were between 3.8 and 35.0 μg percent; seven of them showed values above 10 μg percent. Four schizophrenics after neuroleptic treatment showed low amounts (between 2.4 and 5.6 μg percent). It was observed that the urinary content of bufotenin of four subjects with conversion hysteria remained within the normal range; nevertheless, it was somewhat higher than in the rest of control cases (between 4.9 and 7.0 μg percent, mean 6.8 μg percent).

Summarizing these results, we can say that 70 to 80 percent of untreated acute schizophrenics have urinary bufotenin values that are above the normal limits. One remaining problem is that negative results are obtained in 20 percent of acute untreated schizophrenic cases. It is not possible to give a satisfactory explanation for this circumstance, but technical difficulties or erroneous diagnosis may be responsible. Another problem is the low frequency of an augmented bufotenin elimination in urine of cases treated with neuroleptics, or generally in chronic schizophrenia. After therapy with neuroleptics, Acebal and Spatz (1967) found a gradual diminution of positive findings with the chromatographic method. These experiments should be repeated with use of a quantitative procedure. Unpublished results have shown that electroshock and insulin treatment have no such effect. Axelrod (1962)

found that the neuroleptic drug chlorpromazine inhibits N-methyl-transferase. The effect of other neuroleptics on this enzyme should be studied too.

The low frequency of positive results in chronic schizophrenics who are not symptom-free and thus show a still active process remains to be explained. Sanders and Busch (1967) found in animal experiments that only 6 percent of parenteral bufotenin is eliminated in urine in unchanged form; 15 percent appears as hydroxy-indolacetic acid, and 35 percent appears as glucuronide. O-Methylbufotenin could not be found. There is a possibility that in chronic cases the relation between free and bound bufotenin is changed in favor of the latter. Fischer et al. (1970) compared the values of bufotenin and bufotenin glucuronide. The values of total bufotenin were significantly above the normal limits in both acute and chronic schizophrenic subjects (acute schizophrenics 28.9 μg percent, chronic schizophrenics 18.8 μg percent, control subjects 9.3 μg percent). The situation was different for free bufotenin, which showed abnormally high values only in acute schizophrenia.

Himwich and his co-workers (Tanimukai et al., 1967; Heller et al., 1970) studied the presence of bufotenin, N-dimethyltryptamine, and O-methylbufotenin in schizophrenic urine and blood samples with methods that permit purification of these substances, even though they do not give quantitative results. With such methods Tanimukai et al. (1967) found the three mentioned substances in urines of schizophrenics. Heller et al. (1970) and Narasimhachari et al. (1970) made similar observations with schizophrenic blood. Narasimhachari et al. (1970) observed that chronic schizophrenics whose urine did not contain these substances began to eliminate bufotenin and other N-dimethylated tryptamine derivatives after treatment with a methyl donor, tryptophan, and an amino-oxidase inhibitor. A group of nonschizophrenic subjects given a similar treatment did not react in that way; their urine remained free of these substances.

Similar experiments with methyl donors (methionine, betaine) and amino-oxidase inhibitors were carried out earlier by several workers (Pollin et al., 1961; Brune et al., 1963; Brune and Himwich, 1962; Park et al., 1965), who observed in general an increase in the severity of the symptoms. These findings can be used as arguments for the existence of an excessive or abnormal methylation in schizophrenia, without specifying the chemical character of the substance formed (methoxy or dimethylamino derivatives). Kanazawa et al. (1967) attempted to resolve this problem experimentally, but the results obtained suggested a general amino-acid imbalance and ionic disturbance due to methionine that should be taken into consideration in interpreting the psychic effects. Even though the results of Narasimhachari et al. (1970) show that methyl-donor treatment results in an increased formation of N-methyl derivatives, it cannot be excluded that O-methyl derivatives are also formed. Heath et al. (1966) found that D,L-methionine-D,L-sulfoximine, an antimetabolite of methionine, produces an improvement of psychotic symptoms in schizophrenics. It must be mentioned that Heller (1966) observed an exacerbation of

schizophrenic symptoms after giving an amino-oxidase inhibitor to the experimental subjects even with a methyl donor.

Summarizing the experimental results obtained in studies related to an excessive or abnormal methylation of hydroxy and amine groups, we can state that there remains the possibility of a coexistence of different metabolic errors in schizophrenia. There can exist an excessive methylation of hydroxy and amine groups simultaneously or alternatively.

Besides assays on amine changes in schizophrenia, important research has been done on the alterations of plasma proteins that are possibly connected with amine metabolism (Gottlieb, 1967; Frohman et al., 1960).

Finally, the possible relationship between hallucinogenic effects of drugs and certain schizophrenic symptoms should be discussed. The label "psychotomimetic" was given by Gerard (1956) to such drugs, postulating a similarity between their effects and the symptoms of clinical psychosis. It has already been mentioned that Stockings (1940) found significant resemblances between certain symptoms of schizophrenia and mescaline effects. Bowers and Freedman (1967) arrived at similar conclusions about other hallucinogenic agents. Other authors, however, did not accept such a point of view and argued that there are no meaningful affinities between hallucinogenic effects of drugs and symptoms of mental diseases (Wikler, 1954).

It is well known that different psychiatric schools and even individual psychiatrists sometimes designate different forms of mental or nervous diseases with the term schizophrenia. Some authors speak of schizophrenia as a loosely connected complex of different mental diseases. It is not sensible to extend this nosological category in this way. Even in authentic and correctly diagnosed schizophrenia only certain symptoms can be regarded as fundamental or primary and may be considered hypothetically as derived directly from a specific causative agent. Other symptoms must be looked upon as secondary psychological overstructures. The schizophrenic subject finds himself transported to an apparently wholly changed world, in consequence of his pathologically altered apperceptive and thought processes. He must face in some way this strange world that among other features lacks notable stability, logical structure, and reason. He is challenged to explain all this. The troubled nature of his thought process implies that the explanations he proposes to himself will be sometimes even more strange than the very phenomena he is trying to explain. It might be assumed that a toxic effect alters some psychophysiological functions directly, especially those related to apperception and ideation. Some controls could be faulty, namely those that normally impede the interference of perhaps dream-like appreciative and thought processes in a wakeful state, or such interfering processes could be pathologically stimulated. The chaotic situation created in such a way must be integrated somehow by the personality. It is evident that the condition of a normal person under the temporary, shortlasting impact of a

drug effect is very different. Even if such a person would not know that a hallucinogenic drug was given to him, the short duration of his experience should not force him to take an elaborate position in front of it. Generally he will be simply stunned and afraid. When LSD was given to students as a foolhardy practical joke by their colleagues, the recipients generally expressed fear of becoming mad. The massing of psychopathological experiences must have quite other consequences. Friedhoff (1970) pointed out that chronic amphetaminism produces personality changes very similar to or nearly indistinguishable from those observed in schizophrenia, but that the acute psychotomimetic action of amphetamine, observed occasionally, corresponds rather to the usual effects of hallucinogenic drugs.

Hollister (1962) expressed doubts as to the similarity between drug-induced psychosis and schizophrenia. To compare schizophrenic symptoms and drug induced disturbances, he proposed to ignore all the longitudinal symptoms of the illness, such as "the almost lifelong inability to cope with stressful situations, retreat to a protective situation, disparity between ability and performance, impoverished interpersonal relationships, and often insidious onset and others." He wanted to consider only "symptoms that might be apparent at any moment of time, comparable to the period of a drug trial." Hollister thinks it possible to do this and argues, for example, that a withdrawal from personal contacts is characteristic of a schizophrenic person, a behavior that "in the immediate situation . . . may take the form of a sullen indisposition to converse or otherwise react to others, expressed by muteness in the extreme case." Hollister judges that the conditions of persons in drug-induced psychoses are very different, for here the subjects enjoy their "ruminations and visions" and prefer to have someone to talk to. This comparison is, however, far from valid. It does not acknowledge that the psychological situation of a person under the effect of a drug is very different from that of a schizophrenic subject. Moreover, in the acute phase of schizophrenia the subjects are still not retired from the exterior world and they try very often, sometimes desperately, to communicate and to explain their strange experiences to physicians or to other persons. Some of them also express the fear of becoming insane, similarly to persons who have unknowingly taken hallucinogenic drugs. After a time the schizophrenic begins to realize that his experiences are incomprehensible to other persons, and thus he begins to feel completely isolated and retires more and more from human contacts. This circumstance shows that it is not possible at any time to ignore all the "longitudinal symptoms of the illness," as Hollister proposed, for such longitudinal symptoms are always present and form the very background of the illness, modifying inevitably every symptom "apparent at any moment of time, comparable to the period of a drug trial."

Similar objections can be made to a second example offered by Hollister, when he states that "a drug subject trained in psychology explains his nausea on the basis of rejection of this role as a subject," whereas a schizophrenic attributes the pain he is

suffering to a devil who is pushing a hot poker periodically into his vitals. It is not necessary to give details in order to see that this comparison is also mistaken. His absurd experiences place the schizophrenic out of a reasonable world, and he feels influenced in his innermost self by supposedly outside agents. He cannot construct any logical world view. His critical functions are deranged. Such things will not happen in the case of a drug subject, even if he is not "psychologically trained." Hollister thinks that there is another valid difference between the behavior of schizophrenics and drug subjects, for the latter are usually greatly concerned about the failure of communicating with the world, while schizophrenics are not. This argument does not take into consideration that acute schizophrenics often do mind the lack of communication and that they may resign wholly only later, after many frustrations.

Nevertheless, we must admit that some arguments against a close identification between schizophrenia and drug symptoms are valid, especially the fact that schizophrenics have generally auditive hallucinations, while drug-induced hallucinations are nearly always visual. This can perhaps be explained by the supposition that symptoms produced by a single high dose of a toxic substance may be different from those observed after a long uninterrupted treatment with lower doses. It is also possible that the pathological metabolism of schizophrenics produces several different substances at the same time, with different effects; for example, O-methylated and N-methylated compounds.

Hollister (1962) thinks that the fact that some drug subjects become paranoid and suspect the experimenter of poisoning him, or making fun of him, can be explained by the situation in which he finds himself. This is undoubtedly true, but the explanation may apply equally well to the schizophrenic, except that he does not know who is making fun of him and poisoning him. Understandably, his chronically poisoned, deranged mind will produce occasionally, or even generally, some very grotesque and absurd explanations.

Schizophrenia is an ongoing process and the symptoms present at any given time cannot be separated from it. Osmond (1957) refers justly to the differences between this psychosis and drug symptoms as those "between a transient, artificially induced, experimental state and the prolonged, insidious, creeping illness in an unsuspecting victim whose social life progressively atrophies." This explanation considerably clarifies many of the foregoing arguments.

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10

The Background to the Niacin Treatment

HUMPHRY OSMOND

Prolonged studies of an illness such as schizophrenia, which often starts in youth and continues for life, cannot be undertaken lightly. It is a fluctuating illness, and even the most dramatic early response to treatment does not guarantee the outcome over the next decade or two, or even over the next few hours. Those who have raised a catatonic patient with intravenous sodium amytal have discovered this to their sorrow, for there is nothing sadder or more frustrating than to watch such a patient slip back into the morass.

We began the first double-blind trial of niacin and niacinamide in Saskatchewan in 1952. So far as we can discover, it was the second study of this kind undertaken in North America; we had completed the first some months earlier (Clancy et al., 1954; Hoffer et al., 1957).

In those days the double-blind trial, which has now become something of a sacred cow, was an innovation viewed with suspicion by most clinicians, who accorded it none of the reverence it now receives. Methodologists and statisticians were, however, loud in their praises for the new device, even though they had very little evidence with which to support their enthusiasm. Today, when such trials are

commonplace, sophisticated statisticians and methodologists, such as Chassan (1967) and Hogben (1957), are less enchanted and sometimes highly critical.

We had already obtained striking clinical evidence that niacin and niacinamide were effective in the treatment of schizophrenia. A follow-up of our first eight patients fifteen years after being given niacin showed that our original impressions were not ill founded—all eight were still well (Hoffer and Osmond, 1964). Although eight cases are not many, Lind's (1753) classic study of scurvy was done with only twelve men, and when two who had been given citrus fruit got well, he judged (correctly) that he had a remedy for scurvy. Lister's (1867) paper on compound fractures described eleven patients; one died, one required an amputation, and the other nine recovered. We have no evidence that we would have learned more by using the most modern experimental designs, or more subjects.

The feature of our research with niacin and other methods in the treatment of schizophrenia that is frequently overlooked or underestimated was the feasibility of a prolonged follow-up of our subjects. Because of the size of the population in Saskatchewan at that time (under one million) and the efficiency of its central recording system, we were able to utilize effectively the limited funds and resources available. Today follow-up is one of the most expensive and difficult activities connected with research of this kind.

Because of the special situation in Saskatchewan, we were able to follow up our patients who took niacin whether in double-blind or other studies for five, ten, and even fifteen years. We have a very valuable baseline because the long-term outlook for schizophrenia does not seem to have changed very much during the last fifty years except insofar as death is concerned. Had we begun using niacin after chlorpromazine was introduced it is possible that we would have never recognized its effects, for niacin usually acts more slowly than the phenothiazines. Consequently, after these drugs appeared, doctors, patients, and nurses came to expect, and even demand, rapid betterment. Those who had been prepared to wait weeks for ECT to produce its often too transient benefits, those who had been prepared to spend anxious days hovering over patients in continuous narcosis, or who had striven through the perilous months of deep insulin coma, began to lose patience with these slow and sometimes dangerous treatments. Chlorpromazine was not introduced into Canada and the United States until 1954, so in the spring of 1952 we had no distractions to prevent us from observing the effects of niacin.

We had other advantages which may not be evident to those who were not practicing psychiatry at the start of the 1950s. Tranquilizers did not then exist, so the new treatment began its career in competition only with barbiturates, bromides, chloral, paraldehyde, hydrotherapy, electroshock, metrazolshock, histamine shock, continuous narcosis, insulin shock, and lobotomy. None of these were particularly speedy in controlling severe, acute schizophrenia. None was without danger, and most of them were tedious, complicated, and expensive. There was no conclusive

evidence that any of these treatments had altered the outcome of schizophrenia during a five-year period. There is still none today.

A further difficulty, since remedied, was that we had no simple objective way of measuring the effects of niacin. By 1960 we had developed the HOD Test (Hoffer and Osmond, 1961; Kelm et al., 1967), a simple and surprisingly effective card-sort test for quantifying some of the experimental disturbances found in schizophrenia. This test can be used in clinical practice and is easy to give and to score. From the end of 1951 on we pursued our niacin studies with what would now be regarded as exemplary caution. Unluckily we picked one of the worst possible times for such scientific reserve. Those who were marketing the phenothiazines, having doubtless compared the safety of their substances with the barbiturates and similar compounds, promoted and advertised them with resolve. Millions of dollars were spent developing new ones, testing those already found, and on informing medical men about those considered to be valuable. To be more acceptable in the climate of the 1950s, phenothiazines were frequently and rather ingenuously described as being mere adjuncts to psychotherapy. There was at that time no evidence that schizophrenia was benefitted by psychotherapy; indeed, Freud, Federn, Jung, and many others had at various times expressed doubts as to whether this ever happened. In a survey of the phenothiazines after fourteen years use, Kinross-Wright (1967) noted that

> There is no convincing evidence that intensive psychotherapy with or without inadequate ataractic medication can benefit the majority of psychotic patients. There is ample evidence that adequate phenothiazine treatment without psychotherapy can benefit them. There is also evidence that if these patients are maintained and supervised on adequate doses of phenothiazines for indefinite periods they may be kept out of hospital and remain in the community. Unfortunately, there is also evidence that unless they are actively rehabilitated into a productive life, the majority of chlorpromazine-maintained patients will exist to become chronically disabled citizens.

There is little doubt that the effect upon psychiatric morale of these useful substances encouraged those who worked in mental hospitals to insist upon reforms that were long overdue. The running, staffing, equipping, and general design of mental hospitals have all been beneficially affected by the breathing space given by the phenothiazines. It would be churlish, untruthful, and lacking in gratitude to Laborit, whose ingenuity and perceptiveness played so large a part in furthering the development of these substances, to deny their great value.

However, once the first five years had elapsed many of us were curious to know whether the long-term outlook for schizophrenia had improved. During those heady days little notice was taken of niacin, and we simply continued our studies on the prairies. It took about a decade for psychiatrists to grasp what Dr. J. D. W. Pearce of St. Mary's Hospital, London, had said: "In the old days we had the closed door, then

the open door, and now we have the revolving door." Shortly before this Enid Mills (1962) in a compassionate but rather depressing book had shown that even when good policies were used in a well-run hospital, many people left the hospital to live very miserable lives outside it in spite of phenothiazine treatment.

As the years passed and we studied our niacin figures we found more and more evidence that those who took the vitamin in addition to other treatments did better than those who did not. It was natural that we should become increasingly interested in these findings as the shortcomings of the valuable phenothiazines became clearer. Our double-blind experiments (Hoffer et al., 1957; Hoffer, 1962) and a later one by Denson (1962) suggested that the outcome, particularly in early schizophrenia, could be altered for the better by the rather humdrum method of giving large doses of a well-known vitamin. We had, however, great difficulty in getting anyone else to try our treatment, even though we were advocating one of the cheapest, safest, and easiest of treatments ever suggested in psychiatry. Cynically, perhaps, we have sometimes felt that this was its main disadvantage. In addition, ours was an orphan treatment. No great pharmacological house was prepared to spend a small fortune on testing and promoting a non-proprietary substance, and it would have been unreasonable to expect them to do so. This resulted in very few psychiatrists ever hearing about this use of niacin, and those who did were suspicious. One asked us why more people did not use it if it was as good as we claimed.

Five-year and ten-year follow-up studies continued to show benefits, which no one had been able to claim for the phenothiazines alone. It was clear that niacin did not work as quickly as the newer substances, but luckily they were compatible and possibly synergistic with it. We published repeatedly, but for many years, outside of western Canada, our only source of completely independent data was Dr. Theodore Robie of East Orange, New Jersey. It was only recently that, because of a discussion we had with Dr. George Owen (a Fellow of Trinity College, Cambridge), we began to recognize our inadvertent errors of judgment. Our findings showed clearly that there was a strong probability that large doses of niacin, especially if given early in the disease, change the outcome for the better. Dr. Owen explained that the concept of probability is a comparatively recent one, deriving mainly from man's interest in gaming and insurance. It was devised to make life more certain. Those who understand and believe in probability theory have the advantage of living in a more comprehensible world. It is, however, naïve to assume that because an event is more probable, it is therefore more credible. What is probable according to the appropriate mathematical theory, and what is credible according to the morality of a particular time and place, are two very different matters. Indeed, were this not so, few people would gamble, for most gambling insures that the house must win. Had we understood this, we would from the start have been far less austere in our approach and would have given more attention to establishing credibility rather than to demonstrating the probability that niacin benefits schizophrenics. The history of medicine

does not suggest that probability has ever had much bearing upon the adoption of a new treatment; credibility is what matters.

In 1963, after publishing the monograph on niacin therapy (Hoffer, 1962), which had stirred very little interest, we decided to write a popular book. For a decade we had informed our colleagues about our findings in the accepted professional manner without exciting even the mildest curiosity. Those findings showed that if careful observation and follow-up of several hundred cases, combined with a variety of statistical evaluations and the use of a chemical and psychological test, both of an objective kind, meant anything, then we had evidence that we could improve the long-term outcome of schizophrenia by very simple means. In the course of the years we had developed a concept of schizophrenia very different from that put forward by Kraepelin and Bleuler or by Freud and his disciples. This would have been no surprise in other branches of medicine, but to at least some psychiatrists concepts developed in the late 1890s or early twentieth century are considered sacrosanct. Psychiatrists almost alone in medicine today still parade old ideas as if they were icons rather than guide-posts along the way.

Because of this curious series of accidents many of our colleagues first learned about our niacin treatment from their patients, who had read our only nonprofessional book, *How to Live with Schizophrenia.* This book led some people in the press, radio, and TV to hail the use of niacin as a new discovery. But this is not true—it was an old discovery. Some psychiatrists, indignant at being told something by their patients of which they were unaware, have spoken angrily about this new discovery being made available to the lay public before being told to the profession. Had there been a new discovery and had the profession been uninformed, we would have been the first to deplore such a gaffe. However, since there is no new discovery and since the papers and books have referred to our work repeatedly, we have no intention of apologizing. We are not responsible for the combination of information explosion and ethical advertising implosion which hid the use of niacin from these men.

It has, however, been gratifying to find, as other papers in this book show, that some of our colleagues who have read our papers and have given this treatment a fair trial appear to have had results very similar to ours. These results are not often dramatic, but they exist.

We had thought that psychiatrists in university and mental hospitals would be among the first to use our treatment. We reasoned that the former, who had more time for research, reading, and reflection, would be curious about our discovery, and the latter, working in hospitals often swamped by readmissions and seeing the dismal consequences of long-established schizophrenia, would be most anxious to explore any treatment that might reduce chronicity if employed early. Since niacin is so cheap and safe we assumed that the directors of mental hospitals would be keen to try a treatment which might save money and reduce laboratory work. It seemed to us that private practitioners would be too busy to study such new methods, might be

discouraged because niacin is often rather slow to act, and would await the decision of the leaders of the profession before trying anything new. We have been wholly mistaken. It is in the offices of private practitioners that the shortcomings of current treatments are seen in the most vivid, immediate, and striking manner. In addition, private practitioners see patients who are bold and articulate enough to complain about the discomfort of taking tranquilizers which, useful as they undoubtedly are, often produce side effects. Ayd's (1967) excellent paper shows that about a third of those who take these substances in large doses develop some kind of neuroplegia. It is not, however, only these gross disturbances which discourage patients from taking medicine, even though if used steadily it would keep them out of hospital, but "minor" symptoms often amounting to no more than a vague distressing lack of true well being. Rollin (1967) has noted that in Britain the return of patients to the community is not receiving as much as had been hoped when the Mental Health Act was passed in 1959. In his view tranquilizers had not been as effective as was first believed.

All this would make one think that great and sustained efforts would have been made to inquire carefully into any treatment, however unlikely, which might offer some prospect of changing the long-term outlook of schizophrenia. Yet to expect this would be to ignore not only the history of medicine but also that of science. Medical men are, generally speaking, like everyone else—they do not enjoy innovation and tend to do what is customary. Failure to be convinced by well-planned experiments is not by any means unique to medicine. An article (McConnell, 1967) on learning in planarians (flat worms) puts the matters clearly: "When is a replication not a replication? Answer: When nobody has read the original study and did not believe it anyhow." After quoting some discouraging experiences in which repeated replication did not convince, he continues, "What good does it do to publish replications over and over again if no one reads them? On the other hand, what good does it do to replicate an experiment if no one believes you?" Yet it is far easier to assess results in a laboratory study of learning in flat worms than it is in clinical psychiatry, where human beings are so much harder to control and live so much longer. To assess the result of the psychiatric treatment adequately, experiments must often last for months years, or even decades.

Michael Polyani (1963), describing a 49-year struggle ending in the acceptance of a theory of his, wrote,

> The scientific method is, and must be disciplined by an orthodoxy which can permit only a limited degree of dissent, and such dissent is fraught with grave risks to the dissenter. I demand a clear recognition of this situation for the sake of our intellectual honesty as scientists, and I charge that this situation is not recognized today, but is on the contrary obscured by current declarations about science.

Innovation is rarely welcome, for as Milton observed sourly, "Truth never comes into the world, but like a bastard, to the ignominy of him that brought her forth."

However, there have been many happy and successful bastards, love-children worthy of the name. Our views about unconventional children and unconventional ideas are determined largely by our set, our customary posture when meeting the unexpected or the unknown. There have been times when bastardy was no slur, indeed, when it was thought to confer greater vigor. The niacin treatment is, we hope and believe, robust enough to survive the scorn and disregard of the orthodox; it may even come to thrive on it. This volume shows that it is already doing so.

The niacin treatment is one of the very few treatments in psychiatry that comes close to meeting Claude Bernard's requirements for human experiments: "Those that can only harm are forbidden. Those that involve no forseeable harm to the patient are innocent and therefore permissible. Those that may do good are obligatory." Whoever reads this volume should ask himself of how many other treatments for schizophrenia could this be said?

POSTSCRIPT

During the summer of 1966, not long after our book *How To Live With Schizophrenia* was published, the National Institute of Mental Health dispatched an able medical scientist to Saskatchewan. He visited Hoffer, met some of his patients, inspected the case records of this research, and reported on them. In the spring of 1967 a substantial grant was awarded to the New Jersey State Hospital at Marlboro by the NIMH for a three-year study of the use of niacin in the treatment of schizophrenia. This project, which was carefully planned and includes advances in experimental design which have accrued over the last decade, is now under way. Results will be available sometime in 1972.

During those five years at least 250,000 young people will develop schizophrenia in the United States alone. What is their fate, using every treatment known today, excluding niacin, likely to be? About 40 percent (100,000 patients) will recover from their initial illness, which may last from some weeks to several years. After this they will not have a recurrence. About 30 percent (75,000 patients) will have one or more attacks of schizophrenia requiring further hospital treatment during their lifetime. The 30 percent remaining, another 75,000 patients, will be seriously ill much of the time. At the end of the four years we would expect about 10 percent, that is, about 25,000 of the original 250,000 patients, to be in some kind of psychiatric hospital. There will have been about 150,000 admissions, resulting in some 30,000 years spent in a hospital. Because the suicide rate of patients with schizophrenia is about twenty times that of healthy people of the same age, over 1,000 of them will commit suicide during the five years.

Our findings (Osmond and Hoffer, 1967) strongly suggest that if, in addition to such other treatment as is deemed necessary, niacin were to be given to these same

250,000 patients in the dosage and manner which we advise, as soon as the illness is recognized, the outcome would be different. Between 70 and 80 percent (175,000 to 200,000 patients) would become well and would stay well; between 3,000 and 6,000 patients would be hospitalized, for a total of 20,000 admissions, which would result in some 3,000 years spent in a hospital. Suicides would be substantially less. Our figures indicate that the suicide rate of those taking niacin is close to the normal rate. There might be 80 to 100 suicides during the five years. The cost of saving those several hundred lives would be about 10 cents per patient per day, which does not seem excessive.

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11

Mechanism of Action of Nicotinic Acid and Nicotinamide in the Treatment of Schizophrenia

A. HOFFER

If all the vitamin B3[1] were removed from our food, everyone would become psychotic within one year. This pandemic psychosis would resemble pellagra and it would resemble schizophrenia. It could not be called pellagra because none of the antecedents of that disease would exist. There would be no history of dietary deficiency or other pellagra-producing factors. It could not be called schizophrenia because no epidemic of schizophrenia has ever been recorded and seldom have more than 1 to 2 percent of any population become schizophrenic. There would be no unusual stress or any sudden catastrophic increase in schizophrenic mothers, fathers, grandparents, or societies. Moreover, most of the victims of the psychosis would recover within a few months if vitamin B3 was replaced in the diet. But not everyone would recover with simple replacement. Many people would have been so severely damaged that only massive doses of B3 would alleviate their symptoms, and would be required

[1] I use the term B3 to cover both nicotinic acid and nicotinamide, since both are nicotinamide adenine dinucleotide (NAD) precursors and they are equally effective in preventing pellagra.

for life. This fantasy of a plague psychosis illustrates vividly what does happen to 1 to 2 percent of our population.

No one is ever "cured" of pellagra, for it will strike again as soon as the intake of vitamin B3 falls below a certain level, which varies from person to person. In the same way, no one is ever "cured" of schizophrenia for it is indistinguishable from pellagra by psychiatric criteria alone. We are tied to our need for vitamin B3 just as much as a diabetic is tied to his daily injection of insulin.

But obviously schizophrenia and pellagra are not identical, since they require different quantities of vitamin B3. Most symptoms of pellagra are alleviated by doses of vitamin B3 below 1 gram per day, but a small proportion may need many times as much. Most schizophrenics respond to 3 to 6 grams but a small proportion may require more than 20 grams per day.

A discussion of vitamin B3 in preventing and alleviating schizophrenia is therefore analogous to a discussion of vitamin B3 in preventing and alleviating pellagra.

INTRODUCTION OF VITAMIN B3 INTO PSYCHIATRY

Although Osmond and I introduced the use of megavitamin doses of B3 for the treatment of schizophrenia, we were not the first to introduce it into psychiatry.

Nicotinic acid is an organic acid known chemically as 3-pyridine-carboxylic acid. It had no biological interest until it was extracted from biological material in 1911 by Funk, inventor of the term vitamine (later changed to vitamin). Its presence in a respiratory enzyme first known as DPN (diphosphopyridine nucleotide) and more recently as NAD (nicotinamide adenine dinucleotide) was proved by Warburg and Christian. Its enormous importance in nutrition was demonstrated in 1937 by Elvehjem and his co-workers.

Joliffe (1939) first suggested that the cerebral manifestations of pellagra may be the first evidence of severe or complete depletion of nicotinic acid. Spies et al. (1938) and Frostig and Spies (1939, 1940) described the mental symptoms, although the first English description was by Sir Henry Holland (1817), who wrote about "certain general symptoms, which are important in as much as they indicate the constitutional nature of the malady," which appeared early and included headache, irregular appetite, and general depression of spirit. He wrote that during the second year of pellagra

> The debility is greatly increased . . . all the nervous symptoms are renewed in more severe degree; the mind begins to suffer under the disorder; and the feeling of anxiety and despondence is very strongly marked, [and that in the later stage of pellagra] connected with these latter symptoms is the effect which the pellagra produces upon the minds of those suffering under the malady, which often forms one of the most

> striking circumstances in the history of this disease. The anxiety, watchfulness and moral depression of the patient is rapidly augmented. In the hospitals appropriated to the reception of such cases, the Pellagrosi afford a melancholy spectacle of physical and moral suffering, such as I have rarely had occasion to witness elsewhere. These unhappy objects seem under the influence of an invincible despondency; they seek to be alone; scarcely answer the questions put to them; and often shed tears without any obvious cause. Their faculties and senses become alike impaired and the progress of the disease, where it does not carry them off from debility and exhaustion of the vital powers, generally makes them incurable ideots, or produces occasionally maniacal affections, which terminate eventually in the same state. As a striking proof of this dependency of the disease, I may mention the fact that at the time I visited the Lunatic Hospital at Milan, there were nearly 500 patients of each sex confined there; of which number, more than one-third were Pellagrosi; people brought thither by the termination of their disorder in ideocy or mania. Even this statement gives little adequate idea of the ravages of the disease in this mode of its termination. The public hospitals of the country are wholly incompetent to receive the vast number of persons affected with the pellagra; and the greater proportion of these unfortunate people perish in their own habitations, or linger there, wretched spectacle of fatuity and decay.
>
> The mania consequent upon pellagra is often of a very violent kind, of which I have seen some remarkable instances in the Lunatic Hospital in Milan. Where such affections occur, the progress of the disease appear to be in some degree retarded, and the strength less rapidly declines. Attempts at suicide are frequent among Pellagrosi; and particularly, it is said, by throwing themselves into the water. Strambi has thought it worthwhile to characterize this tendency by the name of Hydromania.

Aring and Spies (1939) and Aring et al. (1939) reported that early pellagrins were quickly cured of their psychosis and neurasthenia by vitamin doses (small doses) of nicotinic acid, but made the significant comment that only some degree of symptomatic improvement occurred in the chronic organic psychoses of pellagra.

Cleckley et al. (1939) moved a step closer to introducing the use of nicotinic acid as a treatment of what they termed atypical psychotic states; that is, psychotic patients who were not clearly pellagrins. Using the term cerebral pellagra, they described 19 subjects whose mental symptoms were similar to those described for pellagra but who did not have any of the somatic changes. The majority were elderly arteriosclerotics. The response to 100 to 300 mg per day of nicotinic acid was often dramatic. Sydenstricker and Cleckley (1941) added another 38 cases to the series of atypical psychotics who rapidly responded to nicotinic acid. Stuporous or psychotic patients promptly improved on less than 1 gram per day. Lehmann (1944, 1949, 1952) and Medlicott (1945) also found it valuable in some organic psychoses. Joliffe et al. (1940) described a disease that they called nicotinic acid deficiency encephalopathy.

The first clear movement in the use of vitamin B3 for treating so-called functional diseases occurred in 1950, when Sherrill reported that four cases of depression improved on less than 1 gram per day and concluded that "this form of therapy puts a

new and valuable tool into the hands of the general practitioner in treating depressed conditions." Washbourne (1950) used nicotinic acid partly because it was a vasodilator. He referred to an observation by Noland D. C. Lewis that schizophrenics often had an aplastic cardiovascular system at autopsy, as well as to other evidence that circulatory changes often accompanied schizophrenia. He treated 15 psychiatric patients with up to 900 mg per day of nicotinic acid; fourteen improved. Some of his patients reported "I have a sense of well being," "I find I can think more rapidly and clearly," "I don't block as much," "After failing an exam three months before, I was able to pass on nicotinic acid." None relapsed while taking nicotinic acid. In eleven cases relapse followed when no more nicotinic acid was taken.

Thompson and Proctor (1953) combined nicotinic acid with phenobarbital to treat successfully depressive and anxiety reactions, and Gould (1953, 1954, 1958) introduced the use of large quantities of B vitamins, of which nicotinamide was a major component, and ascorbic acid for the treatment of deliria following intoxication or infectious diseases.

The recognition of a direct relationship between schizophrenia and nicotinic acid was prevented by a general belief among psychiatrists that schizophrenia was untreatable. In mental hospitals, where pellagrins were most heavily concentrated, the early nutritional pioneers did give up to 1 gram per day, and sometimes more, to many categories of patients. However, whenever a schizophrenic patient recovered on nicotinic acid he was promptly rediagnosed as a case of pellagra psychosis. This maneuver effectively prevented a proper examination of the use of nicotinic acid for schizophrenia until 1951, when Osmond and I decided to run our pilot experiment using 3 grams per day. At that time we were aware of the earlier work, but we did not consider that schizophrenics suffered from an exogenous deficiency of vitamin B3. There were other reasons that led us toward the use of nicotinic acid, nicotinamide, and ascorbic acid as the first vitamins to be used in megadoses (Hoffer et al., 1957). A few years later we began to use megavitamins for treating alcoholics, and this has been widely expanded by Hawkins (1968, 1969a, 1969b; Hawkins et al., 1970) and Smith (1967, personal commun.).

The first double-blind experiment in psychiatry, which was started in 1952, compared the effects of a placebo, nicotinamide, and nicotinic acid on 30 acute schizophrenics. The results showed that the patients given vitamin B3 plus standard schizophrenia treatment fared better than those given a placebo. Standard therapy then was mainly electroconvulsive therapy. The second double-blind experiment, on 82 patients, follow-up studies since 1952, and clinical experience on nearly 2,000 cases treated between 1952 and 1969 have clearly established for me that the treatment of choice for schizophrenia is a combination of megavitamins, tranquilizers, anti-depressants, and ECT, combined with psychotherapy within the framework of the medical model. An example of independent corroboration is the work of Hawkins (Chapters 28 to 30). He and his clinic have treated over 4,000 cases, and the

vast majority were restored to normality. I shall, therefore, not submit any more evidence of the therapeutic efficacy of vitamin B3 for treating schizophrenia. Each psychiatrist who uses the program as it has been described will decide for himself whether or not it works. Many have become more and more enthusiastic about it. Other therapies, such as ECT or tranquilizers, came in with a good deal of excitement and enthusiasm and have gradually settled down as useful treatments, but there is always the wish that we had something better. With these other treatments one does not become more and more enthusiastic, but only more and more resigned.

The evidence that the addition of megavitamins improves the quantity and quality of recoveries is presented in this book. A list of published reports includes Agnew and Hoffer (1955), Ananth et al. (1970), Chinaglia (1965), Denson (1962), Green (1969), Hoffer (1963, 1965, 1966a–f, 1967a–c, 1969a–d, 1970), Hoffer and Osmond (1962, 1963a–c, 1964), Herjanic et al. (1967), Kowalson (1967), Maslowski (1967), Osmond (1967), Osmond and Hoffer (1962, 1967), Robie (1967, 1970), Szatmari et al. (1955), Tobin (1967), Weinberg (1939), Newbold (1960), Rossi (1967), Stefan (1966), Martz (1965), Hilsheimer et al. (1970), Lehman and Ban (1969), Green (1970), and Ivanova et al. (1964).

So far, no investigator has completed an experiment in which the megavitamin approach has been tested in a double-blind experiment. Several experiments are under way but they are testing only one part of the program; for example, they do not use ECT. It is, therefore, necessary to reiterate that the megavitamin program is not one which can be completed in a single month, or six months, or a year. Time alone is no criterion. One starts with the simplest therapy; that is, chemotherapy alone, using megavitamin doses plus all the other chemotherapies available to psychiatry as indicated in each case. Patients who recover are maintained on the program in order to keep them well. Patients who do not recover within three months are then given a series of ECT (unilateral or bilateral), in addition to the chemotherapy. They may require a second and even a third series. With any acute series (using ECT if there is insufficient improvement within three months of beginning chemotherapy) one can expect a recovery rate of over 90 percent within one year, and improvement in the other 10 percent. The proof is in this book and in our case records. Any physician skeptical but not cynical can verify these claims for himself by visiting me (most members of the Committee on Therapy, American Schizophrenia Association, are prepared to demonstrate their cases to physicians), and by using the methods as they have been described. *No experiment can be considered a duplication of our method until in fact it has been duplicated*, whether single-blind, double-blind, or controlled by the usual clinical criteria. The double-blind methods, although very popular, have little valid scientific base (Hoffer and Osmond, 1961a–c, 1963a–c; Hogben, 1957; Chassan, 1957, 1960, 1961, 1970). They are extremely expensive, restrict research to physicians least skilled in psychiatry (that is, residents in a few medical schools or teaching hospitals), and remain unconvincing to the vast majority of

physicians. They have never served to introduce a new treatment, and where they have been used to test new therapy, as when we did the first double-blind study in the history of psychiatry to test vitamin B3, they have been disregarded.

In this report I shall present the evidence for the hypothesis that pellagra and schizophrenia are both NAD-deficiency diseases, at opposite ends of a spectrum of vitamin need. The evidence is that pellagra is caused by a failure to deliver the essential precursors of NAD, tryptophan, vitamin B3, and pyridoxine in the diet. In schizophrenia there is an endogenous failure to deliver enough NAD to vital areas of the brain. Pellagra is a deficiency disease resulting from a lack of certain factors in food. Schizophrenia is a dependency disease resulting from a large and unexplained need for very large quantities of NAD substrate, such that no combination of foodstuffs could meet the need.

The concept of vitamin dependency is slowly making headway. Rosenberg (1969) defined vitamin dependency as a genetic disturbance that leads to specific biochemical abnormalities affecting only one reaction catalyzed by a vitamin, and that responds only to pharmacologic (large) doses. In contrast, an acquired vitamin deficiency responds to the usual physiological (vitamin) doses. Two examples are pyridoxine dependency, in which low B6 levels lead to convulsions in children and to lassitude, weakness, and anorexia in adults with microcytic anemia, which does not respond to iron, and vitamin-B12 dependency, which may call for 1 mg per day to restore normal metabolism.

There are at least four possible biochemical errors for each dependency condition: (1) a defective transfer of the substance into cells, (2) a defective formation of apoenzyme, (3) a defective formation of holoenzyme, and (4) inhibition of enzyme-substrate reaction.

Williams (1967, 1969) was one of the first scientists to prove that there is a wide disparity in requirement for nutrients even among pure-bred strains of animals. Most convincing are his experiments with armadillos. Although normally they give birth to a set of monozygous quadruplets, Williams found that there were wide differences among these genetically identical animals, for example, the amount of adrenaline in their adrenal glands varied 32-fold. He also found a similar wide range in optimum requirements for ascorbic acid and other nutrients. If pure-bred strains of animals with similar genes vary so much, it is certain that genetically heterogeneous animals like man will also have wide-ranging requirements. Mean optimum daily values as recommended by nutritionists are only a very rough guide for society in general, and of little value for any individual.

Sir Archibald Garrod (see Childs, 1970) was one of the first to consider chemical individuality. He suggested that all human differences were chemical, taking their origin from variations in amino-acid composition of proteins in the cell. In 1908 he wrote that "to our chemical individualities are due our chemical merits as well as our chemical shortcomings."

PELLAGRA AND SCHIZOPHRENIA COMPARED

Pellagra is characterized by four D's—dermatitis, diarrhea, dementia, and death—although it would be more accurate to define it by the term NDDDD, where N stands for neurasthenia or neuroses, since the earliest manifestations of pellagra are anxiety, depression, fatigue, and vague troublesome somatic complaints.

The Dermatitis

Dermatitis is the most obvious symptom. It is easy to understand why this would be so, since neurasthenia and diarrhea were not uncommon in communities suffering from malnutrition. The term pellagra comes from *pelle agra*—rough skin in Italian. Gasper Casal, physician to the Spanish king, first recorded his observations on the disease, then also known as *mal de la rosa*, in 1735. Dermatitis was tied to pellagra, although pellagra sine pellagra (pellagra with no skin changes) was also described. Research physicians such as Goldberger (see Terris, 1964) and Wood (1912) would not diagnose pellagra unless the skin changes were present. In referring to pellagra sine pellagra, Wood believed this diagnosis resulted from failure to observe the early pigment changes, which often faded as the disease progressed. Yet in many cases dermatitis developed in patients in mental hospitals after the psychiatric changes were well established.

Wood carefully described the phases of pellagra by referring to the skin changes. During the pre-erythematous phase nervous and gastrointestinal symptoms were prominent. During the erythematous phase skin became pigmented symmetrically and later developed exfoliative changes. At first the erythematous areas appeared sunburned, or as if the patients had been scalded. There were several instances in mental hospitals where these erythematous areas were considered to be burns caused by negligence of the staff. The skin might also be swollen, and the erythematous areas later became brown. Usually only areas of skin exposed to the sun turned brown; these included the face, neck, back of the hands, and the feet. Later the skin became rough and dry. Most characteristic was the symmetry, in that identical pigmented areas occurred on both sides of the body.

The pigmentation tended to begin in the spring, intensify during the summer, and fade during the winter, but often would not disappear.

There was no relationship between the intensity of the dermatitis and the severity of the disease. Severely affected pellagrins might have minimal skin changes, and mild pellagra might be associated with severe dermatitis. Usually the dermatitis lasted a short time, while the nervous and gastrointestinal symptoms became chronic.

Goldberger believed that a deficiency in tryptophan was a causal factor in pellagra. It seems certain today that at least two and possibly three deficiencies were present:

(1) of protein or, more specifically, tryptophan; (2) of NAD, owing to a deficiency of nicotinic acid or nicotinamide; and (3) possibly of pyridoxine.

The four D's of pellagra cannot be considered a pure syndrome of NAD deficiency, because a lack of tryptophan, which is an essential amino acid and a precursor of serotonin, could have contributed. Tanner, in a report to Goldberger (see Sebrell and Harris, 1954), stated that tryptophan has a remarkable effect in improving skin lesions. He wrote, "I might add that the improvement in this patient's skin condition has surpassed anything I have ever seen in a case of pellagra in an equal period of time." Very little is known about tryptophan deficiency, since even the poorest North American diets contain about twice the average daily requirement. Infants receiving too little develop anorexia, which is cured as soon as tryptophan is supplied. Three adults on 63 mg per day for three or four days developed somatic changes. One experienced nausea and vomited, one suffered diarrhea, and the third complained of extreme fatigue.

Recently a chronic schizophrenic woman consulted me. She had the typical changes in perception, thought, and mood. In addition, she had a new symptom that I have seen rarely: she was unable to modulate and lower her voice. Her skin was rough and coppery in color. After one month of nicotinic acid and ascorbic acid she was much improved mentally and was able to speak in a normal tone, but there had been no change in her skin color. She was then started on tryptophan, 2 grams per day. One month later there was a marked decrease in the degree of pigmentation on her face. This single observation supports the finding made by Tanner.

The phenothiazine pigmentation first described in a large series of cases by Greiner and Berry (1964) again brought schizophrenic skin to psychiatric attention. Out of several thousand cases, seventy developed this peculiar pigmentation. All were women. Histological examination showed that there was an accumulation of golden-brown, finely granular pigment in cells around the capillaries in the superficial layers of the dermis. Greiner and Nicolson (1964, 1965) later reported that twelve physically healthy young patients on prolonged chlorpromazine therapy died unexpectedly. Five had the peculiar skin changes described earlier. The authors suggested that the pigment was melanin, produced by an effect of the tranquilizer on the autonomic nervous system.

Satanove (1965), Ban and Lehmann (1965), Zelickson (1965, 1966), Massey (1965), and Greiner (1967; 1969, personal commun.) found that, as in pellagra, the distribution of the pigmentation in schizophrenics on high doses of tranquilizers is symmetrical and confined to areas of the skin exposed to the sun.

Greiner and Berry (1964) described the skin changes as follows:

> Pigmentation of the skin was found only on exposed areas of the face, neck, and upper chest, and occasionally on the dorsum of the hands and exposed parts of the lower legs. On the face it varied from a mild diffuse violaceous discoloration of the cheeks and nose in a butterfly distribution to a deep purplish-grey metallic color

> of the entire face, with occasional sparing in facial wrinkles and in the deep cleft below the lower lip. This color was unlike a deep suntan and was quite distinctive. The discoloration often became first apparent in the summer but did not disappear in the winter, nor did it fade significantly upon cessation of drug treatment at least up to six months. There was no associated blistering of the skin nor were there any changes in skin texture.

Their accompanying illustration is remarkably like a picture of the pellagrin dermatitis. These authors did not refer to symmetry as a main characteristic but it is certainly evident in the illustration. The pigment appeared to be a melanin. Greiner and Nicolson (1964) also found extensive deposits of melanin-like pigment in the viscera of a patient. Massey (1965) suggested that exposure to the sun produced dermatitis on patients receiving high doses of chlorpromazine. A picture of one of his subjects also shows a bilateral symmetrical distribution of pigmentation. Satanove (1965) suggested that the purple pigment might be a compound of melanin and some chlorpromazine metabolite. Satanove's patient also showed the typical symmetrical pattern of pigmentation in sun-exposed areas of the skin. Ban and Lehmann (1965) reported several additional cases. It seems clear from Zelickson's (1966) report that the purple pigment is a compound of melanin and a metabolite coming from chlorpromazine, probably 7-hydroxychlorpromazine (Bolt and Forrest, 1968).

The hyperpigmentation is not simply a phenothiazine phenomenon. So far it has not been reported in other diseases, and according to Greiner and Nicolson (1965) and Greiner (1967) similar increased pigmentation is found in schizophrenics who had never been given phenothiazines. They examined tissues of schizophrenic patients who died between 1947 and 1949 and found that melanin was deposited in the same areas as for phenothiazine-treated cases, but in smaller amounts. Every one of 30 chronic schizophrenics had increased melanin formation in the viscera, whereas none of the nonschizophrenics had the pigmentation. They concluded that increased melanogenesis is a fundamental aspect of schizophrenia, and that phenothiazines increase it. Melanin increases oxidation of NAD and might interfere in the pyridine nucleotide cycle. Phenothiazines (Van Woert, 1968) inhibit this oxidation: perhaps this is an additional way in which they are therapeutic for schizophrenia. The hyperpigmentation can be reduced by a low copper diet and penicillamine (Greiner et al., 1964).

There is, then, no sharp demarcation between pellagra and schizophrenia as far as pigmentation of skin is concerned. In pellagra it is severe, while in schizophrenia similar pigmentation occurs only under the influence of chlorpromazine.

Dermatitis has been found in psychotics not receiving tranquilizers. Harris (1942) described a schizophrenic-like psychosis which was associated with a generalized brownish-yellow pigmentation of the skin. The color was more intense in the areolae, and the nipples were nearly black. In 1960 Osmond and I (Hoffer and Osmond, 1960) reported that many chronic schizophrenics who had not been in the sun for years

were as brown as if they had been sun-tanned. Many acute schizophrenics have a brown discoloration on their faces, similar to that found in some pregnant women. It is possible to judge the rate of recovery by the rate at which the pigment disappears. The skin may be coarse, pebbly, and slightly edematous or puffy, and may secrete excessive quantities of sebaceous material, especially in adolescent boys.

Recently I examined an adolescent schizophrenic girl who had been ill for several months with severe depression, anxiety, change in personality, paranoid ideas, and difficulty in thinking. She had a typical symmetrical erythematous rash on her face, for which she had been receiving treatment by a dermatologist. She looked as if she had been scalded, and there was a crusted serous discharge on her face. Treatment had removed most of the discharge and crust, but there had been no other change. She was started on 3 grams of nicotinamide per day, 3 grams of ascorbic acid per day, and a multivitamin capsule containing many of the B vitamins (Stress caps). The skin lesion began to clear after one week of vitamin medication. When she was seen one month later her face was normal, the only evidence of her rash being a small slightly crusted area over her left ear lobe. She was also normal mentally, free of the symptoms which had forced her to seek help. Her HOD scores, which on December 24, 1969, were Total score 28, Perception 6, Paranoid 0, and Depression 7, had decreased by February 20, 1970, to 1, 0, 0, and 0.

I recently interviewed a chronic schizophrenic woman and her husband. She had been ill for several years, and had been on megavitamins about six months. I had given her a series of ECT, and this was the first follow-up, two months after discharge. She had been mute for some time, but began to talk during the interview. She had improved a good deal, according to her husband. They both wanted me to examine her fingernails. The distal half of each nail was yellow-brown and no pink could be seen, but the proximal half was a normal pink. The demarcation line was sharp, gently curved, and in the same relative position in each nail. It was obvious that a few months earlier she had stopped depositing pigment in her nails, probably within a few days, because the margin was very sharp. Normal nail had grown from then on. The yellow-brown coloration probably was the schizophrenic pigment.

Another woman who recovered after megavitamin B3 therapy reported that while she was ill her nails did not grow, did not need to be cut, and became rough and ragged. She was given nicotinic acid, and after one week her nails began to grow normally, which was a great relief to her. She also observed that the new nail was pinker—that is, more translucent—than before.

The Gastrointestinal System

Diarrhea is the second D of pellagra. The lesions of pellagra seem to have a predilection for ectodermal tissues—the brain, mucosa of the gastrointestinal system, and

skin. In dogs a deficiency of vitamin B3 causes "black tongue," an animal form of pellagra that can be produced in the laboratory, with lesions in the mouth and on the tongue. In most pellagrins diarrhea and constipation alternate, but gastrointestinal symptoms are not found in all cases. Marie (in Wood, 1908) wrote, "There are pellagrins in whom there are no disorders of the skin or of the digestive organs and who suffer most from disturbances of the motor system and from a general disability . . . grave psychic alterations, and changes in mobility and sensibility such as various hyperesthesiae."

Gastrointestinal changes are not nearly as striking in schizophrenia, but they sometimes occur, especially in chronic schizophrenics, who suffer from nausea and vomiting, cramps, diarrhea, and constipation.

Psychiatric Changes

Few psychiatrists in North America have seen cases of pellagra. It disappeared almost completely after 1941, when nicotinamide was added to flour. However, it is still present in some areas, especially among the poor (Newbold, 1969, personal commun.).

The main differential diagnosis in 1912 was between dementia praecox, manic depressive psychosis, pellagra, and even scurvy (Wood, 1912), and only when the typical dermatitis was present was diagnosis relatively simple. Until 1941, pellagra and dementia praecox were often confused. After Goldberger's classic findings became known, a diagnosis of pellagra depended on a history of malnutrition in areas where pellagra was endemic and on the typical skin lesions. Unfortunately, these were not always dependable, for many schizophrenics ate poorly, because of idiosyncrasies or delusions, and it was impossible to decide which was primary, the malnutrition or the schizophrenia. Often the typical dermatitis did not appear.

I suspect that Goldberger insisted on investigating only pellagrins with distinct dermatitis as a way out of the diagnostic dilemma.

Early investigators were so impressed with the rapid and dramatic responses of the pellagra psychosis to nicotinic acid that they expanded their trials to include other organic psychoses, including dementia praecox. Up to 10 percent of the admissions to some southern mental hospitals were pellagrins. When these typical dementia praecox cases were given 1 gram of nicotinic acid per day some promptly recovered, whereupon the psychiatrist in charge would just as promptly rediagnose them as pellagrins, which insured that no schizophrenic would ever be cured with nicotinic acid. This must have been the problem facing Cleckley et al. (1939), who first used megavitamin doses of nicotinic acid to treat what they termed "atypical psychoses" in 19 patients, whose symptoms ranged from hebetude to profound stupor. None of them had the usual dementia of pellagra, but three had delirium. The coincidence of

stupor and glossitis suggested the possibility of "cerebral pellagra." In four cases improvement was substantial; in the others it was dramatic. The authors reported that

> The results of treatment made it evident that these patients presented a form of pellagra evidently common but seldom recognized, even in endemic areas where physicians are alert to the rather protean manifestations of the disease. We are quite certain that the therapeutic test with nicotinic acid was life saving in practically all of the group and equally certain that many persons have been allowed to die because of failure to recognize the cerebral symptom of pellagra when other evidences of the disease are absent.

The only certain way to diagnose schizophrenia and pellagra was by the therapeutic test. If the psychosis cleared rapidly upon treatment with vitamin doses, say 1 gram per day or less, the condition was called pellagra. But even this did not always permit a distinction, because many chronic pellagrins required much higher doses continually for a long time.

In the early stages of both pellagra and schizophrenia the patient suffers neurotic symptoms, which include anxiety, depression, and fatigue. The fully developed syndrome is very similar. The following description given by Wood (1912) closely resembles descriptions of dementia praecox:

> In many cases there is a very gradual development of the stuporous condition. In these cases Gregor states that there is a disturbance of psycho-motor activity without vivid mental disturbances. It is further stated that some patients recognizing their mental unfitness apply for admission to the insane institutions. I have never experienced this, but it is no uncommon thing for them to acknowledge their insanity though the expression is usually of a fear of its subsequent development. There is often seen a gradual development of an "affectless stupor" which is followed by a return to their former mental condition. In some cases psychic impediments are said by this same author to develop in a relatively short time. The feeling of mental insufficiency, as in the above-mentioned case, is apt to have a very melancholy aspect and in some instances there may be manifested suicidal tendencies. It is also noted by Gregor that severe cases may assume temporarily katatonic symptoms of posture and motion stereotypies.
>
> Tanzi noted disturbances of memory in this group, but Gregor says that weakness of memory is not a characteristic of acute pellagrous dementia and that in convalescence memory readily returns, showing that the supposed disturbance of memory was really due to difficulty in performing psychic processes.
>
> Melancholia is the usual mental disturbance in pellagra, and it is said that with the improvement in the physical condition there will be a corresponding improvement in the mental state. This has been my experience, with a few exceptions. One of these exceptions is the case of a woman who has not suffered an outbreak for so long a time that she is counted well of the pellagra but she insists that she has only a few more days to live and has regularly sent for one of her children once a week for many months in order that he should be present at her death. Tanzi considers these cases of

melancholia to be really a mild form of amentia. Gregor counted stupor to be an unfavorable prognostic sign.

Of this group of acute (stuporous) dementia Gregor had ten cases of his series of seventy-two.

Gregor's third group, of which he had thirty-two cases, is the amentia or acute confusional insanity. He says that they were long continued with a tendency to remissions and intermissions. There is first a period of varying length manifesting symptoms of a neurasthenic character, followed by terrifying hallucinations to which is added violent motor excitement. According to Gregor delirium was followed by stupor or the stupor was interrupted by delirium. He says the patient sees the house or village burning, enemies coming, wild animals attacking him, and the devil appearing; that more rarely there is a quiet, dreamy state and the heavens open and the Lord appears and in imagination they return to the scenes of their daily life. There occurs phenomenon of motion in connection with hallucinations. When secluded they are prone to move about and become noisy. The period of excitement lasts from a few hours to several days. These outbreaks may be followed by long intervals of mental and bodily quiet. Stupor may occur but there is only slight disturbance of orientation. Later in the course of the disease they are said to pass into a delirium of the same character as seen in typhoid fever or meningitis. In the presence of diarrhea added to this mental state, Gregor finds his conception of typhoid pellagra. Hallucinosis is said to offer a decidedly favorable prognosis for the first attack. Further, it is stated that dementia does not always ensue after a severe initial attack. The development of katatonic symptoms, which is more apt to occur in juvenile cases, makes the diagnosis more difficult.

Gregor's fourth classification was that of acute delirium, and of this group he reported two cases out of his series of seventy-two. This class is distinguished from the third or preceding group by an exaggeration of all the symptoms of that group. There occurs a condition characterized by hallucinations, motor excitation, and a shorter course than the preceding which ends in death. These symptoms are said to occur in some instances without the bodily signs of pellagra though the two usually occur together. Except for an absence of a rise of temperature, the second, third and fourth groups of Gregor's classification are said to resemble the mental symptoms of acute infectious disease and for that reason are arbitrarily placed in a classification under the infective exhaustive psychoses.

Gregor's fifth group, designated katatonia, is so different from my own experience that I quote the whole:

"The katatonic condition occurs with acute somatic pellagra. Here, considering the concurrence of acute somatic and psychic pellagra, we must assume a pellagrous intoxication as the causative factors, as in pellagrous neurasthenia. Many patients show consciousness of their disease. Hallucinations may precede this condition. Excitement, stereotypy, wild jactitation and verbigeration are common. The katatonia cases pass rapidly into dementia.

"Of the cases of the fifth group, the majority belong to the katatonia subdivision from the symptoms, course, and termination. In all three cases (females) excitation occurred, ending with stereotypy, jactitation, and verbigeration. The patients did not show marked effects. In one case, hallucinations preceded the condition. In all three cases the transition into dementia was rapid, in which posture and motion stereotypies, impulsive actions, and talkativeness were observed. In one case, these symptoms were

followed by a permanent negative phase. In another case, besides many posture and motion stereotypies, interchange of negativism and flexibilita cerea was observed. In one case, the katatonic symptoms were marked from the beginning. A male case showed on admission to the hospital katatonic excitation, and after a few days a remission followed by another katatonic phase.

"Six of these cases ended in dementia more or less rapidly, although remissions may occur."

The sixth group of Gregor is the anxiety psychoses. Of this group he had three cases. He says that the violent, fluctuating anxiety effect, the motor unrest, the anxiety ideas and the "phonemes" completing them, determined the diagnosis. It is complicated, however, by extraneous features. There is shown a sense of insufficiency, and the victim appears stuporous in the intervals between attacks resembling cases classified under the second and third group. Mental weakness increases after the anxiety attacks have disappeared. Psycho-motor weakness alternates with violent anxiety effects and vivid motor unrest. Temporary ideas of persecution and sin followed by stupor were observed by Gregor. One case of this group was typical depressive melancholia.

The seventh and last group of Gregor was manic depressive insanity and two of his cases were thus classified. One showed the condition of mania arising from subjective pellagrous troubles while in the other the mania was followed by a distinct stupor.

The classifications of Mobley are as follows:

(1) *acute intoxication psychosis*, with psycho-motor suspension;
(2) *infective-exhaustive psychosis*, with psycho-retardation or excitation;
(3) *symptomatic melancholia*, with psycho-motor retardation; and
(4) *manic-depressive*, with psycho-motor retardation or excitation.

The . . . correspondence from a man whom I have known in college is interesting. He was a school teacher and well educated. Many of the letters received from pellagrins would show even better the mental states but for the fact that the majority are not well enough educated to express themselves in anything like a normal manner, and again at the time of marked mental change there usually occurs sufficient motor disturbance to interfere with writing. The character of the handwriting itself shows early tiring. . . .

In many cases of pellagra are seen symptoms that would justify the classification of amentia. The clouded consciousness, interference with association memory, hallucinations and delusions, anomalous emotional states as apprehensiveness and fear are often present in pellagra and are also distinctive of amentia. Paton, who well describes this condition, says that there is no sharp line to be drawn between this condition and acute delirium; many cases can be differentiated only by the longer course in the former. In the description of amentia is found reference to a condition in which the patient shows signs of restlessness, slight dissociation in connected thought, apprehensiveness, and fear of being left alone. It is recorded also that he will complain of unpleasant thoughts and unpleasant dreams. Disturbance in association memory increases and distractibility keeps the attention constantly wandering, so that when asked a simple question the patient begins to reply, forgets the subject in hand and passes to something else. All of these symptoms may be noted in pellagra. In both conditions hallucinations hold a prominent place. Ideas of persecution are noted and the patient suspects the physician and attendants in both states. It is said that in amentia the character of the hallucinations in the early stages is constantly changing.

Motor restlessness often associated with extreme talkativeness have been noted in both. Paton says there are two types of this disease: "an asthenic type and one in which the confusional state is more boisterous and the general motor restlessness greater. To the former belongs this confusional or stuporous amentia of Meynert; to the latter, the hallucinatory confusion, delirious amentia, and so-called acute hallucinatory paranoia of other writers." I am of the opinion that many of the psychoses of pellagra are true cases of Meynert's stuporous amentia and that the etiological factor is the pellagra poison, whatever that may be, just as parturition is a recognized cause of the same condition.

It must be remembered that certain katatonic symptoms occur both in amentia as well as in dementia praecox, and these katatonic symptoms are not unusual in pellagra. In dementia praecox, however, these symptoms are much more definite than in the other conditions, while in amentia there is greater impairment of consciousness and more defects in association memory.

Many cases of pellagra suggest the diagnosis of manic depressive insanity, and this condition, too, is easily confused with amentia. Paton says that in genuine cases of mania the flight of ideas has certain specific qualities and the interference with consciousness or with the reception of all forms of sensory impressions is less marked. The very fact that in this group of manic depressive insanity there occur phases of melancholia which later are replaced by mania suggests just the condition in pellagra, but it must be said that the same alternation of phases also occurs in other mental states. During the motor phase of manic depressive insanity the general restlessness, the psycho-motor activity, the lack of coordination of movement with the peculiar jerky and impulsive actions, sometimes also tremulousness and unsteadiness would not be foreign to the psychosis of pellagra. But the animation, the obstrusiveness, the tendency to be meddlesome, and the grandiloquence would be very foreign to pellagra. In pellagra I have seen maniacal states but they were never of the violent type seen in manic depressive insanity. During the stage of depression in manic depressive insanity occur symptoms which are very suggestive of the pellagrous psychosis. The tardiness in replying to questions, the emotional depression, the change in handwriting due to retardation of voluntary movements, the consciousness of subjective difficulties in the association processes, vague apprehension which is often increased to marked anxiety point strongly to pellagra.

The psychosis of pellagra does not materially differ from the other psychoses in the sense that the whole symptom complex must be considered, making due allowance for the various phases which are constantly changing in so many different states, in arriving at a diagnosis.

It seems to be admitted that the mental condition of pellagrins undergoes an early modification. This early mental state may be ill-defined or show itself by a greater moral impressionability, or greater psychical excitability, or it may be described under the general term of neurasthenia. Later, inertia appears, the patients are apathetic and show psycho-motor impediments. There is said to be intellectual hebetude, stupor or even mutism. Thus Lombroso's psychical catalepsy may appear. If they are not silent, pellagrins respond with difficulty, or have the air of not understanding what is said to them. Insomnia is almost universal and depression (psychic pain) is characteristic. Stupor often ensues, and confusion, the type of exhaustion and intoxication psychoses, dominates the scene. The patients appear frightened, become suspicious, refuse food and medicine, are subject to hallucinations, illusions,

delusions, are suicidal (hydromania) and have other criminal tendencies. Episodic disorders of memory and orientation are observed.

The effect is sometimes made to classify the mental condition of pellagrins as acute and chronic. The acute commoner symptoms are: Temperature 39 to 41 degrees C; neuromuscular excitement, contractions, muscular rigidity, exaggerated reflexes, confusion with phases of exaltation, and marked insomnia.

This condition is more common with alcoholism but may be engrafted upon the so-called chronic form. It is often manifested as an acute collapse-delirium, and is probably the typhoid pellagra (pellagra typhosus) of some writers.

In chronic cases: depression, confusion, paresthesias, hallucinations and illusions, memory disturbances, insomnia, exaggerated reflexes, ataxia, and terminal dementia.

Intermediate forms occur, being marked by alterations of depression and exaltation with remissions and apparent recovery. Excitement may break forth without cause, especially in the spring and summer.

Polyneuritis is sometimes observed.

For the chronic form, dementia is the common termination, but it may be complicated by paralysis or tuberculosis.

In the first attack the pellagra psychosis is an amentia (confusional insanity). In the latter and progressive phase, marked by chronic and incurable cachexia, it is a dementia. It is an intermittent and progressive amentia, which if not cured, or not early fatal, terminates in dementia (Tanzi). Or it may end in chronic mental confusion or in pellagrous pseudo-general paralysis (Regis).

Depression and confusion are the more common mental symptoms associated with pellagra, but periods of exaltation (excitement) occur episodically.

Strictly there is no mental symptom-complex characteristic of pellagra, but pellagra may act as the exciting cause of several forms of nervous and mental states, varying from neurasthenia to polyneuritis and meningitis, and from simple depression to paretic conditions and dementia.

Under the influence of the pellagrous intoxication patients commit crimes—suicide (hydromani), homicide, infanticide, incendiarism, etc.

According to the degree or duration of the pellagrous intoxication or possibly from idiosyncrasy, the patient is liable to develop the symptoms of acute collapse delirium at any time, and die in the attack.

It is not unlikely that the mental symptoms of pellagra may differ by seasons or in different countries and in different parts of the same country, just as, broadly speaking, do the physical signs and symptoms of the disease.

After all, may not Baillarger be right in questioning whether pellagrous poisoning does not, like alcohol, produce these various neuroses and psychoses according to the reaction of different individuals?

I have quoted at length from Wood to show the marked similarity between schizophrenia and the pellagra psychoses as described many years ago.

With use of clinical criteria only, it has always been difficult to differentiate between schizophrenia and other psychoses. Perhaps if psychiatry had not turned completely against the excellent definition of insanity commonly used up to about a century ago, we might have more lucid and scientific definitions of schizophrenia

today. John Conolly (1830) described insanity as a disease of perception combined with an inability to distinguish whether these perceptual changes were real or not. Conolly did not write as if he had enunciated a new principle of diagnosis but as if his ideas were common knowledge. A perusal of Griesinger and other authors shows that they considered perceptual changes basic in a consideration of the psychopathology of insanity.

Hoffer and Osmond (1966a–c) had come to the same conclusion before becoming aware of Conolly's work. This point of view was elaborated in the book *How To Live With Schizophrenia* (1966c).

During the last century this clear and elegant definition was overthrown, mainly by the efforts of men like Kretschmer, who presented many intricate subcategories of dementia praecox based upon minutiae, and by Bleuler, who replaced dementia praecox with schizophrenia but denied that there were any perceptual changes. He considered that schizophrenia was a disease of association and that this was the cause of the attendant thought disorder. Hallucinations were described as examples of pathological associations: over and over he insisted that there were no perceptual changes. Freud had little interest in diagnosing schizophrenia, probably because he had never been trained as a psychiatrist and his hypotheses never had to be tested against the harsh realities of chronic schizophrenia in a mental hospital.

Bleuler enlarged the variety of conditions called schizophrenia but even with his definition only chronic cases could be so diagnosed because thought disorder and the other Bleulerian primary symptoms seldom occur early in the illness. Diagnosing schizophrenia with Bleuler's criteria is like waiting for one lung to be consumed by mycobacteria before diagnosing tuberculosis. Fortunately, perceptual theories of schizophrenia have become much more popular again, especially since the development of our HOD test (Hoffer and Osmond, 1961a, 1961b; Kelm et al., 1967) and the EWI test (El Meligi and Osmond, 1967).

With Bleuler's criteria it was very difficult to examine pellagra and schizophrenia for similarities and differences. Pellagra severe and chronic enough to produce thought disorder also produces delirium (disorientation, confusion, and memory disturbances). I shall therefore use the Conolly scheme as we have elaborated it in our book *How To Live With Schizophrenia.*

One of the best and most recent descriptions of pellagra was recorded by Spillane (1947). The description of pellagra which follows is based on that in his book.

Changes in Perception

Sight. In pellagra, a high proportion of patients complained of visual changes, including failing vision, hypersensitivity to light, amblyopia, illusions, and hallucinations. Spillane quoted Gowers' statements that the retina "was a sensitive outpost

of the nervous system" and that it "presents the most delicate example in the body of the relation of the nutrition to the nerves."

Hearing. In pellagra, patients suffered from tinnitus, vertigo, and auditory hallucinations. There was also difficulty in hearing and, very rarely, deafness.

Smell. In pellagra, the sense of smell was sometimes hyperacute.

Taste. In pellagra, the sense of taste was frequently dulled. In up to half the cases, patients mentioned a persistent salty taste.

Touch. Wood (1912) reported that pellagrins suffered paresthesias.

These changes in perception are of course very similar to those reported by schizophrenics when they are questioned or when they do the perceptual tests such as the HOD or the EWI. They are also the perceptual changes commonly produced by the hallucinogens (Hoffer and Osmond, 1967). In fact, so characteristic are these changes that the quickest way to explain schizophrenia to a young person today is to compare it to a bad trip, a freakout.

Changes in Thought

I have described changes in thought in two categories: content and process. When thought content is altered the patient is still able to think logically but his premises are wrong, usually because perception is disordered.

For example, a patient who hears his own thoughts, a not uncommon perceptual change, may conclude that alien forces have planted them in his mind, or that he is a radio receiver, or that people can read his mind. When process is altered it becomes impossible to reason logically, thoughts become too fast, too slow, nonexistent, or jumbled. In severe states there is disorientation, confusion, and memory disturbance. All these changes also occur in pellagra.

Changes in Mood

The earliest changes in pellagra are in mood. Patients become depressed, anxious, and fatigued. This was well known to the early pellagrologists and to the communities where pellagra was endemic. And the same prodromal symptoms occur in schizophrenia. It is very common for anxiety neuroses and depressions to be treated for years until the perceptual changes become so gross that the diagnosis of schizophrenia is forced. I doubt that there is any psychiatrist who has not been rudely surprised by the emergence of schizophrenia in his neurotic patients.

Changes in Behavior: Crime, Pellagra, and Schizophrenia

The killing of John F. Kennedy, Martin Luther King, and Robert Kennedy, and the bizarre events which followed have focused critical attention on the problem of crime and mental illness. While it is true that schizophrenic patients commit crimes, it is equally true that the vast proportion of them are law abiding, moral citizens who have a greater propensity to commit suicide than when they are normal, but whose crime rate is not greater than that of the general population. However, schizophrenic crimes when they do occur are more apt to be spectacular, since they are based upon perceptual changes and delusional ideas which make no sense to normal people.

Sirhan Sirhan's trial illustrates a general confusion in the minds of lawyers and the public as to whether a killer is to be looked upon as an evil man or as a sick man. It seems obvious that Sirhan was mentally ill and this was admitted by his lawyers although Sirhan himself had not accepted this. However, his behavior before, during, and after the killing suggests that schizophrenia was present.

Behavior depends upon personality, programming (education, social setting, culture), and upon one's assessment of the environment. Schizophrenics who commit crimes most often do so because of perceptual changes and their assessment of them; for example, a man who believes his enemies are hiding in a building might in self-defense burn it down. If pellagra is similar to schizophrenia, I would expect the same association between pellagra and crime.

Kholy (1951) studied the relationship in Egypt. He described pellagra as follows:

> Before the onset of the symptoms referable to one or more of these systems, there are usually varying intervals of weeks or months during which rather indefinite symptoms are in evidence, such as weakness, giddiness, depression, anorexia, constipation, headache, etc. The characteristic skin lesions are usually accompanied by burning sensations which may extend to the palms of the hands and soles of the feet. The digestive symptoms are in a large number of cases the first to appear, and they include the inflammation of the mucosa of the mouth and tongue, the latter being red and raw with denuded epithelium and the whole buccal cavity being sore and painful, often with increased salivation; they also include gastro-intestinal disturbances such as vomiting, salty or bitter taste in the food, and a history of alternating diarrhea and constipation. The nervous symptoms may be of a general nature and consist mainly of paraesthesiae occurring throughout the body, and of muscular asthenia, especially of the legs; there may also be encountered weakness of vision, diplopia, photophobia, and especially loss or decrease of sexual desire. It is important to note that the mental symptoms may often begin when the other prominent physical symptoms are at a standstill or have actually disappeared.
>
> There is nothing characteristic in the form of the mental symptoms. The most frequent manifestation is that of an intermittent delirium of the usual toxic type; that is a confusional psychosis which is usually subacute, but may sometimes be acute and accompanied by restlessness and even by a manic excitement. Another not uncommon form is that of a state of depression, which is often a reactive depression

related to the patient's realization that he is suffering from a dreaded and serious physical illness. In a third small group of cases there is a mental retardation without deep depression, a sort of chronic organic reaction with memory loss, indolence, and indifference.

Over an eight-year period, I examined 1,150 persons accused of a crime. Of this group, 206 suffered from pellagra, and of these, 118 (57 percent) were involved in crimes of violence, broken down as follows:

murder or manslaughter—56 cases
attempted murder—15 cases
threatening murder—1 case
serious assault—9 cases
common assault—20 cases
kidnapping children—3 cases
destroying property—3 cases
arson—6 cases
sexual assault—4 cases
attempted suicide—1 case.

The remaining 61 were accused of non-violent crimes: theft, entering buildings with the intention of committing a crime, forgery, and so on. Only 10 percent of non-pellagrins were accused of murder, compared with 27 percent for pellagrins. Over one-third of all murderers diagnosed as insane were pellagrin. One can conclude that had they not had pellagra, there would have been a major decrease in crimes of violence.

The conclusion that it is often impossible to distinguish between pellagra and schizophrenia was made long ago and has been repeatedly confirmed. Evans (1939) reported the case of a woman who had been ill for 11 years and became clearly psychotic, but with no physical changes. When given 500 mg per day of nicotinic acid she was normal in four days. The author said, "If it had not been for her response to nicotinic acid therapy the case would probably have been classified as schizophrenic or toxic psychosis."

Frostig and Spies (1940) examined 60 patients with subclinical and mild pellagra. The initial syndrome consisted of hyperesthesia, increased psychomotor drive, depression and apprehension, fatigue, headaches, and insomnia. They were readily classified as anxiety neuroses. The authors concluded that nutritional deficiencies may cause a disintegration of the personality, including a breakdown of morale.

The final similarity and perhaps the most important one is the fact that both conditions respond to treatment with vitamin B3, and, even more important, adequate doses will prevent relapse in both. Each person must have the correct dose to keep himself free from pellagra (schizophrenia): whether this is 5 mg per day or 5,000 mg

per day, the principle is the same. All the data suggests that a daily intake of 1 gram of vitamin B3 for our population would nearly eradicate schizophrenia, much as fortification of flour with smaller quantities has nearly eradicated pellagra.

Hypoglycemia

Between one-half and two-thirds of schizophrenic patients suffer from relative hypoglycemia (Cott, 1967, 1969; Hawkins, 1968; Ward, 1967; Meiers, 1967; Hoffer, 1967a–c). This has not been tested in pellagrins but probably is the case. Mainzer (1939) reported that of 21 patients with pellagra, 16 showed a deep and prolonged decrease in blood sugar after subcutaneous injection of 5 units of insulin.

Pellagra, Schizophrenia, and the Pyridine Nucleotide Cycle

The pyridine nucleotide cycle includes the formation of NAD from tryptophan and vitamin B3 and its degradation to its component molecules (Gholson, 1966). Since pellagra is due to a deficiency of NAD any discussion of the biochemistry of pellagra (and of schizophrenia) must begin with tryptophan.

Tryptophan is one of the ten essential amino acids; that is, it cannot be synthesized in the human body. We all may suffer from hypotryptophanemia in the same way that we suffer from hypoascorbemia (Stone, 1965, 1966). In the body a variety of derivatives are formed. Many of those formed in plants are hallucinogenic. Most of the tryptophan is cleaved at the pyrrole portion of the indole by enzymes known as pyrrolases. This initiates a series of reactions which lead to the synthesis of nicotinic acid, nicotinamide adenine dinucleotide, and nicotinamide. These reactions are shown in Figure 11-1.

Theoretically, enzyme blocks can occur anywhere from reactions (*a*) to (*i*). Enzyme blocks at several of these sites have already been implicated in human disease.

Reaction (*a*). The formation of 3-hydroxykynurenine from kynurenine requires the presence of reduced coenzyme 2 (NADPH). In the absence of sufficient coenzyme too little NAD would be formed.

Reaction (*b*). Lozovskii (1962) suggested that this enzyme is blocked to some degree in schizophrenia. He found that after loading with L-tryptophan the excretion of N-methylnicotinamide was decreased in schizophrenic patients when compared with a normal comparison group, and the excretion of xanthurenic acid was increased. Benassi et al. (1964) corroborated these findings. Not only schizophrenics but also their normal twin siblings reacted in the same way. They gave their subjects 100

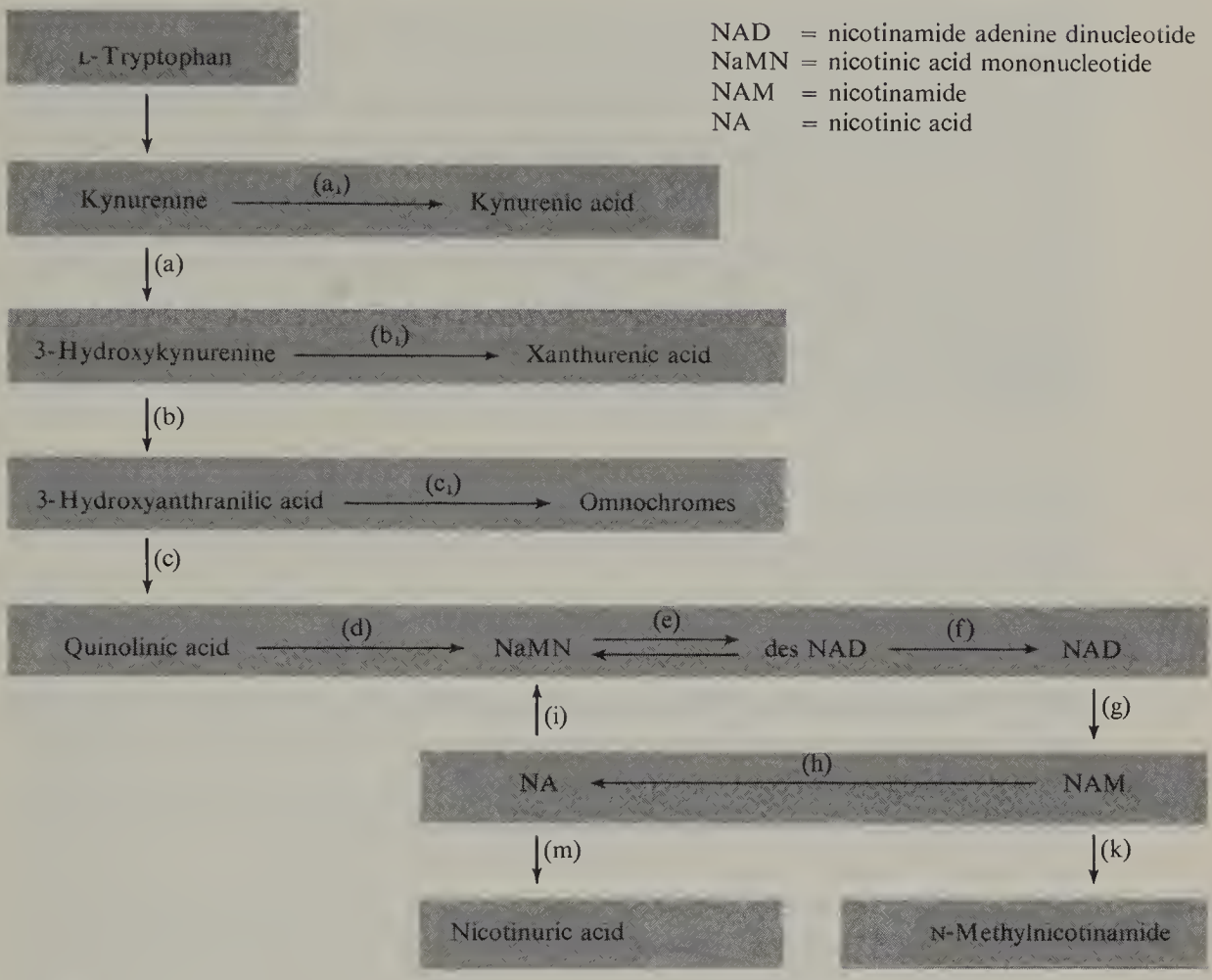


FIGURE 11-1.
Reactions leading to synthesis of nicotinic acid, nicotinamide adenine dinucleotide, and nicotinamide.

mg/kg of L-tryptophan. The schizophrenics excreted more kynurenine, more kynurenic acid, and more xanthurenic acid, but did not excrete more 3-hydroxyanthranilic acid.

Komrower et al. (1964) reported that mentally retarded children improved when treated with nicotinic acid, and excreted large amounts of kynurenine, 3-hydroxykynurenine, and xanthurenic acid. Komrower et al. suggested that this was due to a deficiency of kynureninase (reaction *b*).

A deficiency in reaction (*b*) might account for the known incompatibility between schizophrenia and rheumatoid arthritis. In rheumatoid arthritis the excretion of kynurenine, 3-hydroxykynurenine, anthranilic acid, 3-hydroxyanthranillic acid, N-methylnicotinamide and N-methyl-2-pyridione-5-carboxamide seems to be overly active (Spiera, 1963; Pasquarielo and Tenconi, 1964). A block at reaction (*b*) if present in schizophrenic patients would slow this reaction and either prevent or cure

rheumatoid arthritis. Conversely, having rheumatoid arthritis would indicate there is no block at reaction (*b*), which would decrease the probability of developing schizophrenia. Ehrentheil (1957), Ehrentheil and Marchand (1960), Gregg (1939), Nissen and Spencer (1936), and Trevathan and Tatum (1954) found a decreased incidence of arthritis among schizophrenics. Of course, these two conditions depend upon pyridoxine or its derivative, the coenzyme pyridoxal-5-phosphate, which are involved in several decarboxylation reactions. In its absence the kynureninase reaction is inhibited. There is a reduction in the excretion of anthranilic acid and nicotinic acid and an increase in xanthurenic acid and kynurenic acid. The administration of tryptophan increases these changes.

Reaction (b_1). According to O'Brien and Groshek (1962) this reaction is blocked in Mongolian idiocy. He found an increase in the excretion of 3-hydroxyanthranilic acid and a decrease in the excretion of xanthurenic acid.

Reaction (*c*). Ehrensvard et al. (1960), and Heath and Leach (1962) found that schizophrenic serum oxidized less 3-hydroxyanthranilic acid than normal serum. The unmetabolized 3-hydroxyanthranilic acid could be converted into a group of chemicals known as phenoxazines (omnochromes). They are similar in structure to the phenothiazine tranquilizers. Ehrensvard et al. suggested that therapeutic properties of phenothiazine are related to this similarity.

Reactions (*d*) *to* (*i*). According to Gholson (1966) nicotinamide adenine dinucleotide (NAD) synthesis begins with the reaction of quinolinic acid and 5-phosphoribosyl-1-pyrophosphate to nicotinic acid mononucleotide. This is converted to desnicotinamide adenine dinucleotide (reaction *e*) and then into nicotinamide adenine dinucleotide (reaction *f*); these reactions occur in the liver. NAD is then cleaved by NAD glycohydrolase, but nicotinamide is reutilized by conversion into nicotinic acid by nicotinamidease (reaction *h*), and nicotinic acid is converted into nicotinic acid mononucleotide by pyrophosphorylase. This completes the cycle. Gholson stated:

> It is difficult to understand what is accomplished by the rapid breakdown and resynthesis of NAD, for the resynthesis of this coenzyme from nicotinamide requires three moles of ATP and represents a considerable expenditure of cellular energy. The widespread occurrence of this recycling phenomenon, however, argues for an important, but as yet unknown function for the NAD glycohydrolase reaction in cellular metabolism.

Reactions *c*, *d*, *e*, and *f* make up the de novo pathway of NAD biosynthesis, while reactions *g*, *h*, *i*, *e*, and *f* form a salvage loop for again using nicotinamide released from NAD. Organisms genetically blocked at any point up to and including reaction (*d*) must depend upon nicotinic acid and nicotinamide provided by the diet. But

organisms with the de novo pathway intact can also use nutrient nicotinic acid or nicotinamide and thus can spare the de novo precursors. In nature nicotinamide is found in the nicotinamide nucleotide and not as free nicotinamide.

Nicotinyl molecules are lost from the salvage cycle when nicotinic acid or its derivatives are excreted. Nicotinamide is also excreted unchanged, or converted to N-methylnicotinamide or to other derivatives.

Pyridoxine also is involved in the conversion of quinolinic acid into nicotinic acid nucleotide (reaction *d*). In the absence of pyridoxine quinolinic acid accumulates in the urine. According to Graham (1966) a low nicotinic acid diet with adequate tryptophan will cause pellagra if there is insufficient pyridoxine in the diet. The formation of quinolinic acid from its precursor is very rapid. Graham suggested quinolinic acid might be a more valuable additive than nicotinic acid.

There are so many unknown factors and so many enzymes that might be inhibited that detailed predictions of changes to be expected are rash. Thus, Price et al. (1959) found that schizophrenics given a test dose of tryptophan excreted less than normal quantities of N-methyl-2-pyridone-5-carboxamide. This would be expected if there is a block between tryptophan and NAD and if methylation of nicotinamide were excessive, as was found in vitro by Buscaino et al. (1963) and Buscaino et al. (1965, 1966), for less nicotinamide would be available for further oxidation. On the other hand, Brown et al. (1960), Heyman (1964), and Heyman and Merlis (1963) found that schizophrenics given a test load of 1 gram of nicotinamide excreted more N-methyl-2-pyridone-5-carboxamide and less N-methylnicotinamide. The difference is that a test dose of tryptophan would yield a small increase in nicotinamide while a 1 gram dose of nicotinamide would yield a sudden abrupt increase in substrate.

Effect of Abnormal Nicotinic Acid Metabolism on Other Tryptophan Metabolites

The effect of enzyme blocks on tryptophan metabolism depends upon the site of inhibition. A deficiency in reactions (*a*) to (*d*) would back up indole metabolites somewhere in the precursor chain. Tolerance to tryptophan would be decreased and overloading could occur. This would accommodate the scheme of Berlet et al. (1964) that under stress more tryptophan can be released endogenously to produce toxic metabolites. There would be no increase in 3-hydroxyanthranilic acid and therefore no arthritis.

Tryptophan is implicated in schizophrenia chiefly by its metabolites, but several authors have reported abnormalities in tryptophan metabolism. These include lower levels of urinary tryptophan in schizophrenic urine, lower levels in schizophrenic urine of a still unidentified tryptophan metabolite, and less excretion of N-methyl-2-pyridone-5-carboxamide before and after tryptophan injection.

A small proportion of the tryptophan appears in urine as indolic substances. For example, indoleacetic acid comes from the oxidation of tryptamine, the decarboxylation product of tryptophan, and from indole pyruvic acid; and 5-hydroxyindole acetic acid comes from 5-hydroxytryptamine (serotonin or 5 HT). Other indoles are formed by the action of intestinal bacteria on tryptophan. Some of these indoles are indole and skatole. They can be reabsorbed from the intestinal luman, oxidized, and excreted in urine as indoxyl and hydroxylated or sulfatoxy skatoles.

Relationship of Indole Derivatives to Schizophrenia and Other Psychiatric Diseases

Indole theories of mental disease were common around the end of the 19th century. They were kept alive by the strenuous efforts of men like Buscaino, De Jong, and Baruk. The chief difficulty was that the biochemistry of indoles was in its infancy (in strong contrast to the state of knowledge of indole dye stuffs). No measure of total indoles in urine could be expected to differentiate schizophrenics consistently from others, but throughout the years competent scientists have continued to find greater quantities of indoles in schizophrenic urine. Thoughtful and serious surveys of the literature (for example, Sprince, 1961, 1962, 1966; and Sprince et al., 1963) force the conclusion that there are differences in indole metabolic patterns between schizophrenics and normal subjects. Sprince (1961) reviewed the evidence linking indoles to schizophrenia. The various lines of evidence are:

1. Disturbed indole metabolism is well defined in at least three psychiatric diseases: *phenylketonuria*, in which there is an increase in the excretion of indole acetic acid and indole lactic acid, *Hartnups disease* (H or Harts disease), or *hereditary pellagra*, which is characterized by increased excretion of tryptophan, indican, indole acetic acid, and indole acetyl glutamine (there is apparently a special defect in transport of tryptophan in the cells of the jejunum and proximal renal tubules allowing increased concentrations of tryptophan in the gut, which accounts for the increase in excretion of all the metabolites found in this disease; see Asatoor et al., 1963); and in *pellagra*, with increased excretion of tryptamine and indican.

2. Most of the known psychotomimetics or hallucinogens present in animal or plant tissues are indoles. This was first drawn to the attention of scientists by Hoffer and Osmond (1952), and later amplified by Hoffer et al. (1954).

In 1952, five natural hallucinogens, mescaline, LSD-25, harmine, ibogaine, and the active principle of hashish were known. We suggested that adrenochrome is another. Mescaline may be cyclized in vivo, or could combine with indole receptors and thus, in effect, act like an indole. Tetrahydrocannabinal, not an indole, is the

active substance in marijuana. Many other indoles have been found to be active. Thus, it appears that one of the requisites of many natural hallucinogens is that they are indoles. This does not mean that all indoles are hallucinogens, or that all hallucinogens must be indoles.

Tryptophan itself, in large quantities, does produce changes in man. Sourkes' (1962) statement that "tryptophan is without pharmacological action" is quite incorrect and even meaningless because he does not specify the dose, the subjects, or the activity being studied.

3. Indoles have definite neurophysiological and biochemical effects on the brain. They depress synaptic transmissions, they may alter spontaneous electrical activity of the brain, they alter rhythmic contractions of brain cells in pure culture (of these, adrenochrome is the most toxic), and one indole, serotonin, may be a synaptic hormone.

Indoles interfere in many biochemical processes in the brain. Many indoles inhibit amine oxidase (harmaline and hydroxytryptamine), inhibit pseudo-choline esterase (eserine, LSD-25, serotonin, tryptamine, bufotenine) and choline esterase (LSD-25 and others), depress glucose oxidation in the brain (adrenochrome), inhibit hexose monophosphate, and markedly inhibit glutamic acid decarboxylase (adrenochrome).

4. Chemicals such as sedatives, vitamins, and tranquilizers which are therapeutic for some schizophrenics also antagonize the effects of many indole hallucinogens on normal volunteers.

5. Many of a large number of indoles found in normal urine are apparently related to mental illness. These include: (1) indican, whose relationship to schizophrenia is unclear because indican excretion is so sensitive to many other variables; (2) tryptophan, already discussed; (3) tryptamine, found in increased concentration in urine in pellagrins; (4) indole acetic acid, which is found in increased concentration in the malabsorption syndrome; (5) serotonin; and (6) 5-hydroxyindole acetic acid. But the relationship to schizophrenia is not clear.

Two newer indole derivatives which may be related to schizophrenia are indole acetylglucuronic acid and 6-hydroxyskatole (Sprince, 1961). Sprince (1962) reported that about ten different groups of investigators had reported more frequent occurrence of 6-hydroxyskatole in the schizophrenic population than in normal populations. He also found that schizophrenic's urine had more indole acetamide than normal comparison subjects and more frequently had 6-hydroxyskatole when subjects were under age 35. Both compounds were present in the schizophrenic and comparison groups who were over age 60. Heacock et al. (1964) developed a chromatographic method for determining all four isomeric hydroxyskatoles. Using this method they found that 5-, 6-, and 7-hydroxyskatoles (from the sulfatoxy derivatives) were present in urine. No 4 derivative was found by this method, but the method may

not have been sensitive enough to do so. What was considered to be 6-sulfatoxyskatole in the literature by previous authors is undoubtedly a mixture of these isomers. Heacock et al. (1964) examined urines of some normal and psychiatric subjects for the presence of these substances. Results are shown in Table 11-1.

TABLE 11-1.
Subjects Who Excreted Hydroxyskatoles in Urine

Group	Number	Hydroxyskatoles		
		5	6	7
Normal	9	6	4	3
Psychiatric	13	12	11	11

It is evident that psychiatric patients have some difficulty in the excretion of these indoles. The 5-hydroxy compound seems to be a normal constituent of urine and probably comes from substances like serotonin. But the 6- and 7-hydroxy derivatives are found in a few normal subjects and in most of the mentally ill subjects that were studied.

PSYCHOLOGICAL EFFECTS OF TRYPTOPHAN

Gullino et al. (1956) found that L-tryptophan is the most toxic amino acid of all ten essential amino acids. It is much more toxic for rats than methionine. Olson et al. (1960) gave subjects 10 grams of DL-tryptophan by mouth. All of the 16 normal comparison group had psychological changes, such as changes in perception (lightheadedness, dizziness) and changes in mood, mainly euphoria, but none of the 34 chronic alcoholics had these symptoms.

About ten years ago I took 5-gram doses of L-tryptophan orally for several days. To my great surprise I became dizzy, lightheaded, and euphoric. At the time I compared it to the effect produced by 1 ounce of whiskey. However, being somewhat inhibited by the opposition to subjective experiments, I did not report these findings. Smith and Prockop (1962) corroborated Olson et al.: after receiving 2 grams by mouth, five out of seven normal volunteers became drowsy after one to two hours. After 6 grams all became restless and yawned frequently. One subject showed marked social disinhibition.

Alexander et al. (1963) gave 5-gram doses of L-tryptophan with and without tranylcypromine to six chronic schizophrenic patients and two nonpsychotic psychiatric patients. They listed 16 symptoms. If each patient had every symptom a total of 128 would be scored. Patients on placebo had a score of 0, on tryptophan alone a score

of 10. Methionine yielded a score of 6. Tryptophan plus the amino oxidase inhibitor gave a score of 19, but methionine plus inhibitor gave the highest score, 32. The non-psychotic subjects reacted in a similar way. Coppen et al. (1963) tried to potentiate the antidepressive action of tranylcypromine by feeding the subjects about 10 grams of L-tryptophan per day. Many of the subjects complained of drowsiness or of feeling slightly drunk. Pollin et al. (1961) corroborated Olson et al. (1960). L-Tryptophan given to nine schizophrenic subjects already getting iproniazide, an amine oxidase inhibitor, produced an increase in symptoms in four.

There is little doubt that L-tryptophan is a toxic amino acid when large quantities are consumed. The body is not able to metabolize it quickly, and when amine oxidase, one of the enzymes which helps destroy tryptophan, is blocked, tryptophan becomes more toxic. Excess tryptophan can occur following injection of too much pure amino acid, following consumption of too much protein if the liver is not working well, and even if tissue proteins are metabolized too quickly. Berlet et al. (1964) found that exacerbations of schizophrenic behavior are associated with elevation of urinary tryptophan metabolism. They suggested that free tryptophan possibly arising from breakdown of muscle protein may act like an exogenous toxic substance in producing behavioral worsening. Some of the spontaneous activation of psychotic symptoms may be intensified by endogenous liberation of tryptophan (and also methionine).

Perhaps overloading with tryptophan swamps the enzyme system which leads to NAD and forces an increase in formation of the indole derivatives which come from tryptophan. These are shown in Figure 11-2.

The toxic effect of methionine has been explained as a transmethylase phenomenon but the findings of Sprince et al. (1965) that methionine inhibits the transformation of tryptophan to nicotinamide and increases excretion of indoles have great relevance. Any decrease in NAD production will decrease excretion of nicotinamide derivatives and, according to the views presented here, should make schizophrenics worse.

Tryptophan is hydroxylated to 5-hydroxytryptophan by an oxidase and is then decarboxylated to 5-hydroxytryptamine (serotonin). Serotonin does not cross the blood brain barrier but its immediate precursor does, and then is quickly changed to serotonin. Serotonin is inactivated by several pathways: (1) to 5-hydroxyindoleacetic acid; (2) via 5-hydroxyacetaldehyde derivatives to pigmented and fluorescent substances; (3) by ceruloplasmin to para-quinone imines similar to adrenochrome; (4) by N-acetylation; (5) by conjugation with glycine: and (6) by conjugation with glucuronic acid.

The relationship of serotonin to mental disease was first clearly suggested by Woolley and his colleagues (Woolley, 1958, 1962). This work was then continued by Brodie and Costa (1962). Serotonin was considered to be a neurohormone for the following reasons: (1) it is readily available; (2) it is protected from enzyme inactivation until after it has served its function; and (3) it is distributed in a manner very similar to noradrenaline.

Increasing the quantity of serotonin in the brain of dogs by giving them 5-hydroxytryptophan six hours after pretreatment with mono-amine oxidase inhibitors produces major behavioral changes (Himwich and Costa, 1960). The kind of reaction depended upon the dose (Costa et al., 1962). Slight increases in brain serotonin produce sedation and EEG sleep patterns. High doses result in excitation, EEG arousal, and uncoordinated motor behavior.

Reserpine depletes serotonin and noradrenaline from their storage sites. Depletion of serotonin seems to be the more important, since cold-stressed rats given reserpine did not release serotonin nor was sedation induced even though noradrenaline was depleted. Alpha-methyl-*m*-tyrosine causes 90 percent depletion of noradrenaline up to 16 hours and has a very transient effect on serotonin. It does not produce sedation. Apparently only compounds which release 50 percent of the serotonin produce sedation.

Vander Wende and Johnson (1970) showed that serotonin is an effective inhibitor of enzymatic oxidation of dopamine and norepinephrine, through forming an inhibitor-substrate complex. The inhibitor effect on epinephrine is very pronounced, and is biphasic: at low concentrations it accelerates adrenochrome formation, whereas at higher concentrations it inhibits it.

These authors reported,

> The present studies provide a basis for suggesting a role for serotonin which does not involve neurotransmission. Serotonin could act to modulate the activities of the catecholamines on a purely molecular level through complex formation. Such a relationship between serotonin and dopamine might be suggested by the distribution of these compounds in certain brain nuclei. The substantia nigra and caudate nucleus contain relatively high concentrations of dopamine and serotonin. Laverty et al. examined the subcellular distribution of dopamine relative to other amines in the caudate and found that most of the dopamine was in the soluble fraction, whereas serotonin was bound. In view of the suspected transmitter role of dopamine in this nucleus, this is a convenient arrangement in that bound serotonin should have little influence on dopamine, whereas upon its release, complex formation would result in the modulation of dopamine's action. This type of relationship between serotonin and dopamine in the substantia nigra would also have interesting possibilities. That dopamine may serve as the precursor of neuromelanin found in this area of the brain has recently been discussed. An excessive release of, or a failure to bind, serotonin could then lead to a reduction of melanin. Indeed, a depletion of melanin in the substantia nigra occurs in human Parkinsonism, a disease in which there are alterations in both dopamine and serotonin levels.

In a second report Vander Wende and Johnson (1970) showed that when serotonin concentration is below that of epinephrine the formation of adrenochrome is increased. When the concentration of serotonin is greater than that of epinephrine the oxidation of epinephrine to adrenochrome is inhibited. The authors further stated,

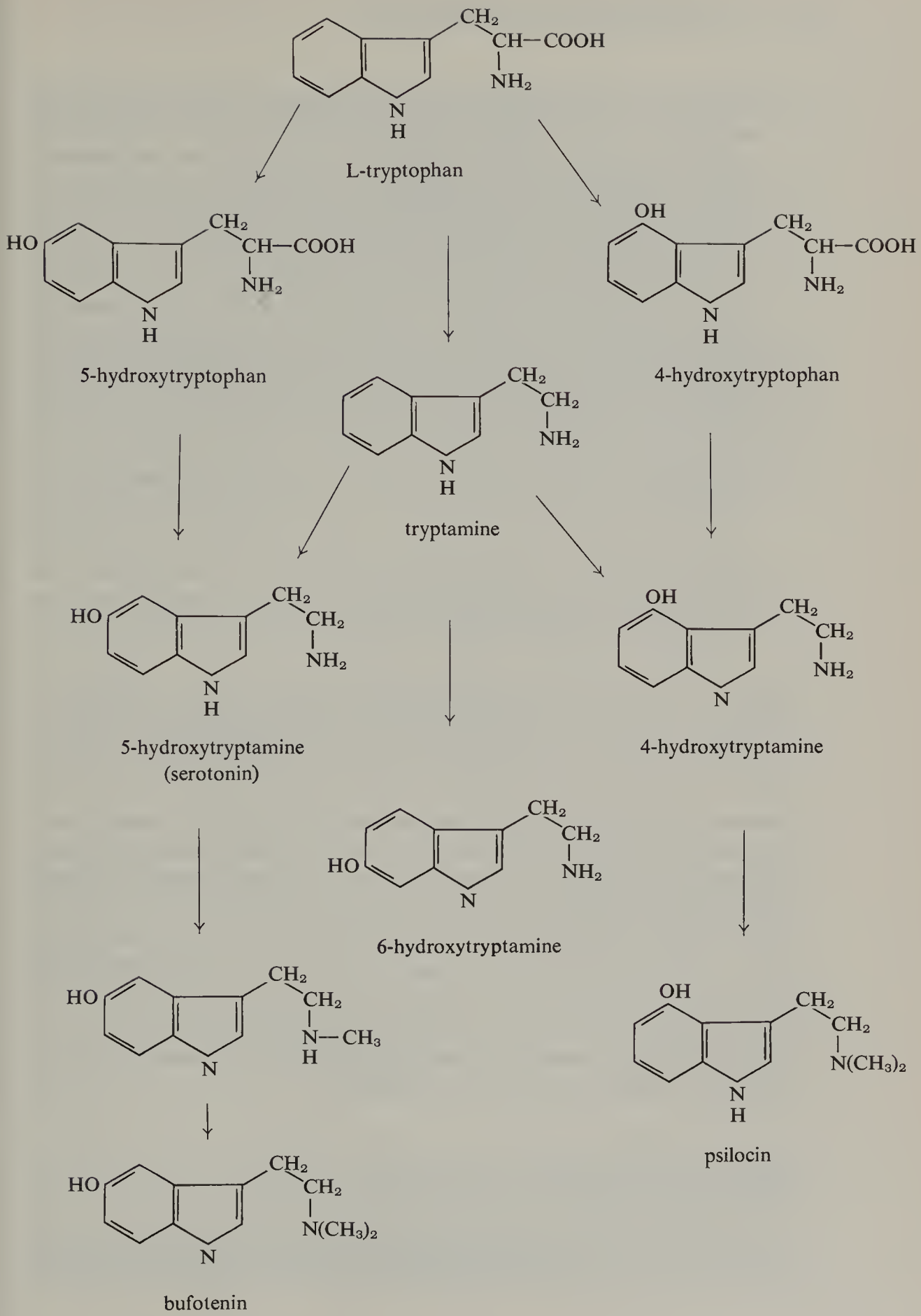


FIGURE 11-2.
Indole derivatives from tryptophan.

> Hoffer and Osmond proposed that the oxidation of epinephrine to adrenochrome may play a role in the etiology of schizophrenia, but this concept never gained favor with other investigators. Instead, attempts have been made to relate norepinephrine and/or serotonin to the control of behavior and, therefore, to the disease. It has been difficult, however, to identify the specific roles of any of these compounds from the conflicting literature. It is our belief that this difficulty lies in the fact that the catecholamines and serotonin are probably more intimately related than may be apparent at the levels of biological organization thus far studied. The results reported here and in our preceding paper would support this argument. These results provide a basis for establishing a more unified picture of the role of these substances in the control of both normal and abnormal behavior. Serotonin would be modulating the activities of the catecholamines on a purely molecular level and, consequently, any alteration of the brain or systemic levels of the indoleamine would necessarily alter the activities of the catecholamines. The reverse situation could also apply. There is no reason to believe that what we see in vitro does not apply to the environment in vivo. It is interesting that the ratio of epinephrine concentration to serotonin concentration is very critical and actually determines the effect which results. If the proper ratio is maintained, adrenochrome formation would be suppressed or even absent completely. However, if the serotonin concentration is lowered to trip the balance in favor of epinephrine, adrenochrome formation would be accelerated. In spite of the fact that formation in vivo of adrenochrome has never been accepted, it would seem significant to reconsider the question, taking into account the possibility that serotonin may be modulating its formation.

Greiner recently reopened the question of the abnormal pigment formation in schizophrenic patients and concluded that there is an increase of melanin formation either from enzymatic or auto-oxidative mechanisms. Our postulate provides a common basis for Greiner's observation and the suggestion by Woolley that the disease results from a deficiency of serotonin. Not only would adrenochrome formation be accelerated at low levels of serotonin and, consequently, melanin formation from epinephrine, but also melanin formation from dopamine; and norepinephrine would be freed from the inhibitory effect of the indoleamine.

The evidence is strong that serotonin has a major function in controlling brain function, as Brodie and Costa (1962) suggest. It is also clear that major disturbances in serotonin concentration which increase or decrease it beyond still unknown limits produce behavioral changes in animals. But what is not clear is whether serotonin is directly implicated in the etiology of certain mental diseases. It is possible that other tryptophan metabolites are more directly implicated.

Hallucinogenic Derivatives of Tryptophan

Tryptamine. De Jong (1945) reported that tryptamine produces catalepsy and paralysis in animals. Later, Ernst et al. (1961) injected 1 to 3 mg into the cisterna

magna of cats, which produced catatonia lasting several hours to several days. No human studies have been reported.

Bufotenin. This substance is one of the active constituents of *Piptadena peregrina* (Cohoba), the narcotic snuff of ancient Haiti. Also present is N,N-dimethyltryptamine, which is more clearly hallucinogenic. Bufotenin is also found in skin secretions of some frogs, and in some mushrooms used in northern Europe for producing psychadelic experiences.

Bumpus and Page (1955) reported they had found bufotenin in urine. Rodnight (1956) was unable to demonstrate any but since then Fischer et al. (1960, 1961a–d) in a series of studies found that the majority of schizophrenics had a substance in their urine which acted like bufotenin in paper chromatographic assays (see Chapter 9). The normal subjects did not have any. Perry (1962) found this substance in the urine of four children receiving monoamine oxidase inhibitors and in one child who was not getting any medication.

Dimethyl and diethyltryptamine. The dimethyl derivative is present in *P. peregrina* and also in *Prestonia amazonicum.* According to Lewin (1964), natives mixed *Banisteria caapi* (harmine) with *Prestonia amazonicum.* The addition of the latter changed the character of the effect.

Szara (1957) reported that both diethyl and dimethyltryptamines are hallucinogens when given parenterally. Taken orally they are not active. The experiences were quite similar to those produced by LSD-25 but the response occurred more quickly.

Ibogaine. This complex indole is present in the bark of the root of *Tabernanthe iboga.* Natives consider extracts of this plant to be better than alcohol because they found it a stimulant which did not disturb thought. In large doses the roots produce marked central nervous stimulation, hallucinations, and even convulsions. Pharmacological studies (Gershon and Lang, 1962) have corroborated the observations of the natives.

Harmine. This substance is the active ingredient of *Banisteria caapi.* As stated earlier, natives often mix it with *P. amazonicum* to create a state of ecstasy. It produces experiences similar to LSD-25 but is more deliroid (Pennes and Hoch, 1957).

Harmine-like substances are found in vivo. McIsaac (1961) synthesized 1-methyl-6-methoxy-1,2,3,4-tetrahydro-2-carboline. It is apparently present in pineal gland tissue. McIsaac (1961) and McIsaac et al. (1961) suggested that some psychoses are due to endogenously produced harmala-like alkaloids. In their scheme, melatonin (in the pineal gland) is converted to 10-methoxyharmaline.

Mitragynine. This substance is the major alkaloid in the intoxicant *mitragyna speciosa* of Borneo. It is a 4-methoxyindole related to 1,2,3,4-tetrahydroharmine. It was the first 4-methoxyindole isolated from natural products. In Siam leaves of *M. speciosa* called Kratom are chewed as a narcotic. It should be hallucinogenic.

Psilocybin. This substance is 4-phosphoryloxy-N,N-dimethyltryptamine, the active ingredient of the hallucinogenic mushroom of Mexico, *Psilocybe*. Most of the credit for bringing psilocybin to the attention of the modern scientific world belongs to Wasson and Wasson (1957) and to Hofmann (1959). About 10 to 30 mg taken by mouth produces an experience very similar to that caused by 100 mg of LSD-25, but the experience comes on more quickly and does not last as long. Psilocybin produces cross tolerance with LSD-25; that is, a subject who has been given several doses of psilocybin and no longer reacts will not react to LSD.

Psilocybin is apparently safe but it is possible that prolonged use can produce chronic poisoning. Central American Indians and Mexicans use their mushrooms only when there is some great need, not regularly the way the members of the Native American Church of North America take peyote.

Yohimbine. The main source of this substance is yohimbine bark. When it is given to normal subjects they become tense, irritable, restless, and anxious. A few schizophrenics suffered an increase in psychotic symptoms. Holmberg and Gershon (1961) look upon yohimbine as a substance which produces a model of anxiety.

Relationship of Tryptophan Derivatives to Schizophrenia

The serotonin hypothesis of mental illness is a focal one which can be related to the tryptophan metabolites. If serotonin is indeed a brain neurohormone then any substance that will interfere with its function should alter brain function. Attempts have been made to increase brain serotonin in schizophrenic patients. Zeller (1957, 1959), Lauer (1958), and Lauer et al. (1958) treated seven schizophrenic patients with daily doses of 1 gram of tryptophan and the amine-oxidase inhibitor iproniazide. There was a general activation of the patients.

Similar changes have been observed by Pollin et al. (1961). Alexander et al. (1963) also found that the behavior of schizophrenic and other psychiatric patients was altered when they were given an amine-oxidase inhibitor and tryptophan.

The evidence is still somewhat conflicting, because it seems that tryptophan feeding can alter behavior in both directions—making some schizophrenics worse and some better.

The hallucinogenic properties of the methylated derivatives of indole listed above suggest that in schizophrenics an abnormal pathway of tryptophan degradation is

present. Evidence for this is as follows: (1) Some of these substances have been found in increased quantities in urine of schizophrenic patients. (2) Methionine, one of the methyl donor amino acids, produces behavioral changes in man (Alexander et al., 1963; Park, Baldessarini, and Kety, 1965). Increased availability of methyl donors could facilitate the formation of hallucinogenic indoles. (3) The best known methyl acceptor, nicotinic acid, is a very good antischizophrenic substance. It could conceivably prevent the formation of hallucinogenic indoles but it is such an important component of the respiratory enzyme that it is more likely that other mechanisms are altered. (4) McIsaac (1961) injected rats with 5-methoxytryptamine, iproniazide, and disulfiram and found that some harmala-like alkaloid was secreted in the urine. Melatonin, a constituent of pineal tissue, is easily converted into 10-methoxyharmalan. McIsaac suggested that some serotonin might be converted into 5-methoxytryptamine and then to a harmine-like substance, which, since harmine compounds are potent mono-amine oxidase inhibitors, would reduce the destruction of serotonin and thus increase the production of toxic indoles.

Nicotinamide adenine dinucleotide is synthesized by the reaction of nicotinate, ribose, 5-adenosinetriphosphate, and glutamine to yield NADP, adeninediphosphate, adenosinemonophosphate, pyrophosphate, and glutamate. Six enzymes are necessary.

NAD is hydrolyzed by NADase. This enzyme is strongly inhibited by nicotinamide and by para-aminobenzoic acid. The suggested relation between the pyridine nucleotide cycle, pellagra, and schizophrenia is shown in Figure 11-3.

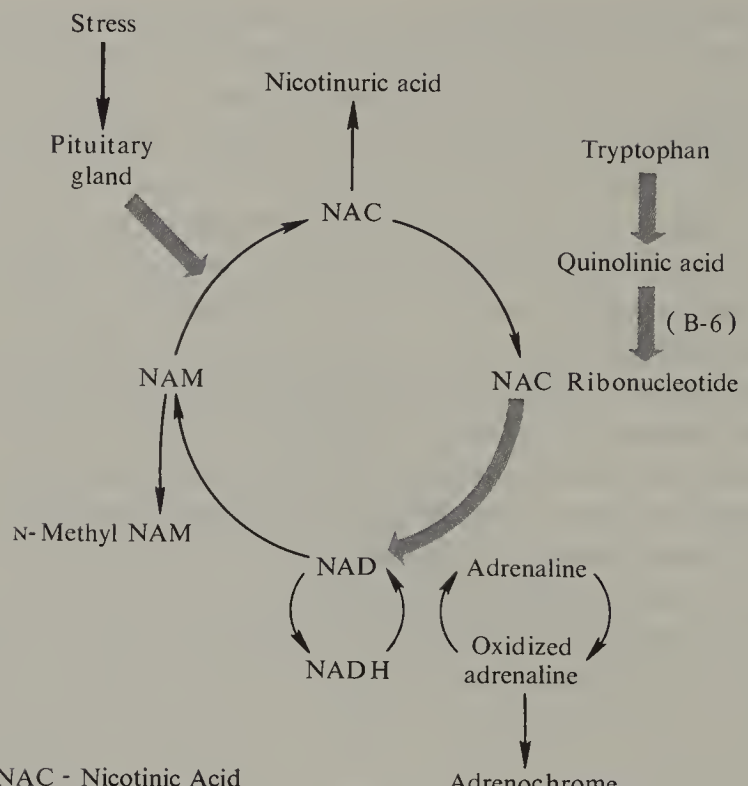
Effect of Deficiency of Vitamin B3 in Animals

Nicotinic acid deficiency also produces behavioral changes in animals. Brozek (1962) reviewed some of the work reported in the Russian literature. In two dogs a dietary deficiency of nicotinic acid and tryptophan strikingly reduced excitability of the cerebral cortex, as measured by an EEG. Changes in "higher nervous activity" took place long before clinical symptoms appeared. In one dog the intensity of the response to unconditioned stimuli was reduced. In the other there was a paradoxical increase in conditioned responses. Restitution of normal reflex activity was a slow process.

NAD Deficiency

According to the hypothesis of schizophrenia the essential biochemical reactions are represented by the scheme shown in Figure 11-3.

If we assume that these reactions must be normal for proper brain function it



NAC - Nicotinic Acid
NAM - Nicotinamide
NAD - Nicotinamide Adenine Dinucleotide

FIGURE 11-3.
The suggested relation between the pyridine nucleotide cycle, pellagra, and schizophrenia.

follows that any interference in the cycle will cause a breakdown in brain performance. I suggest that the factors that interfere with this essential cycle are the biochemical factors that cause schizophrenia. Conversely, the factors that restore this cycle will be therapeutic for schizophrenia. I shall, therefore, use this biochemical chain of events as a guide in discussing the problem of schizophrenia and its relationship to vitamin B3 and its coenzyme.

A deficiency of NAD will result from a deficiency of pyridine or from a deficiency in enzyme activity that leads to its formation. But, it can also come from a deficiency of the other constituents of NAD, that is, of glutamine, ATP, or ribose. Ribose and glutamine are unlikely to be deficient and will not be considered further.

DEFICIENCY OF ESSENTIAL NAD COMPONENTS

Adenosinetriphosphate (ATP). A deficiency of ATP would be particularly disastrous, since ATP plays a vital role in the synthesis of NAD and NADP. Jones

(1965) reviewed the evidence which shows that ATP promotes NAD synthesis. In its absence nicotinic ribonucleotide is degraded back to nicotinic acid rather than being incorporated into NAD.

Clark and Pinder (1966) found that in rats 500 mg of ethionine[2] per kg decreases liver NAD and NADP up to 60 percent within 4 hours; 7 hours after injection NAD levels were normal but NADP had not returned to normal. Ethionine forms S-adenosylethionine by means of methionine adenosyl transferase, thus causing a deficiency of adenine. When nicotinamide is given the NAD levels increase but the ATP levels decrease. Palma-Carlos et al. (1966) discovered that it produced porphyria. There is no direct relationship between porphyria and schizophrenia but psychological changes are frequent in porphyria. Porphyrinuria was a frequent finding in pellagra (Spies et al., 1938) and disappeared as the pellagra was cured with nicotinic acid.

Methionine may decrease NAD synthesis by competing for adenine. It can also increase transmethylation of nicotinamide and so deplete the pool of pyridine molecules. Park and others (1965) reported that methionine given to schizophrenic patients pretreated with amine oxidase inhibitors made a number of them worse. A number of subjects who were not schizophrenic also suffered various symptoms on a similar regime (Sprince et al., 1965).

Zelinskii (1956) suggested that schizophrenics lack phosphorylation activity. When his patients were given thiamine, riboflavin, and nicotinic acid, oxidation was improved. Positive therapeutic results were found when blood levels of these vitamins became normal or elevated. Acute patients responded better than chronic cases. A large number of studies have suggested disturbances in phosphorylation in schizophrenic tissues (Hoffer and Osmond, 1960; Hoffer, 1962). As far as we know, Zelinskii was the first to suggest that schizophrenics cannot synthesize adequate quantities of NAD from nicotinic acid.

DEFICIENCY OF PYRIDINE MOLECULES

Dietary. When either vitamin B3 or tryptophan, or both, are lacking in the diet, the animal or human develops pellagra. In unfortified foods nicotinic acid and nicotinamide are found chiefly in the form of nucleotides.

Malabsorption. Malabsorption conditions may also lead to NAD deficiency. Dohan (1966) found a highly significant relationship between changes in consumption of cereal grains such as wheat and rye and changes in the incidence of first-admission schizophrenics. He gathered statistics from Finland, Norway, Sweden,

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[2] Ethionine has not been given to humans so its effect on normal or schizophrenic subjects is not known.

Canada, and the United States. In Finland, the consumption of wheat decreased from 69.5 kg per person per year in 1936–1939 to 48 kg in 1943–1945, and the mean annual hospital admissions decreased from 1,217 to 832. Similar trends were found in Norway and Sweden. In Canada in 1942 only 721 schizophrenic patients were admitted and annual wheat consumption was at its lowest. In 1943–1945 the incidence increased to 871 and the annual consumption of wheat rose to its previous or pre-war level. In the United States wheat consumption from 1940–1942 to 1943–1945 increased by 6 percent while the incidence of schizophrenia increased by 5 percent, but during the same period Canadian wheat consumption went up 13 percent and schizophrenia went up 21 per cent. The increase in schizophrenia in the United States thus was much less than in Canada. This unusual observation may well be related to the fact that nearly all the flour in the United States was enriched with thiamine, riboflavin, and nicotinic acid in 1942–1943, whereas in Canada enrichment was not permitted until about 1948. Dohan suggested that the effect of wheat might be explained by a mild gluten enteropathy. He reported that there is a high association between gluten enteropathy (celiac disease) and psychopathology. In one series of 32 adults with celiac disease, three (nearly 10 percent) had schizophrenia. In another series of 94 patients with nontropical sprue, five were psychotic. Conversely, four out of 37 men with schizophrenia had a history of celiac disease. Normally, celiac disease is found in about five cases per 10,000 births. When celiac patients are placed on gluten-free diets, the psychopathology they show is the first symptom to disappear.

Gluten enteropathy could decrease absorption of nicotinic acid, and when there is a deficiency in ability to synthesize NAD this could be an added pathological factor. The smaller increase in the United States' incidence of schizophrenia might have been due to the fortification of flour with extra nicotinic acid, which would counteract the pathological effect of the gluten.

LACK OF GLUTAMINE

Perry et al. (1970) found that a deficiency of plasma glutamine was more characteristic of the degree of mental retardation in phenylketonuria than was an excess of phenylalanine. One bright phenylketonuric subject had normal glutamine levels, while his retarded brother was deficient in glutamine. Twelve retarded patients were all low in plasma glutamine. Since glutamine is essential for the synthesis of NAD it is conceivable that retardation results from a deficiency of NAD.

It is possible that a deficiency of glutamine later in life would lead to serious mental changes; most likely they would be schizophrenic in nature. This suggests that glutamic acid should be re-evaluated as a therapy for schizophrenics who fail to respond satisfactorily to megadoses of vitamin B3.

EXCESSIVE LOSS OF NICOTINIC ACID OR NICOTINAMIDE

Increased excretion. Gopalan and Srikantia (1960, 1963) and Gopalan et al. (1969) discovered that excessive consumption of leucine increases the loss of nicotinic acid in urine. Pellagra has been associated with the eating of maize, but is rare among rice-eating populations. Maize contains nearly twice as much leucine as rice. The authors gave 5 g of L-leucine per day to volunteers. There was an immediate increase in excretion of N-methylnicotinamide to 50 percent above the base level. Excretion was normal a few days after leucine was stopped. This was a specific effect, as isoleucine did not increase the excretion of N-methylnicotinamide. Gopalan and Srikantia (1960) gave 5 grams of L-leucine per day for seven days to four patients with pellagra. There was no change in the clinical picture. Another two pellagrins were given much larger doses and became psychotic. One was normal four days after admission. He was then given 10 grams of L-leucine every six hours. That evening he was agitated and incoherent and had delusions of grandeur. He suffered periods of excitement which alternated with shorter periods of severe depression. Next morning he was given an additional 10 grams and by noon he was uncontrollable and violent. He was then given nicotinic acid intramuscularly and 48 hours later he was normal (see also Gopalan, 1969).

The second patient with pellagra was mentally normal when he was started on 20 grams per day of L-leucine. Three days later the diarrhea was much more severe and he complained of insomnia. On the sixth day he was severely depressed and apprehensive and he answered questions slowly. On the sixteenth day he was disoriented. The L-leucine was stopped, and three days later he became much worse mentally. He became violent, had paranoid delusions, his speech was incoherent, and he had to be restrained forcibly. He was started on nicotinic acid and was normal in 48 hours. During the sixteen days of L-leucine feeding he lost over five pounds of weight. When L-leucine was stopped the weight loss also stopped.

Leucine may have inhibited synthesis of NAD and so increased excretion of N-methylnicotinamide.

EXCESSIVE METHYLATION OF NICOTINAMIDE

N-Methylnicotinamide is not used in the cycle which regenerates NAD and is excreted. This may account for the aggravation in schizophrenic symptoms when excessive quantities of methionine are given.

Substances which inhibit methylation of nicotinamide should increase the synthesis of NAD. Burton (1960), Burton et al. (1958), Salvador and Burton (1965), Burton and Salvador (1962), and Burton et al. (1960) found a significant correlation between the tranquilizing activity of reserpine and some phenothiazines and their ability to maintain high NAD levels in the livers of animals given nicotinamide.

Greengard and Quinn (1962) corroborated these findings, and also found that hypophysectomy produces marked elevation of NAD levels. Thus, 24 hours after injection of nicotinamide the NAD levels were still ten times as high as normal levels. Nonlethal combinations of chlorpromazine and nicotinamide were lethal in hypophysectomized rats. The dose was 0.5 gram of nicotinamide per kg. In adrenalectomized animals the NAD levels were also elevated, but not as much as in hypophysectomized animals. These effects were reversed by ACTH, and less efficiently by cortisone. Perhaps this explains why ACTH produces so many psychotic reactions. Cortisone has been less toxic in this respect.

When rats were kept at 4°C the combination of reserpine and nicotinamide did not produce any sedation nor elevate NAD levels. At room temperature both sedation and elevation of NAD levels were found. In sharp contrast, the reverse was found with chlorpromazine and nicotinamide. A dose of 25 mg/kg chlorpromazine sedated only rats which were cold stressed. In these animals the NAD levels were elevated, but not in those maintained at room temperature. Finally, Greengard and Quinn reported that those animals which had the least sedation had the lowest NAD levels, and those animals which were strongly sedated had the highest NAD levels.

Woolley (1958) found that large doses of nicotinamide produce marked tranquilization in mice, more severe than that induced by reserpine. It seems to be an indirect antagonist of serotonin. This effect was ascribed to its interference in the action of calcium ions in muscle contraction, which could result from inhibition of NADase or transmethylation processes.

Burton et al. (1962) confirmed earlier findings that nicotinic acid but not nicotinamide elevates blood NAD levels in animals and human subjects (see also Altschule, 1964). They gave three subjects 1 to 2 grams of nicotinic acid plus 50 mg of chlorpromazine per day, and found no significant elevation of NAD levels. An examination of their Figure 1 suggests that there was a slight effect, since during the control period the NAD levels among both groups were the same, whereas during the combination treatment 13 of the mean NAD values were higher for the combination and only two were lower. Had they used chlorpromazine doses in line with those in clinical usage, different results could have been found. However, their evidence does provide some corroboration of the view of Zelinskii (1956) that a primary disturbance in protein metabolism in schizophrenics leads to a faulty vitamin metabolism in schizophrenia. Where they were not incorporated into their respective enzymes Zelinskii found decreased levels of both thiamine and riboflavin in schizophrenic patients. Nicotinamide blood levels were normal but blood levels of NAD and NADP did not go up in spite of intensive treatment with nicotinic acid.

Methionine-D,L-sulfoximine is an antimetabolite of methionine (McLennan and Elliott, 1951), and so could prevent the NAD lowering effect of methionine (by analogy with ethionine). This may be the explanation for the finding of Heath et al.

(1966) that chronic schizophrenic patients given 400 mg per day showed an insignificant decrease in psychotic symptoms.

EXCESSIVE OXIDATION OF NICOTINAMIDE

Heyman (1964) reported that schizophrenic patients oxidized more nicotinamide to N-methyl-2-pyridone-5-carboxamide than normal controls. Tranquilizers decreased this oxidation and hallucinogens increased it.

Apparently, mentally retarded children excrete slightly less N-methylnicotinamide, while Mongolian idiots excrete the same quantity as normal subjects. But Mongols excreted over twice as much N-methyl-6-pyridone-5-carboxamide. When they were given 2 mg of nicotinic acid per kg intramuscularly, there was a slight increase in excretion of the 6-pyridone derivative. Normal subjects and retarded patients on the same quantity of nicotinic acid more than doubled their excretion (Careddu et al., 1963).

EXCESSIVE CONJUGATION OF NICOTINIC ACID

If excessive quantities of glycine were released in the body, it would increase the excretion of nicotinuric acid. Perhaps this is why with rapid loss of tissue (weight) schizophrenic patients usually become worse.

ANTIMETABOLITES OF NICOTINIC ACID

Antimetabolites of nicotinic acid are incorporated into nucleotides and the corresponding respiratory enzymes but do not permit proper function of these enzymes. Thus, these antimetabolites produce a deficiency of NAD, and could lead to the increased loss of nicotinic acid and nicotinamide from the pyridine pool.

Antimetabolites are very toxic and are not given to humans. In animals neurological and mental changes are produced. Quastel (1959) referred to his findings that 3-acetylpyridine leads to severe lesions in the hypothalamus. This effect was prevented by nicotinamide but not by nicotinic acid. Another nicotinic acid antimetabolite, 6-aminonicotinamide, also affects the developing nervous system of chick embryos. Quastel stated "There is little doubt that interference with the DPN carrier system in brain brings about a variety of nervous disturbances."

Deficiency in Synthesis of NAD

A block anywhere between tryptophan and nicotinic riboside could cause a deficiency of NAD. This possibility has already been discussed. It provides a reason for giving

pyridoxine to schizophrenic patients, and may explain the response of some childhood schizophrenics or autistic cases to high doses of pyridoxine.

A block in the synthesis of NAD could arise from a deficiency of ATP. Excess methionine or ethionine could also act this way.

Greengard and Quinn (1962) and Greengard et al. (1967) found that deamidation of nicotinamide is accelerated in hypophysectomized animals. Apparently the pituitary gland secretes deamidase inhibitor; therefore, excessive activity can block this reaction even more.

Wakoh (1959) reported that the mental illness of the vast majority of women patients first became noticeable in the latter half of their menstrual cycle. There appears at that time to be an excessive build up of estrogens without a balancing production of progesterone. Hoffer (1967a) reported one schizophrenic who did not recover until given progesterone every month at the time of ovulation, even though she had received very intensive chemotherapy for over a year and a half. This imbalance in the estrogen-progesterone cycle could come about from excessive production of FSH. The factors which lead to excessive pituitary activity are unknown, but relative hypoglycemia may be one.

Nicotinamide is one of the most powerful inhibitors of NADase. Large quantities of nicotinamide would, therefore, not only force the production of more NAD but would also slow down its destruction in the brain. Brain tissue is very rich in NADase and the turnover of NAD is rapid.

Destruction of NAD

Nicotinamide adenine dinucleotide is hydrolyzed by the glycohydrolase NADase. Hoffer et al. (1957) listed nine possible mechanisms to account for the therapeutic action of vitamin B3 in schizophrenia. One of these was its effect as a powerful inhibitor of NADase, which is a very powerful enzyme and rapidly destroys NAD. Fortunately, NADase is bound to cell surfaces, where it can do little damage. If, however, the cell membrane were injured and did not function efficiently some NADase could penetrate into the cell where it would interfere with NAD-catalyzed reactions. Substances which increase cell membrane permeability include acetylcholine and adrenaline, and indoles such as serotonin and indole-3-acetic acid. The effect of adrenochrome and adrenolutin has not been determined. If there were a generalized indole toxemia in schizophrenia, it would lower cell membrane permeability, allow penetration of NADase into the cell, and disrupt energy metabolism. Nicotinamide, one of the most powerful inhibitors of NADase, would prevent the destructive effect of NADase and so be therapeutic.

Recent research on tuberculosis shows that this model can exist and may explain

the high association between schizophrenia and tuberculosis where modern epidermiological and treatment approaches are not used.

Bekierkunst and Artman (1961) reported that lungs, livers, and spleens from tuberculous mice had two to three times as much NADase as did tissue from normal animals. The NAD levels were only half of normal in infected animals. They suggested that NADase levels might be responsible for the depleted NAD level. Chaudhuri et al. (1963) reported that nicotinic acid and isonicotinic hydrazide inhibit the elevated NADase activity in tuberculous tissue. There is no proof the elevated NADase is directly responsible for lowered NAD in cells, but this possibility is supported by the therapeutic effect of isonicotinic hydrazide and of nicotinic acid on tuberculosis. Bekierkunst et al. (1964) state that "the appearance of a soluble NAD splitting enzyme whatever its origin should facilitate the contact between NAD of the cell and the NADase, thus bringing about a breakdown of NAD and eventually NAD deficiency observed in tuberculous animals."

Hoffer and Osmond (1966a,b,c) drew together two chemical systems as relevent in the etiology of schizophrenia. These were tryptophan (already discussed here) and tyrosine, and their metabolites. Tryptophan leads to a series of indoles and NAD, while tyrosine leads to a series of sympathomimetic amines and their derivatives (such as 3,4-dimethoxyphenylethylamine; that is, methylated derivatives and their chrome indoles). Arising from tyrosine are L-dopamine, which yields dopachrome, and methylated phenylethylamines or degradation products. In a parallel way, noradrenaline and adrenalin, which are made from dopamine, can go into noradrenochrome and adrenochrome as well as derivatives of the simpler amines. Eventually, the chrome indoles (dopachrome, noradrenochrome, and adrenochrome) can be converted into dihydroxyindoles, which are not toxic, and trihydroxyindoles, which are hallucinogenic. These are the lutines. They have been found in increased concentration in erythrocytes of schizophrenics (Altschule, 1954, 1960, 1962).

Figure 11-3 shows how the pyridine nucleotide cycle impinges upon the adrenaline adrenochrome cycle. It could equally well apply to the dopamine dopachrome and noradrenaline noradrenochrome cycle. That dopachrome may be very important is shown by the work of Yaryura-Tobias (1970). When L-dopa became available as an anti-Parkinson substance, Yaryura-Tobias was interested in determining whether it would antagonize the extra-pyramidal effect of the phenothiazines. He gave a small series of chronic schizophrenics enough tranquilizers to induce extra-pyramidal symptoms, then they were given 1 gram per day of L-dopa. The experiment had to be terminated because every patient became much more psychotic. In addition, Yaryura-Tobias examined Parkinson patients who were mentally normal before they were given L-dopa as a treatment for their disease. Several, while showing a decrease in their Parkinson symptoms, became psychotic on L-dopa, and the dose had to be reduced. An examination of the current literature suggests that a greater than normal proportion of Parkinson cases given L-dopa will become schizophrenic.

Friedhoff (1970) has found that administration of L-dopa did not increase excretion of 3,4-dihydroxyphenylethylamine. It is nearly certain that L-dopa in the brain would be converted to some degree into dopachrome. By analogy with adrenochrome, known to be hallucinogenic, dopachrome would probably have the same effect. Adrenochrome has anti-tension properties (Hoffer and Osmond, 1960), which suggests the possibility that the anti-Parkinsonism effect of L-dopa is due to this mild anti-tension property. Perhaps the chief problem of the neurologist treating Parkinsonism with L-dopa will be the need to give enough to control the symptoms but less than enough to make the patient psychotic.

Recently, Galzigna (1969, 1970) discovered another mechanism by which vitamin B3 is therapeutic for schizophrenia and for LSD-induced reactions. Nicotinamide competes with acetylcholine for noradrenochrome. The acetylcholine complex is relatively stable toward reduction by ascorbic acid, whereas the reduction of nicotinamide-noradrenochrome complex is much faster than the reduction of noradrenochrome alone. In other words, in the presence of nicotinamide and ascorbic acid the aminochrome-acetylcholine complex is rapidly broken up and hydroxyindoles are produced. Galzigna then concludes,

> We can postulate that if a central catecholamine is leaking at any synapse devoid of the enzymatic system that destroys it, the slightly oxidative conditions together with the hydrophobicity of the medium are sufficient to bring about a physiological aminochrome formation, as occurs in our in vitro system. If this takes place at the level of cholinergic synapses the aminochromes so formed can accumulate and be stabilized by acetylcholine. The leak of catecholamine and the stabilization of its oxidation products could produce an aberrant communication which, on the one hand, might be the chemical event leading to a short circuit between adrenergic and cholinergic systems and, on the other hand, might be the origin of irritative foci of stabilized psychotogenic agents at cortical level. Both effects could possibly explain the onset of mental illness.

It had been shown earlier that the reduction of adrenochrome by ascorbic acid produces 5,6-dihydroxy-N-methylindole, which is non-toxic, and adrenolutin, which is psychotomimetic (Hoffer and Osmond, 1967). Thus, nicotinamide alone, in the presence of ascorbic acid, reduces the toxicity of adrenochrome by half. This may account for the slow response of many patients to vitamin B3.

Penicillamine in vitro reduces adrenochrome mainly into the nontoxic derivative. In vivo it has been very helpful in accelerating the response of schizophrenics to vitamin B3 (Hoffer and Osmond, 1960). Galzigna's work provides a rationale for the synergistic effect of vitamin B3 and penicillamine.

I shall now briefly review the situation as described by Hoffer and Osmond (1967). Adrenaline, by losing one electron, becomes an unstable oxidized adrenalin. In the presence of adequate concentrations of NAD and NADH it is reduced to adrenalin, but in the absence of NAD it loses one more electron to become adrenochrome,

which no longer is reducible to adrenalin. Thus, a deficiency of NAD leads to an increase in production of adrenochrome and its derivatives. In the same way there could be an increase in production of dopachrome and noradrenochrome.

The Treatment that is Called for by the Scheme

It is obvious that replacement of NAD–NADH is one of the essential elements in the treatment of schizophrenia. Direct replacement has been discussed but it may be neither the most effective nor the most economical way of treating schizophrenics. Ideally the exact nature of the metabolic defect should be discovered for each patient, which could then be repaired by the use of appropriate substances. In discussing therapy based upon the scheme, I shall assume that this is a reasonable working hypothesis, to be refined and modified as more knowledge accumulates.

FORTIFICATION WITH COMPONENTS OF NAD

Between 1952 and 1957, Nieto (1966) treated a few schizophrenic patients with adenosine triphosphate (ATP) injections administered intramuscularly, and felt that it was beneficial. Because it is readily hydrolyzed it could not be given by mouth unless it was specially protected. It also blocked the effect of the mushroom *Stropharia cubensis*, which contains psilocybin.

Nieto conducted more extensive trials with adenylic acid (adenosine monophosphate, AMP), a similar but less phosphorylated precursor of NAD. He used AMP 200 mg intramuscularly daily for one week, followed by 200 mg three times per week for two weeks, then less, depending upon progress. In most cases he also used other chemotherapy (tranquilizers, antidepressants). He reported that 25 out of 32 patients showed very good recoveries. The response was more rapid and more impressive than with other chemotherapy alone.

Earlier I have stated that glutamine deficiency is unlikely. That it can occur is suggested by the results obtained in giving retarded children glutamic acid, which is readily converted to glutamine in the body. Glutamic acid is one of the component amino acids of glutathione. Glutathione levels tend to be low in the erythrocytes of schizophrenic patients (Martens et al., 1956; Altschule et al., 1957). Surikov et al. (1957) reported that intravenous glutathione improved four out of nine schizophrenics but did not help any who had involutional depressions.

A deficiency of adenine is hardly likely to occur unless unusual situations are created. Excessive quantities of methionine, ethionine, and similar substances could create such a deficiency by binding too much adenine.

Replacement of Pyridine Molecules

DIETARY

The decision to fortify flour and other cereal products was one of the most important measures ever taken for preventing mental illness. By this simple action innumerable people have been protected against pellagra and the accompanying neuroses and psychoses. It is not too far-fetched to believe that if the next step (increasing the amount of enrichment substantially) were taken, there would be an even more dramatic decrease in mental illness. If the equivalent of 1 gram of nicotinamide were added to the average daily diet, preferably in bread and in sugar-rich foods, the majority of people now destined to become schizophrenic would not. I urge that such an experiment be done without delay, for nicotinamide is safe and inexpensive, and the precedent of enriching foods is already established and accepted in the United States.

The diet must also contain adequate quantities of tryptophan and of other vitamins, such as riboflavin, thiamine, and ascorbic acid. Acute pellagra is easily cured by the administration of nicotinic acid, nicotinamide, or nucleotides from natural sources. The word cure may be erroneous here, if the word is restricted in its use to conditions which, having vanished under therapy, do not require more therapy; for example, acute appendicitis, pneumonia, etc. In this sense no human is ever "cured" of pellagra. We are all arrested pellagrins, because when the daily intake falls below a critical level the pellagra soon recurs.

Subjects who have suffered from chronic pellagra may require much longer daily intake of vitamin B3. This has been established for animals and is true also of humans. The present chronic pellagrins in North America are former prisoners of war of the Japanese and inmates who survived German concentration camps. It is hardly likely that they would escape pellagra plus other deficiency conditions such as scurvy and beri beri.

I have seen patients from each group recover on megavitamin B3, when they had previously failed to respond to doses of vitamins which according to conventional ideas should have cured them.

One Canadian soldier was kept in a Japanese prisoner-of-war camp for 44 months. His weight decreased from 195 to less than 145 pounds, and he changed from a healthy, athletic, physically active, outgoing, and cheerful man to a pain-ridden, crippled, insecure, and complaintive individual. After he was released he was treated with intensive vitamin doses and began to look physically well. However, from 1945 to 1960 he was never free of severe crippling pain, he suffered excruciating tension and depression, and was eventually classified as a neurotic. He was usually given two thorough physical examinations each year and twice was treated by psychiatrists, who advised him to learn to live with his condition. This was worse than a

death sentence, because he found his condition unbearable in the present and intolerable if it was to be his future. In 1960 he began to take 3 grams of nicotinic acid per day. Within two weeks he was normal, and he has been normal since except for a period of several weeks when he and his son went mountain climbing in the Alberta Rockies and he forgot to take his nicotinic acid with him. When he returned home he was nearly as ill as he had been before. After ten years on nicotinic acid his file with the Veteran Affairs Department of the government of Canada showed only routine entries and two physical examination reports not initiated by the subject, in contrast to his bulky file covering the 15 years he was not taking nicotinic acid. To my knowledge every chronic pellagrin, prisoner or inmate, who has taken 3 grams of nicotinic acid a day has recovered.

The sluggish response to a smaller intake of vitamin B3 is not surprising, for it has been described for pellagra. Frontali (1939) reported that of 14 psychotic pellagrins given 120 mg of nicotinic acid daily by mouth and 40 mg by intramuscular injection the skin lesions cleared in one to two weeks and normal digestion became normal in four to five weeks, but the nervous symptoms were removed very slowly. Comessatti (1938) confirmed these observations. Aring et al. (1939) found that acute psychotics (pellagrins) were quickly helped by 0.5 to 1 gram of nicotinic acid per day, but chronic psychotics responded very slowly (Gillman and Gillman, 1951).

Malabsorption Syndromes

The solution to the problem of malabsorption syndromes is to prevent them by avoidance of gluten and other dietary factors that cause malabsorption. When this cannot be done or when organic lesions in the gastrointestinal tract prevent normal absorption one should give megavitamin B3 doses.

Recently, Cott (1969), and Hawkins et al. (1970) have been using parental nicotinamide, ascorbic acid, thiamine, pyridoxine and vitamin B12 for schizophrenics who have continued to relapse while consuming megavitamin oral doses of the same vitamins. It has greatly improved the results, and in a series of several dozen patients (out of many hundred) who had suffered repeated relapses, none have had any relapses, and hospital treatment has been avoided. I have seen similar results on a small series of five cases, all of whom recovered.

Excessive Loss of Nicotinic Acid or Nicotinamide

EXCESSIVE EXCRETION

Excessive quantities of leucine increase excretion of vitamin B3. If vitamin levels are marginal this may be a factor, and foods rich in leucine, such as maize, might throw

the person into pellagra. Perhaps schizophrenics should also avoid these foods during the acute phase of their illness.

EXCESSIVE METHYLATION OF NICOTINAMIDE

Excessive methylation of nicotinamide can be reduced by avoiding excessive intake of methionine, by using phenothiazine tranquilizers, and by sharply increasing the consumption of nicotinamide.

Antimetabolites of methionine, such as methionine-D,L-sulfoxamine, may be useful in treating some schizophrenic patients, but should be used very cautiously.

EXCESSIVE OXIDATION OF NICOTINAMIDE

Reducing substances such as ascorbic acid may prevent excessive oxidation of nicotinamide.

Excessive Conjugation of Nicotinic Acid. This is theoretically possible if large quantities of glycine are consumed or released endogeneously. If it is a factor, one could control it by giving benzoic acid, which would combine with glycine to form hippuric acid, or salicylates, which would form salicyluric acid derivatives. Aspirin in large amounts might be a useful therapy for schizophrenics.

Nicotinamide Deamidase

If hyperpituitary activity blocks nicotinamide deamidase and it is a factor in the genesis of schizophrenia every treatment program should consider methods of reducing this activity.

The pituitary gland has an intimate push-pull relationship to the other glands under its control. Thus, secretion of thyrotropic hormone increases secretion of thyroxine, which in turn tends to suppress secretion of TSH. In the same way progesterone can decrease secretion of FSH.

Perhaps part of the therapeutic value of thyroid hormone and progesterone lies in their ability to decrease activity of the pituitary gland.

The working scheme discussed here can account for most of the chemotherapies for which success has been found. These include:

1. The therapeutic response to megavitamin B3.
2. The similarity between schizophrenia and pellagra.
3. The association between tranquilizer properties and the ability to maintain elevated NAD levels.

4. The inability of schizophrenics to synthesize NAD as efficiently as normal subjects (Zelinskii, 1956).
5. The therapeutic response to mega ascorbic acid.
6. The relationship of schizophrenia to relative hypoglycemia and the therapeutic response to diet, thyroid, and progesterone.
7. The association between psychosis and malabsorption.

DISTRIBUTION OF PELLAGRA AND SCHIZOPHRENIA

Schizophrenia has been present for as long as we have records and its distribution is worldwide. About 1 to 2 percent of any population during their lifetime will become ill. The usual incidence estimates of schizophrenia are based upon mental hospital admissions. Thus only severely psychotic patients are counted, while patients incapacitated by their schizophrenia to some degree but tough enough to remain free in the community are omitted. As would be expected, careful community studies using scientific sampling techniques show that this is a gross underestimate. For example, Leon (1970, personal commun.) in a study in Colombia found the real incidence of schizophrenia was several times higher. Heston (1966, 1970) in a thorough review of the genetics of schizophrenia concluded that "The contribution of genetic factors to the etiology of schizophrenia has been confirmed decisively." The genetic studies showed that relatives of schizophrenics suffered a marked degree of psychopathology, and have been referred to as schizoid. These independent genetic studies provide striking corroboration for the mauve factor (malvaria) studies of Irvine (1961), Irvine et al. (1969), and Hoffer and Osmond (1961a,b,c; 1963a,b,c). In a substantial number of families tested for malvaria, one-third of the first-order relatives of schizophrenics excreted mauve factor in their urine. Of this group nearly 90 percent showed schizoid features as described by Heston. In striking contrast only 10 percent of the nonmalvarian relatives were schizoid.

This being the case, it is clear that true incidence figures for schizophrenia and for schizoidia will run closer to 5 percent. Pellagra may have been present for as long a time as has schizophrenia, but it became endemic about 1900 and widespread only in certain geographical areas, namely Egypt, the United States (especially in the corn belt), Serbia, Bulgaria, Russia, Italy, Spain, and India.

Pellagra is rare in Mexico, perhaps because the corn is treated with calcium carbonate before it is cooked, which makes more of the B3 available. Also it does not occur so widely in corn consuming areas of South America (Peru, Bolivia, Colombia), perhaps because people here also drink large quantities of coffee, which contains nicotinic acid, and eat bananas, which are rich in tryptophan, serotonin, and other

indoles. At one time it was estimated that one-third of the population of Egypt suffered from pellagra, and in the United States about 400,000 cases occurred each year. In some poverty areas of the southern United States, about 10 percent of admissions to mental hospitals were diagnosed as psychiatric due to pellagra. It was this high accumulation of pellagrins that led Goldberger to carry out his classical nutritional studies there. Goldberger eventually proved that pellagra was a deficiency disease due to a lack of protein and vitamin B3 associated with malnutrition and was not due to lack of sanitation or infection. His conclusions were not greeted with great enthusiasm.

There is a clear and distinct relation between pellagra and poverty, which is not surprising, as pellagra is caused by poor nutrition. When this is corrected pellagra vanishes. In this respect it differs from schizophrenia, for which there is a tenuous relation between schizophrenia and poverty. It is very possible that this is mediated by diet. Where only diet depleted in protein and vitamins and rich in carbohydrate foodstuff is consumed, subjects who require more vitamin B3 than average will succumb first. Thus, we should expect a slight increase in schizophrenia among the lowest socio-economic groups.

Pauling (1968a,b,c) has defined orthomolecular psychiatric therapy as "the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the body." Examples given by Pauling included phenylketonuria treated by diet. Other examples which could be used are the use of large doses of pyridoxine for treating pyridoxine dependent diseases, B12 for B12-dependent diseases, and ascorbic acid for treating hypoascorbemia. It is our opinion that schizophrenia is a vitamin B3-dependent condition or an NAD deficiency disease (Hoffer and Osmond, 1966a, b,c).

If schizophrenia is such a vitamin B3-dependent condition, then the biochemical changes and the possible evolutionary advantages which allow the condition to survive and perhaps expand must be determined.

Pauling estimated that the loss of a gene or genes that controlled synthesis of ascorbic acid occurred about 25 million years ago. For a mutation rate of 1/25,000 per gene generation a very small advantage of 0.01 percent more progeny would lead to a complete replacement of the earlier gene in about a million years. There is obviously a disadvantage in becoming dependent upon dietary sources of ascorbic acid, but this is more than offset by the greater advantage of getting rid of the chemical machinery required to make ascorbic acid and freeing materials for other syntheses. A combination of less than optimum quantities of ascorbic acid plus some chemical made available by release of the energy required to make ascorbic acid presents a net gain to the cell and provides the evolutionary advantage. Stone (1965, 1966) has described this condition as hypoascorbemia.

The vitamin concept is so firmly established that it inhibits the use of vitamins for

any other condition than the vitamin deficiency diseases. This concept implies that the deficiency is in our present diet due to poverty, ignorance, or malabsorption and that these conditions can be cured and prevented by improving diets and nutrition. The improved diets would be enriched with vitamin doses, as is being done with enriched flour, which contains added thiamine, riboflavin, nicotinamide, and iron, or with juices enriched with ascorbic acid.

The newer concept of vitamin-dependent disease changes the emphasis from simply dietary manipulation to consideration of the endogenous needs of the organism. It comes within the field of orthomolecular disease. Pyridoxine and vitamin B12 dependency conditions have already been described. The borderline between vitamin deficiency and vitamin-dependency conditions is merely a quantitative one when one considers prevention and cure. Hopefully, it will be possible to include megavitamin doses in some cases in our food, so that people with vitamin-dependent conditions can overcome them by proper diets. Examples would be to enrich juices with sufficient ascorbic acid to give subjects 1 to 3 grams per day, or to enrich cereal products with nicotinamide to provide the vitamin B3-dependent person (which we equate with schizophrenia) with at least 1 gram per day. This quantity will cure childhood schizophrenia if treatment is started within a few months of onset of the illness. In doing so we merely introduce an intelligent modification of our foods, a process man has followed for millions of years by trial and error.

Zuckerkandl and Pauling (1962) pointed out that every vitamin, every essential amino acid, and every other essential nutrient represents a molecular disease which our ancestors learned to control by proper selection of the diet. Each one of us may be said to suffer from about 40 nutrilite-deficiency or nutrilite-dependent diseases, which are incurable. Hypoascorbemia is as incurable as pellagra; both demand a steady intake of ascorbic acid and vitamin B3. We all have arrested scurvy or arrested pellagra. If all the vitamin B3 were removed from our diet we would undoubtedly develop a condition which would resemble schizophrenia more than pellagra, because tryptophan would not be deficient and it is probably a deficiency of tryptophan which leads to major skin and gastrointestinal changes.

Scriver (1966) and Rosenberg (1969) have elaborated the vitamin-dependency concept. They point out that there are a large number of steps or reactions between the ingestion of the vitamin and its final combination in the substrate-enzyme complex. These are: (1) transfer into the cell; (2) conversion into the coenzyme, which requires phosphorylation; (3) formation of holoenzyme, the combination of coenzyme plus apoenzyme; and (4) enzyme-substrate reaction.

Any one of these steps may be deficient and may lead to a vitamin-dependent condition. Theoretically there should be a vitamin-dependent condition for every vitamin, and all would be under genetic control.

Molecular diseases subdivide into vitamin-deficiency conditions (the usual avitaminoses) and vitamin-dependency conditions. Pauling (1968a) suggested that

some people may have a sort of cerebral pellagra caused by a difficulty in transfer of vitamins into the brain, or because rates of reaction are limited; thus, some tissues may have adequate quantities, and others, such as the brain, may not. In his conclusion Pauling suggested that "the genes responsible for abnormalities (deficiencies) in the concentration of vital substances in the brain may be responsible for increased penetrance of the postulated gene for schizophrenia and that the so-called gene for schizophrenia may itself be a gene that leads to a localized cerebral deficiency in one or more vital substances."

Summarizing this general discussion, I have shown that schizophrenia is a genetic disease in the production of which the environment can do no more than shape the content or direction, that there is a clear relationship between the pyridine nucleotide cycle and schizophrenia, and that schizophrenia is a molecular disease dependent upon vitamin B3, in contrast to pellagra, which is a molecular disease resulting from a deficiency of both tryptophan and vitamin B3 in the diet.

Many scientists have recognized that genetic studies of schizophrenia cannot go much farther until the gene or genes and the reactions they control are located. Pauling has pointed to genes which control molecular levels of vitamin B3 in the brain. I now propose that schizophrenia is a molecular disease, a vitamin B3-dependent condition where there is a decreased formation of NAD from tryptophan and consequently a greater dependency upon exogenous precursors of NAD. I suggest that at least two genes are involved, and thus agree with Karlsson (1966, 1967), who suggested a two-independent-gene theory. One, a dominant gene, is concerned with thought disorder and occurs in one out of fifteen people. I suggest this may be the gene which controls formation of adrenolutin and that it controls perceptual changes plus thought disorder. The other is a recessive gene homozygous in one out of six people. I suggest this one controls conversion of tryptophan to NAD by some unknown mechanism. According to Karlsson, these two genes would account for the known distribution of schizophrenia in the population.

I shall consider Karlsson's gene *s* as the dominant gene which prevents excessive formation of adrenolutin, *SS* represents normal adrenolutin production (very little), *Ss* represents one dose for excessive adrenolutin, and *ss* a double dose. This gene therefore controls perceptual changes and thought disorder. The way these determine the clinical condition of schizophrenia has been described by Hoffer and Osmond (1966). The recessive gene *p* is assumed to control pyridine nucleotide metabolism in the brain. The condition *PP* represents normal metabolism, *Pp* represents one dose for abnormality, which will not express itself, and *pp* represents a major defect or the vitamin B3-dependent condition.

Karlsson's calculation based upon his genetic studies may be shown as follows:

1. 75 percent *SSPP* or *SSPp*. This is the normal condition with adequate provision of NAD and normal (that is, low) production of adrenolutin.

2. 15 percent *SSpp*. Here there is a dependency on B3, but as there is no excessive production of adrenolutin there is no schizophrenia. Karlsson suggests this group may predispose toward alcoholism. This is a remarkably shrewd guess, and it is supported by findings of Hawkins (1968) and Smith (1968), as well as mine, that megadoses of vitamin B3 are particularly successful in controlling anxiety and depression of alcoholics, most of whom are thereby able to remain sober. It also provides for those few depressions that respond remarkably well to megavitamin B3 (Sherrill, 1950; Washbourne, 1950; Thompson and Proctor, 1953). Group *SSpp* might be particularly vulnerable to psychosis by overuse of alcohol, the hallucinogens, antidepressants, and amphetamines.

3. 5 percent *SsPP* or *SsPp*. Those in this group have normal pyridine nucleotide function but have too much adrenolutin. Perhaps this is why they are creative or gifted. If true, they would be particularly susceptible to decreased consumption of vitamin B3, which could easily throw them into schizophrenia. The schizophrenic patient while on megadoses of B3 would represent such a group. This group may have the evolutionary advantages discussed earlier and may be the basis for the genetic morphism. They would also be particularly sensitive to malnutrition and perhaps for this reason the lowest socio-economic classes would have a higher incidence.

4. 1 percent *Sspp*. This condition is a combination of too little NAD and too much adrenolutin and represents schizophrenia. Administering vitamin B3 would change it into group 3 or group 1.

5. 0.1 percent *ssPP* or *ssPp*. This represents a condition characterized by a double dose of adrenolutin in the presence of normal vitamin B3 metabolism. If, as Karlsson suggests, it represents autism, it will account for the fact that vitamin B3 in megadoses does not help autistic children. However, autism is often confused with schizophrenia (Rimland, 1968). One could diagnose as autistic, any psychotic child not responsive to B3, while any child who responds to B3 would be a schizophrenic. They would, however, be more responsive to measures which decreased production of adrenochrome, such as megadoses of glutathione, ascorbic acid, and other reducing substances, or to substances (for example, penicillamine) which divert adrenochrome into leukoadrenochrome, an inert indole, rather than into adrenolutin, the hallucinogen. Similarly, substances such as ceruloplasmin that bind adrenochrome might be useful.

   According to Rimland (1968), ascorbic acid has been successful in helping some cases of infantile autism, and I have also seen several similar responses. Therapeutic trials with penicillamine seem indicated for cases of infantile autism. I have used it successfully for chronic schizophrenic patients who have failed to respond to ECT, tranquilizers, and megadoses of B3.

6. 0.01 percent *sspp*. This represents a lethal condition of inadequate vitamin B3 metabolism plus double-dose adrenolutin production.

Of course, these are hypotheses, and they are useful only in directing further research. They do, however, satisfy both genetic data and physiological and therapeutic data and for this reason demand serious consideration.

I suggest then that Karlsson's gene is a dominant gene that switches adrenochrome conversion from leukoadrenochrome to adrenolutin, while the *p* gene is a recessive gene that inhibits formation of NAD from tryptophan.

THE POSSIBLE EVOLUTIONARY ADVANTAGE IN BEING SCHIZOPHRENIC

Huxley et al. (1964) suggested that the constant proportion of schizophrenics in any population is due to a genetic morphism (Huxley, 1964). The increased fecundity of schizophrenics and schizoids (relatives who carry schizophrenic genes) may be a result of the increased ratio of female to male offspring born to schizophrenic women (Taylor, 1969; Taylor and Levine, 1969; Shearer et al., 1967; Hoffer, 1969). This remarkable fecundity is due to a combination of schizophrenia, partially controlled by tranquilizers, and modern practices of keeping patients out of hospitals as much as possible. I predict that for the next few decades there will be a major increase in schizophrenia in all nations or areas where these two factors operate.

Women who are schizophrenic give birth to more girls than boys. If this is due, as I have suggested, to a deficiency of NAD, then there should be a similar increase in birth of girls in any malnourished population. A schizophrenic woman conceiving a male may suffer a resorption and thus does not carry the fetus to term. This could be very advantageous for the mother in terms of her own survival. However, she could quickly become pregnant again and the chances of producing a girl would still be great. Girls born of schizophrenic mothers are more apt to survive to adolescence and schizophrenic girls are more apt to become pregnant. I have noted the large number of schizophrenics who become pregnant while ill. They will have intercourse simply because they are lonely and yield to maintain a relationship, because they have delusions about bearing babies for some special reason, or because they do not bother to practice birth control. I doubt that they are more promiscuous; they are simply less careful. I have also been impressed with the number of adopted children who later become schizophrenic.

Stevens (1969) maintained a follow-up file until 1966 on a large number of schizophrenic women who had been admitted to a London hospital between 1955 and 1963. The total fertility remained lower than that in the normal population because the probability of marriage was decreased, especially after one admission. Chronic

patients spent more time in the hospital and so their chances of becoming pregnant were reduced. However, the rate of illegitimate fertility was three times as high as for the normal population.

It is possible that only the policy of chronic incarceration practiced for centuries has kept the incidence of schizophrenia at its present level. The modern policy of community psychiatry effectively removes one brake. Each year a larger than average number of schizophrenic girls who are physically healthier, and breed faster and more indiscriminately, are added to society.

The only solution is to remove the reproductive advantage by preventing schizophrenia. This, I suggest, can be done in most cases by the addition of adequate quantities of nicotinamide to our food.

WHERE IS THE GENETIC ERROR?

It is possible and, if the views presented here are reasonably close to the truth, even highly probable, that the genetic error which underlies the schizophrenias is an enzymatic block between tryptophan and NAD. Such a block would lead to two main areas of biochemical abnormality. There would be a decrease in NAD and in vitamin B3, and an increase in the other system of tryptophan metabolites; that is, in some indoles. Lis et al. (1968) found that all of a small group of schizophrenic patients they tested excreted below-normal quantities of a nicotinic acid derivative.

Observations of Fischer (Chapter 9) and of Himwich and Costa (1960) confirmed the suspicion that an increased formation of indoles such as serotonin, bufotenin, and their derivatives would be found. Overloading with tryptophan would be harmful not because of the increased production of vitamin B3, which is harmless, but because of an increase in psychologically powerful indoles.

The decreased production of NAD and vitamin B3 would have other serious effects not directly dependent upon NAD deficiency, which has already been described in this report. Vitamin B3 is one of the few major methyl acceptors and may serve a very important role in using up and so regulating methyl transfer metabolism. Where there is too little vitamin B3 labile methyl groups could accumulate and produce the kind of harmful changes reported when excess methionine is given to schizophrenic patients. Methionine is a methyl donor. There could be an increase in transmethylation of phenylethylamines, such as dopamine, noradrenalin, and adrenalin, to form substances such as 3,4-dimethoxyphenylethylamine (the pink factor). Although there is no consensus that pink factor is related to schizophrenia, the pink factor has been found in some schizophrenic patients. But if it is an end product (due to a lack of vitamin B3) it is not surprising that it is not a consistent or predictable finding, nor that DMPEA is not a hallucinogen for man. Perhaps a few pellagrins will also excrete the pink factor.

The postulated block between tryptophan and NAD may provide an evolutionary advantage in the presence of adequate exogenous vitamin B3. There would be a tryptophan-sparing action, and more would be available for synthesis of essential indoles; for example, serotonin. Perhaps too there would be a protein-sparing action, which would confer quite an advantage when diets are deficient in protein.

Thus the postulated block will account for (1) deficiency of NAD and the subsequent syndrome of pellagra or schizophrenia, (2) increased production of substances like dopachrome, noradrenochrome, and adrenochrome, (3) increased production of tryptophan-derived indoles and their acids, and (4) increased transmethylation and formation of substances like the pink factor.

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12

Levodopa and Mental Illness

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INTRODUCTION

3,4-L-Dihydroxyphenylalanine (L-dopa, levodopa) was first isolated from the bean *Vicia faba* by Torquati in 1913. It had been synthesized by Funk in 1911. The levo form is the naturally occurring form. It is soluble in water. In the presence of moisture dopa is rapidly oxidized by atmospheric oxygen and turns green.

The catecholamines are synthesized in the organism from phenylalanine or tyrosine by one or two hydroxylation steps to dopa, which is then decarboxylated by the enzyme aromatic-L-amino acid decarboxylase to form dopamine (DA). Subsequently, DA is hydroxylated on the side-chain enzymatically by phenylethylamine-β-hydroxylase to form noradrenaline (NA), which by N-methylation is converted to adrenaline (A).

DISTRIBUTION

Most L-dopa is formed and metabolized outside of the CNS, with formation of active catecholamines that do not cross the Blood-Brain Barrier (B-B-B) (Weil-Malherbe, 1960). Seiden and Carlsson (1964) have found that in mice the concentration of DA is approximately five times higher in the heart than in the brain. L-Dopa is located in the chromaffin tissue of the adrenal glands (Goodall, 1950), in the enterochromaffin-like cells of gastric mucosa of the rat (Hakanson and Owman, 1967), and in the mouse pancreas, which has an efficient mechanism for uptake and storage (Alm et al., 1967). In patients with malignant neural tumors the presence of dopa and dopamine is increased, whereas none is found in pheochromocytomas (Kaser, 1966). Levodopa is able to cross the B-B-B (Bertler et al., 1966) only in very small amounts, as much of it is metabolized in the periphery (Blaschko and Chrusciel, 1960). L-Dopa administered by mouth is largely destroyed in the stomach, the organs through which it passes as it becomes distributed throughout the body, and at the capillary walls as it enters the interstitial fluid. Very little reaches the brain, even as DA. To increase the amount reaching the brain it may be given parenterally, and the amount may be further increased by preventing decarboxylation in the periphery. One way of altering this distribution and increasing the passage of L-dopa into the rat brain, demonstrated by Bartholini et al. in 1967, is by injecting 50 mg/kg seryltrihydroxybenzyl-hydrazine (RO4-4602), which inhibits extracerebral dopa-decarboxylase activity but has little effect on the enzyme in the brain.

The distribution of dopamine in the brain is uneven, and follows a characteristic pattern, which is similar in cats, dogs, and man, showing that 80 percent is concentrated, in decreasing order, in the caudate nucleus, lentiform nucleus, hypothalamus, and hippocampus (Bertler and Rosengren, 1959).

Vogt (1957) has shown that labelled DA is rapidly incorporated from the circulating blood into many portions of the brain, but it is metabolized at different rates, so that high concentrations persist longer in the caudate nucleus than in other regions of the brain. Similar results were obtained (McGeer and McGeer, 1964) by injecting labelled tyrosine into the caudate nucleus and hypothalamus of cats.

It has been suggested that granulated vesicles in sympathetic axons and endings are of andrenergic nature (Pellegrino de Iraldi and De Robertis, 1961). In the brain, the cellular localization of catecholamines has been studied by a special fluorescent method (Falck, 1962; Carlsson et al., 1962; Gonzalez Aguilar and De Robertis, 1963; Fuxe, 1965). The subcellular distribution of catecholamines has been studied by Weil-Malherbe and Bone (1957), Bertler et al. (1960), Chrusciel (1960), and Inouye et al. (1963). Hornykiewicz (1968) has demonstrated the presence in the human brain of dopamine-containing fibers in the internal capsule running in rostral direction to the striatum, probably having its origin in the substantia nigra.

Other important aspects in the study of these neurotransmitters are their transport, uptake, and storage, and the regulation of these processes. Magnesium and calcium ions are essential in transport and storage of amines and in neurochemical transmission. Yoshida et al. (1963) suggested that L-dopa might have its own carrier system, because in brain cortex slices of guinea pigs omission of calcium increased the transport of L-dopa and omission of sodium, potassium, and magnesium caused a decrease. Matussek et al. (1966) have shown that Na^+ and K^+ ions inhibit catecholamine synthesis from L-dopa in rat brain homogenates. Different pharmacological mechanisms are also offered to explain storage and release of catecholamines. Carlsson (1966) proposed that drug-induced catecholamine depletion might be the result of the following reactions operating alone or in combination:

1. Increased release through functional hyperactivity (for example, insulin hypoglycemia after reserpine injection); impairment of storage sites; increased permeability of the cell membrane if damaged (Corrodi, 1965); and displacement by a false transmitter (for example, metaraminol).
2. Block of amine uptake by storage particles (reserpine), or cell membrane (for example, tricyclic antidepressants, by blocking membrane pump).
3. Inhibition of synthesis (dopacetamides; Carlsson et al., 1963) and α-methyltyrosine (Nagatsu et al., 1964).

Another way to increase the amount of active L-dopa metabolites in the central nervous system is to reduce the rate of oxidative inactivation by using monoamine oxidase inhibitors (Zeller and Sarkar, 1952).

The presence of dopa decarboxylase and MAO in the capillary walls in the CNS of the rat and mouse might be an example of regulating the conversion of dopa to dopamine in the brain (Bertler et al., 1963).

METABOLIC AND PHARMACOLOGICAL INTERACTION

Since L-dopa seems to have no direct pharmacological action (Blaschko and Chrusciel, 1960; Carlsson, 1964) it is believed that effects observed are mainly caused by its catabolites DA, NA, and adrenaline. Catecholamines stimulate the mobilization of free fatty acids (FFA) from adipose tissue in vitro, as has been shown by Gordon and Cherkes (1958). They also increase gluconeogenesis from lactate (Exton and Park, 1966), and they might exert a hypoglycemic reaction, probably related to an increasing utilization of glucose resulting from the long-lasting decrease of circulating FFA (Randle et al., 1963).

It has been postulated that L-dopa may induce pyridoxine deficiency (Golden et al., 1970) and also that pyridoxine antagonizes the anti-Parkinson effect of levodopa and reduces the dyskinetic side effect (Duvoisin et al., 1969; Jameson, 1970).

Catecholamines also stimulates O_2 consumption in the human liver (Bearn et al., 1951), skeletal muscle (Euler, 1931), cardiac muscle (Starling and Visscher, 1927), smooth muscle (Bulbring, 1953), adipose tissue (Lynn et al., 1960), and anterior pituitary (Roberts and Keller, 1955). Vasodilating effects have also been reported (Furchgott, 1955), either ascribed to stimulation of β-receptor or blocking of α-receptor. Dopamine exerts both vasodilating and vasoconstricting actions, depending upon vascular bed, dosage, and species (Goldberg et al., 1969). The same occurs with blood pressure where, in man, hypertension (Friend et al., 1965) or hypotension can be recorded (Yahr et al., 1969). Anden et al. (1966) have found that in the spinal cord of the cat L-dopa increases the synthesis and liberation of transmitter from the terminals of a descending noradrenergic pathway. Grillner et al. (1967) have observed that in unanesthetized cats after the injection of L-dopa the resting discharge frequency increases in afferents with secondary endings, and volleys in the flexor reflex afferents evoke a long-lasting acceleration of the discharge in these afferents.

Grechishkin in 1969 demonstrated that in dogs L-dopa intensifies pepsin production with histamine secretion and prevents the drain of pepsinogen reserves in a depleted mucosa. In rats, L-dopa prevents the development of dystrophy of the gastric wall induced by electrical stimulation and immobilization, and it also exerts antiulcerous action in the gastric tissue (Zabrodin, 1969).

BEHAVIOR

L-Dopa has been used to investigate the behavioral and psychiatric properties of the DA and NA systems in animal and human brains. Recently the interest on this compound became more intense as L-dopa began to be used for Parkinson's disease and, as a result, psychiatric side effects were reported. First, it is important to review the behavioral effects of L-dopa in animals in order to broaden the understanding of the same properties in human behavior. According to Blaschko and Chrusciel (1960) and Smith and Dews (1962), the effect of L-dopa on behavior in mice is the production of marked changes in autonomic functions, such as sweating, salivation, piloerection, and tachypnea. Injection of 100 mg/kg L-dopa in the rat did not produce a significant change in lever-pressing rate, but did produce marked neurovegetative symptoms, characterized by piloerection, salivation, and exophthalmus (Butcher and Engel, 1969). In contrast, when dopa decarboxylase activity was inhibited peripherally by seryl-trihydroxybenzyl-hydrazine no autonomic manifestations were observed, and concomitantly it was noticed that there was an

increase in the rate of avoidance responding, suggesting an excitatory action. Thus, it was concluded that autonomic symptoms and depressant effects were probably caused by dopa catabolites in the periphery and the central effects of L-dopa appear to be excitatory.

The administration of dopa to animals gives different behavioral responses depending upon the dose used and the species tested. By using MAOI, alone and also in combination with dopa, it is possible to produce graded increases in alertness, responsiveness, irritability, and aggressiveness in mice (Everett, 1961). These experiments were also done on rats, dogs, cats, monkeys, and rabbits with corroboration of previous results. When 500 mg/kg D,L-dopa was given to mice intravenously, in addition to the administration of pargyline (MAOI), it caused strong biting behavior (Katz et al., 1967) and increased activity and irritability (Everett and Wiegand, 1961). Woolley and Van der Hoeven (1962) demonstrated that a deficiency of dopa improved learning ability (maze) in adult mice. Another important experiment was performed by VanderWende and Spoerlein (1962), who injected intravenously mice with slightly alkaline or acid solutions of L-dopa (400–500 mg/kg), after which symptoms of psychosis characterized by catatonia, stupor, and rage developed.

In contrast to Everett et al., Fisher, and Saavedra et al. (1970) presented evidence that the combination of L-dopa with an MAOI depressed the searching activity of mice, and Smith and Dews (1962) found that L-dopa suppressed the locomotor activity in mice. In rats, L-dopa caused rage reaction followed by stereotyped behavior, and when L-dopa was given with MAOI they became depressed (Scheel-Kruger and Randrup, 1967; Schekel et al., 1965).

Ernst and Smelik (1966) have shown that the rat has an intense compulsion to gnaw following implantation of L-dopa at such sites as dorsal caudate nucleus and globus pallidum.

In the chick, Spooner and Winters (1964) have found alertness and EEG arousal after administration of 300 mg/kg of L-dopa or 100 mg/kg of DA, but they also found akinesia. According to Kramer et al. (1965), the administration of L-dopa and DA produced catatonia in chicks, characterized by immobility, exaggerated upright posture, and wide-eyed stare (type I), accompanied by a synchronized EEG associated with deep sleep (paradoxical arousal).

According to Ernst (1962), cats pretreated with O-methylated products of dopamine, such as bulbocapnine, laudanine, papaverine and laudanosine, developed a hypokinetic rigid syndrome of catalepsy which was antagonized by L-dopa. In the same animal treated with reserpine, the decreased conditioned avoidance response (CAR) was reversed by the action of L-dopa (Hanson and Utley, 1965). Mantegazzini and Glasser (1960) have shown in the *cerveau isolé* cat a slowing of EEG activity after L-dopa administration. However, dopamine, according to the same authors, does not have a significant effect on the EEG of the intact animal, which

would indicate that these changes are due to the catecholamines which L-dopa affects within the brain.

In the cat, after injection of L-dopa and DA into the lateral cerebral ventricle (LCV) spontaneous locomotor activity was increased. At the same time EEG desynchronization occurred (Bogdanove and Nir, 1965). According to Reis et al. (1970), L-dopa administered to cats pretreated with the MAOI phenylazine resulted in striking behavioral changes, including shrieking, defensiveness, probable hallucinations, and attempts to escape.

As was stated at the beginning of this section, L-dopa had different actions at different dosages. Baker and Anderson (1970) showed in cats that small doses of levodopa increased motorneural excitability and blocked excitatory effects of group II and III afferent fibers, while larger doses blocked the inhibitory actions mediated by the flexor reflex afferents.

Primates (Wada and McGeer, 1966) treated with D,L-dopa exhibited more obvious emotional tension and less obvious changes in alertness, when compared to cats. Scheckel et al. (1965) found an increase of motor activity in monkeys after small doses of L-dopa.

BEHAVIORAL CHANGES IN HUMANS

It is generally agreed that antidepressant drugs elevate brain amine levels either by MAO inhibition or by blocking re-uptake into the presynaptic nerve endings, as by tricyclic compounds.

On the contrary, reserpine, which depletes brain amines, causes depression. Therefore it has been suggested that biogenic amines play a preponderant role in the affective disorders. Rosenblatt and his colleagues in 1959 hypothesized that depression might be associated with a decrease of NE or serotonin (see Rosenblatt et al., 1960). Based on this hypothesis, Pare and Sandler in 1959 gave small doses of D,L-dopa (equivalent to 125 mg of L-dopa) to three depressed patients, with negative results. Later, the same authors reported "activation" in some patients. A clinical trial of dopa (1,200 mg daily) alone or combined (dopa + MAO inhibitor) did not show any improvement in twelve depressed patients (Klerman et al., 1963). Improvement in various aspects of mood and self-confidence were reported (Turner and Merlis, 1964) after the administration of dopa and pargyline. In the same study, two patients developed delirium (disorientation for time and place, person, and visual hallucinations): one was given 150 mg of pargyline and 150 mg of dopa daily for two weeks; the other had 75 mg of pargyline and 150 mg of dopa daily for six weeks. The effect was thought to be similar to that of amphetamines.

Another positive study (Ingvarsson, 1965) showed prompt improvement in two cases of long-standing refractory depression after intravenous injection of levodopa

in doses of 50 mg. Since then, many studies have shown contradictory results, some claiming antidepressant affects (Matussek et al., 1966; Bunney, 1967), and others negative results (Praag, 1969).

In a study of 22 reserpine-treated patients the administration of 350 mg of L-dopa caused a feeling of well-being with fatigue (Degkwitz et al., 1960).

In a very interesting study (Goodwin et al., 1970), L-dopa was administered in large oral doses (five to twenty times more than those used in previous studies of L-dopa depression) and an antidepressant therapeutic response was observed in only four of the 16 patients. All the responsive patients had retarded depressions. In the same study, anger unaccompanied by an antidepressant effect was reported in all patients who received 4 grams daily of L-dopa. Furthermore, Goodwin et al. observed induction of hypomania or mania in the five depressed patients who had a prior history of mania. In the same study, an increase in the average evoked response amplitude-intensity slope was produced by L-dopa (Buchsbaum et al., 1970).

For those readers interested in this aspect of the catecholamines, the review articles of Schildkraut (1965) and Bunney and Davis (1965) are excellent.

L-DOPA IN PARKINSONISM

The anti-Parkinsonism properties of levodopa have made this compound an important tool for the neurologist. After the work of Carlsson in 1959, Ehringer and Hornykiewicz (1960) demonstrated that dopamine was depleted from the basal ganglia of patients with Parkinson's syndrome. One year later it was found that Parkinsonian patients excreted less dopamine in their urine than did subjects not having the disease (Barbeau et al., 1961). Since then systematic evaluation of levodopa for the treatment of Parkinson's disease (Cotzias et al., 1967, 1969; Yahr et al., 1969; Klawans and Garvin, 1969; McDowell et al., 1970; Stellar et al., 1970) and drug-induced Parkinsonism (Yaryura-Tobias et al., 1970) has been conducted. Valuable information has been gathered, not only in reference to its therapeutic qualities but also to its toxic reactions and untoward side effects. Gastrointestinal side effects have been limited to anorexia, nausea, and vomiting. In the cardiovascular system, hypertension, orthostatic hypotension, cardiac arrhythmias, and palpitations have been reported. In McDowell's study, 32 cases of flushing were observed in Parkinsonian patients receiving from 1 to 6 g daily of L-dopa; in one patient severe flushing in the late afternoon and evening was associated with delirium and insomnia.

Side reactions of the neurological system have also been reported. They include involuntary movements, ranging from fleeting to severe; and the induction of athetotic or choreiform movement, usually with higher dosages and after prolonged treatment (Yahr et al., 1969). Dyskinesias, quite diverse in their manifestations,

include facial movements such as grimacing, yawning, gnawing, nodding of the head, and opisthotonus. Spontaneous trunk and limb movements also occurred.

The incidence of psychiatric disturbances in patients receiving L-dopa for the treatment of Parkinsonism is variable, according to different authors, with a range of 2.5 to 55.5 percent (Calne et al., 1969a, 1969b; Barbeau, 1969; Cotzias et al., 1969; Goodwin-Austen et al., 1969; Yahr et al., 1969; McDowell et al., 1970; Klawans and Garvin, 1969; Celesia and Barr, 1970).

Behavioral changes are usually characterized by assaultiveness, aggressiveness, increased sexual interest, and withdrawal. In some patients, alertness, euphoria, and improvement of their memory have been reported (Jenkins and Groh, 1970).

Measurement of intellectual functioning after L-dopa therapy did not reveal changes (Boshes et al., 1969). However, after monitoring the intellectual functioning of Parkinsonian patients treated with L-dopa, Meir and Martin (1970) found a significant increase in the Wechsler Adult Intelligence Scale (WAIS), particularly on the perceptual organization deviation quotient (PDQ).

Disturbances of thought processes that included delusions of grandeur, jealousy, and persecution were observed. Auditory and visual hallucinations as well as confused states with impaired judgment, orientation, and memory have been reported. In other instances, agitation, acute anxiety, and modification of affect, mainly depression, and in some patients insomnia, fatigue, and lethargy were noticed. In our own experience with Parkinsonian patients we have observed depression, aggravation of pre-existent depression, agitated depression with suicidal ideation, assaultive behavior, paranoid thinking, and auditory and visual hallucinations (Yaryura-Tobias et al., 1970).

Although no correlation has been established between levodopa dosage, duration of administration, and the onset of psychiatric symptoms, it seems that an improvement of the neurological symptoms (Yaryura-Tobias et al., 1970) and a period of latency are necessary before psychiatric symptoms become manifest. For others, the presence of dementia (impaired cognitive function) affected the chance of improvement (McDowell et al., 1970). According to Sacks et al. (1970), the dementia of Parkinsonian patients under L-dopa treatment is aggravated, and coherent perception and action is virtually lost. They also observed diminished cortical inhibition with the release of snout and grasp reflexes, exaggerated stretch reflexes and extensor plantar responses. Patients with Parkinson's disease consequent to encephalitis or associated with chronic organic brain syndrome tend to develop acute psychosis.

In the "Parkinsonism dementia" that appears to be unique to the Chamorro-speaking people of Guam (Kurland and Mulder, 1954; Reed et al., 1966; Brody and Chen, 1968) cell loss occurs in the substantia nigra, locus coeruleus, substantia innominata, and often the globus pallidus, sometimes with severe generalized brain

atrophy. Brody et al. (1970) reported that monoamine levels in this condition were similar to those found in Americans with idiopathic Parkinsonism.

During the administration of levodopa to schizophrenic patients with drug-induced extrapyramidalism (Yaryura-Tobias et al., 1970), an aggravation of their psychoses was observed. Ataxia was present in some patients. Celesia and Barr (1970) found an association of involuntary dyskinetic movements and psychic disturbances in 87.5 percent of their cases.

LEVODOPA IN SCHIZOPHRENIC PATIENTS

The administration of levodopa to schizophrenic patients without natural or drug-induced Parkinsonism presents interesting features which are worth reviewing. In a study done by Yaryura-Tobias et al. (1970), levodopa was given to schizophrenics who were kept on their neuroleptic medication. At the dose level of 1 g of levodopa daily they began to manifest an aggravation of their psychosis and appearance of new psychiatric symptoms. At a 2-gram level of levodopa, patients worsened. They were placed on placebo (single-blind fashion), whereupon symptoms subsided and their mental state returned to baseline level. On this L-dopa regimen, some patients showed alertness, improved verbal communication, increased sexual urge, and bothersome penile erection, and in others depression became an important symptom. In still others an increase of paranoid ideation was accompanied by seclusiveness and withdrawal. Nonhypnagogic auditory and visual hallucinations developed in several patients.

The presence of toxic delirium was not observed in any of the 12 cases. In two cases of alcoholic psychosis with impaired judgment, loss of memory, and disorientation for time and space, levodopa caused depression in one case, and elevation of mood in the other, without major changes in the pre-existent symptomatology.

Modifications of the galvanic skin resistance (GSR) under painful stimuli (electrical shock) in schizophrenic patients receiving L-dopa and phenothiazines have been reported (Diamond et al., 1969). On the same group of patients, no major EEG changes in the awake or asleep patients were recorded (Burnett et al., 1970).

DISCUSSION

The administration of L-dopa in Parkinsonian patients, and the subsequent appearance of psychiatric manifestations in many of them, suggest the following explanations: (1) a pre-existent psychosis or dementia; (2) a subclinical or latent psychosis; (3) an untoward reaction; and (4) a new clinical entity (psychosis).

The first three premises have been described by various authors and have been mentioned in this chapter. The coexistence of Parkinson's disease and mental illness is not uncommon, as has been shown by reports in the medical literature. Investigational data indicate a relationship between the caudate nucleus and schizophrenia (Mettler, 1955). Stimulation or lesions in the caudate have caused gross behavioral changes (Akert and Anderson, 1951; Heath and Hodes, 1952; Buchwald and Ervin, 1957; Forman and Ward, 1957; Davis, 1958; Dean and Davis, 1959). It has also been noted that lesions and stimulations of the caudate nucleus in several animal species produced changes in behavior tasks involving the performance of learned activity (Rosvold and Delgado, 1956; Thompson, 1958, 1959). Stimulation of the caudate nucleus head in man has produced transitory amnesia (during stimulation), speech disorder, euphoria, and lack of response to visual and/or auditory stimuli (Van Buren, 1963). Therefore, it seems probable that the caudate nucleus is involved in higher nervous activity. Two other diseases that reflect combined symptoms of mental disorder and Parkinsonism are chronic manganese poisoning and carbon monoxide intoxication. In the latter, areas of softening were reported in the basal ganglia.

Some of these effects produced by lesions or direct stimulation of certain areas of the basal ganglia have been observed after L-dopa administration; therefore, the possibility of a histochemical complex that plays an interconnecting role between mental illness and Parkinson states exists. Furthermore, the incidence of psychiatric or neurological predominance would depend on the concentration of such a chemical and on the tissue integrity. There is ample evidence that L-dopa exerts both neurological and psychiatric actions in the central nervous system. The neurological effect is usually manifested by improvement of clinical symptoms (rigidity) and sometimes by the occurrence of undesirable reactions (dyskinesias). The psychiatric effect is characterized by modification of mental status (psychosis) and sometimes by desirable effects (alertness).

The apparent capacity of L-dopa to possess a biphasic action in regard to affect, as elation and depression have been reported, are of interest and would indicate an excitatory and inhibitory neuronal activity in explaining psychiatric changes. In patients suffering from depression the response to L-dopa is not uniform and is ineffective in many instances. Undoubtedly, the clinical form of depression, amount of the L-dopa dose, and duration of treatment are some of the variables that will account for the many contradictory reports.

When given to schizophrenic patients, L-dopa produces mental changes, which implies that the drug may aggravate the illness, or it may be toxic.

Our experience suggests that the drug does aggravate the existing conditions; we have not observed psychiatric symptoms that would indicate toxic delirium. On the contrary, our schizophrenic patients have described the onset or exacerbation of their mental symptoms as a continuation of their primary illness. Two observations

were made of schizophrenic patients with drug-induced Parkinsonism who were treated with L-dopa. First, they showed psychiatric deterioration in spite of high amounts of neuroleptic drugs administered, and second, L-dopa was ineffective in suppressing the Parkinsonian symptoms; in fact, a paradoxical aggravation was observed. This clinical evidence suggests a competitive action between L-dopa and neuroleptic drugs, indicating that drug-induced Parkinsonism might not be the chemical model of Parkinson's disease.

It has been demonstrated that chlorpromazine interferes with the metabolism of dopa in rat brain (Gey and Pletscher, 1962; 1964) and that it lowers the hypothalamic DA content in cat brain (Laverty and Sharman, 1965). Chlorpromazine and haloperidol cause a significant increase in DA and homovanillic acid (HVA) in urinary excretion, when schizophrenics treated with large therapeutic doses show marked extrapyramidal symptoms (Bruno et al., 1963; Bruno and Allegranza, 1965). It has also been shown that L-dopa antagonizes reserpine-induced Parkinsonism (Degkwitz et al., 1960). These reports would contradict some aspects of our findings in regard to L-dopa and phenothiazine interaction. These interesting clinical observations lead us to the following statements:

1. L-Dopa improves the neurological symptoms of Parkinson's disease and in doing so causes mental symptoms, some of them similar to those found in schizophrenics.
2. When L-dopa is given to schizophrenic patients with drug-induced Parkinsonism, it worsens the neurological and psychiatric symptoms.
3. L-Dopa aggravates schizophrenia.
4. Neuroleptic drugs, which constitute the main weapon of the psychopharmacological armamentarium, arrest psychotic symptoms while producing drug-induced Parkinsonism in some patients.

According to Haase and Janssen (1965), to obtain psychoneuroleptic action, fine motor hypo- or akinesia has to be present. An extensive literature in reference to psychotropic drugs and basal ganglia is available, and we recommend reading Crane and Gardner (1968).

What is the relationship, if any, between schizophrenia and Parkinson states, and what is their pharmacological interaction with L-dopa and neuroleptics? If minimal drug-induced Parkinsonism is necessary for neuroleptic efficacy, and if DA is hereby depleted, this model would assist in explaining the presence of psychiatric symptoms in L-dopa-treated patients. As we have previously reported, when the neurological symptoms improve, psychiatric symptoms develop; therefore, a correlation between the two does appear to exist. As an additional observation, it is important to remember the presence of vitamin B6 as pyridoxal phosphate as

indispensable for the conversion of L-dopa to dopamine. This would explain its antidyskinetic action, and its deficiency if a large amount of L-dopa is given. It is feasible to theorize that if L-dopa is not completely utilized (after DA storages have been repleted), the vestige will follow a pathological pathway through different areas of the brain, allowing various symptoms (delusions, increased sexual urges, dyskinesia, and the like) to develop.

Another aspect of the discussion is the pathological action of L-dopa in schizophrenic patients. Many years after Cannon (1915, second edition, 1963) had described the interrelationship between emotions and the adrenal glands, Osmond and Smythies (1952) formulated the hypothesis that schizophrenia is the product of a metabolic aberration of the catecholamines. The challenging hypothesis that oxidized derivatives of epinephrine (E) were etiological factors in schizophrenia (Hoffer et al., 1954) renewed the interest in the chemical aspects of this illness. Harley-Mason (1952) cited work that indicated 3,4-dimethoxyphenylethylamine (DMPEA) as the cause of a catatonic-like state in animals. This compound was found in the urine of schizophrenics but not in the urine of normals (Friedhoff and Van Winkle, 1962). Their findings were confirmed by some (Kuehl et al., 1964; Bourdillon and Ridges, 1966) but not by others (Faurbye and Pind, 1964; Nishimura and Gjessing, 1965). Although DMPEA has been reported not to be psychotomimetic (Hollister and Friedhoff, 1966; Shulgin et al., 1966) it might reflect an aberrant metabolic pathway of an endogenous psychotogen.

The chemical similarities between L-dopa and certain hallucinogenic drugs such as mescaline and its derivatives (Shulgin et al., 1969) have been used to develop theories of hallucinogenic phenomena. We must not forget that L-dopa is a naturally occurring substance in animal and man, but a pharmacological action can be observed only when the level of L-dopa is above normal. Therefore, its use as a pharmacological agent does not introduce a foreign substance into the body.

In addition, the clinical application of L-dopa in humans opens a new road to further investigation of biochemical theories of schizophrenia based upon alterations in the metabolism of catecholamines.

Finally, by existing as a natural substance in human chemistry, L-dopa becomes a relevant psychiatric tool that could help answer some of the questions concerning the etiology of neuropsychiatric illnesses.

ADDENDUM

Since the writing of this chapter, additional findings on L-dopa and behavior have been reported. One is the increase in verbal communication in psychotic patients

treated with L-dopa, an observation that could be of help in treating autistic patients or improving verbalization in noncommunicative patients (Yaryura-Tobias, Diamond, and Merlin, 1971).

Another report indicated that some psychotic symptoms caused by L-dopa administration to psychiatric patients were blocked after the administration of nicotinic acid (Yaryura-Tobias and Diamond, 1971).

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13

Glycolytic Activity in Schizophrenia

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During the past 25 years several groups of investigators (Cohen et al., 1944; Jones and Mellersh, 1946; Linko, 1950; Holmgren and Strom, 1959) have demonstrated that standard exercise causes undue fatigue and excessive production of lactic acid in patients with anxiety neurosis, and frequently precipitates symptoms of acute anxiety. Impressed by the association of anxiety with lactic acid production in neurosis, Pitts and McClure (1967) conceived the idea that elevated systemic lactic acid per se, without exposure to exercise, should produce anxiety attacks in susceptible persons. To test their hypothesis, these investigators injected 500 mm of sodium-DL-lactate (10 ml per kilo body weight), producing a peak venous concentration of 12 to 15 mm lactate (108 to 135 mg per 100 ml blood). Disappearance of lactate from the circulation followed a first-ordered reaction curve, returning to fasting levels within 60 to 90 minutes after injection. Lactate perfusions provoked attacks of anxiety in anxiety-prone neurotic patients, but not in controls. From their observations, Pitts and McClure (1967) concluded that high blood lactate concentrations might be the decisive factor in the causation of anxiety in susceptible individuals.

Pitts and McClure (1967) were not, however, the first investigators to examine lactic acid metabolism and its possible relationship to psychiatric illness. Lactic acid and pyruvic acid metabolism had been studied in the psychotic patient by Looney and Childs (1934), Lowenback and Greenhill (1947), and Hannenman (1954); however, they did not equate elevated blood lactate levels with anxiety. Their concern was with the apparent shift from aerobic to anaerobic metabolism in situ in mental illness.

During an evaluation of glucose tolerance response in psychiatric patients we observed symptoms of anxiety during the course of the test procedure. These symptoms, as related by the patients, included:

apprehensiveness	fatigue	sighing
breathlessness	insomnia	syncope
chest pain	nervousness	trembling
dizziness	palpitation	weakness
faintness	shakiness	

The incidence of anxiety in relation to blood glucose concentration was then investigated. It was observed that symptoms of anxiety became prominent when the patient's blood glucose fell below fasting levels, usually during the second or third hour following ingestion of glucose. As a consequence of this observation and the findings of Pitts and McClure (1967), it was decided that the direction and magnitude of serum glucose, blood lactate and pyruvate, and adenosine triphosphate concentrations would be measured during the course of the glucose tolerance test.

Data reflecting the changes in clinical chemical parameters that we noted following a standard glucose challenge have been included in this paper, along with our findings about disturbances in lactate and pyruvate metabolism, and in adenosine triphosphate concentrations, and their possible relationship to a bioenergetic dysfunction in certain psychiatric conditions. Finally, we offer a speculative discourse on the role of niacin in correcting these phases of aberrant carbohydrate metabolism.

MATERIALS

Selection of Patients

All patients we evaluated were selected on a random basis, and as a consequence of their being referred for psychiatric consultation, evaluation, and therapy. The psychiatric evaluation and biochemical studies were performed independently; that is, the biochemist had no knowledge of the patient's psychiatric evaluation, and the psychiatrist was not informed regarding the biochemical data generated.

A comparative evaluation was undertaken only after the clinical laboratory findings had been collected. In essence, this was a double-blind study.

Every effort was made to perform the biochemical studies before medication was prescribed, and before the patient was placed on the Seale-Harris diet. If the patient was receiving tranquilizers, psychic energizers, or other psychopharmacologics at the time admitted to the study, a medication-free period of not less than 72 hours elapsed before the biochemical evaluation was made.

TABLE 13-1.
Patient Psychiatric Classification

Group	Number	Percent
Schizophrenia, all types	28	52.0
Chronic	*2*	*3.7*
Chronic, paranoid	*9*	*16.8*
Acute	*2*	*3.7*
Acute, paranoid	*3*	*5.5*
Childhood	*4*	*7.4*
Mixed-type	*1*	*1.9*
Borderline	*7*	*13.0*
Psychoneurosis	15	27.8
Other psychiatric disorder	3	5.5
Alcoholic	3	5.5
Somatic disease	3	5.5
Asymptomatic	2	3.7
Total	54	100.0
Controls	6	

Several patients long maintained on megadose quantities (3 gram/day) of niacin were accidentally included in the study. When the biochemical data, usually reflecting a diabetic-type curve, were correlated with the psychiatric evaluation and patient history, and a prior history of therapy was discovered, the data on those patients were excluded from the final statistical evaluation.

The data presented were gathered from fifty-four psychiatric patients. The diagnostic composition was 52 percent schizophrenic, 30 percent psychoneurotic, and the other 18 percent represent other types of psychiatric conditions (Table 13-1). Six ostensibly well, non-diabetic subjects from a general hospital population were employed as controls. All sixty subjects were given 100 grams of glucose in a cola-flavored drink, regardless of body weight. The serum glucose, blood lactate and

pyruvate, and adenosine triphosphate were assayed at regular timed intervals thereafter.

At the completion of the biochemical study, the patients were categorized according to their principal psychiatric disorder, and each was subcategorized with respect to an anxiety component uncovered during the psychiatric interview or observed during the course of the glucose challenge.

Statistical Evaluation of Data

Grouped and ungrouped data were treated with classical statistical methods. These included standard deviation (S.D.), standard error of the mean (S.E.), and probability (P). Where appropriate, the standard error of the standard deviation ($S.E._{SD}$), coefficient of correlation (r), and coefficient of variation (C.V.) were also determined.

METHODS

Collection and Treatment of Blood Specimens

Blood samples for glucose analyses were collected in vacutainer tubes devoid of anticoagulant. Blood samples for assays of lactic acid, pyruvic acid, and adenosine triphosphate were collected in vacutainer tubes containing sodium fluoride (10 mg per ml whole blood).

Frozen serum was assayed for glucose within eight hours of collection. Blood for lactic acid, pyruvic acid, and adenosine triphosphate analyses was transferred immediately to tubes containing cold 6-percent perchloric acid, and thoroughly mixed. After centrifugation (and, when necessary, re-centrifugation), the clear supernatant was transferred to clean tubes, stoppered, and frozen.

Analytical Procedures

GLUCOSE

During the course of these studies, two different methods of glucose analysis were employed. During the initial phase of the study we used the glucose oxidase procedure of Keston (1956), as modified by Fales et al. (1961), then subsequently the o-toluidine method of Dubowski (1962). A series of five replicate primary chemical standards and ten serum quality controls were analyzed by both methods. The

difference between the two methods was less than 2 mg per 100 ml. Since the standard deviation of either method was ±4 mg per 100 ml, it was concluded the values from either method were interchangeable. The normal range of values for fasting glucose is 65 to 110 mg per 100 ml.

LACTIC ACID

The enzymatic method of Scholz et al. (1959), as modified by Hohorst (1957), was used to determine lactic acid in blood. Lactate reacts with nicotinamide-adenine dinucleotide (NAD^+) to form pyruvic acid and reduced NAD ($NADH + H^+$). The equilibrium of this reaction favors lactate and NAD^+; consequently, the reaction must be driven. This is accomplished by adding an excess of NAD^+ in an alkaline medium (*p*H 9.0), and trapping the formed pyruvate with hydrazine. Under these conditions the lactate is converted quantitatively to pyruvate: the NAD^+ being hydrated in stoichiometric proportions. The resulting NADH is a measure of the activity. It should be emphasized that only the L(+) isomer is measured, in contrast to chemical methods that measure both isomers.

Recrystallized lithium L(+)-lactate was employed to prepare solutions of known concentration which, added to control serums, were employed to determine precision, reproducibility, and recovery. The results of these determinations are shown in Table 13-2. The standard error of the mean was 0.012 mg per mg or less, with a maximum standard deviation of ±0.22 mg; recoveries ranged from 99.7 to 101.5 percent.

TABLE 13-2.

Lactic Acid Standard Curve. Analytical Precision, Reproducibility, and Recovery of Lactic Acid Employing the Method of Hohorst.

Replicates	Concentration (mg/100 ml)		$S.E._m$	Percent Recovery	S.D.	$S.E._{S.D.}$	C.V.
	Added	Found					
5	8.00	8.13	0.095	101.5	0.19	0.067	2.34
5	16.00	15.95	0.070	99.8	0.14	0.050	0.88
5	24.00	23.92	0.005	99.7	0.11	0.039	0.46
5	32.00	31.84	0.070	99.8	0.14	0.050	0.44
5	40.00	40.01	0.110	99.9	0.22	0.078	0.55

Source: Hohorst (1963).

PYRUVIC ACID

Pyruvic acid was determined by the method of Buecher (1963). Lactic dehydrogenase (LDH) catalyzes the reduction of pyruvate with reduced NAD^+. The equilibrium of this reaction also favors lactate and NAD^+. The reaction proceeds to completion in the presence of increased hydrogen ion concentration and sufficient excess reduced NAD^+. Under the conditions specified in the procedure, pyruvate is quantitatively converted to lactate. Reduced NAD^+, acting as the hydrogen donor, is converted stoichiometrically, and is the measure of activity. With this method there is no interference from β-hydroxypyruvate, glyoxalate, oxalacetate, or β-hydroxybutyrate; γ-ketobutyrate may introduce a positive error as great as 60 percent. To circumvent this problem, the 5-isomer of LDH* was employed in the present study. This isozyme has a low affinity for γ-ketobutyrate (Klotzsch, 1968, personal commun.). As indicated in Table 13-3, the standard error of the mean was 0.07 mg per mg or less, with a maximum S.D. of 0.18, and recoveries ranging from 98.9 to 106.0.

ADENOSINE TRIPHOSPHATE

We used the method of Adam (1963), which involves a coupled reaction wherein phosphoglycerate kinase (PGK) catalyzes the reaction between 3-phosphoglycerate and adenosine triphosphate, yielding 1,3-diphosphoglycerate and adenosine diphosphate. The 1,3-diphosphoglycerate is then reduced by glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and reduced NAD^+. The glyceraldehyde-3-phosphate is trapped as its hydrazone and measured colorimetrically.

TABLE 13-3.

Pyruvic Acid Standard Curve. Analytical Precision, Reproducibility, and Recovery of Pyruvic Acid by the Method of Buecher

Replicates	Concentration (mg/100 ml)		$S.E._m$	Percent Recovery	S D.	$S.E._{S.D.}$	C.V.
	Added	Found					
5	0.05	0.53	0.035	106.0	0.08	0.025	15.0
5	0.75	0.74	0.027	98.8	0.06	0.019	8.1
5	1.00	1.05	0.045	105.0	0.10	0.032	9.5
5	2.00	2.01	0.063	100.5	0.14	0.044	7.0
5	4.00	4.03	0.080	100.6	0.18	0.057	4.4

Source: Buecher (1963, p. 253).

TABLE 13-4.
Acceptable Normal Values for Lactate in Whole Blood Appearing in the Literature

Reference	mg/100 ml
Friedemann, T. F. et al. (1945). *J. Biol. Chem.* **157,** 673.	8.7
Altschule, M. D. et al. (1956). *Arch. Int. Med.* **98,** 35.	4.3–12.75
Horwitt, M. K. et al. (1949). *Am. J. Physiol.* **156,** 92.	8.7
Henry, R. J. (1964). *Clinical Chemistry.* New York: Hoeber.	5–20
Marbach, E. P., and Weil, M. H. (1967). *Clin. Chem.* **13,** 314.	8.3
Campanacci, L. et al. (1968). *Clin. Chim. Acta* **20,** 341.	10.08
This study	9.3–15.8

TABLE 13-5.
Acceptable Normal Values for Pyruvate in Whole Blood Appearing in the Literature

Reference	mg/100 ml
Henry, R. J. (1964). *Clinical Chemistry.* New York: Hoeber.	0.3–0.9
Segal, S. et al. (1956). *J. Lab. Clin. Med.* **48,** 137.	0.4–0.9
Henley, K. S., and Pollard, H. M. (1955). *J. Lab. Clin. Med.* **46,** 785.	0.3–1.1
Marks, V. (1961). *Clin. Chim. Acta* **6,** 724.	0.2–0.8
Bianchessi, M. (1958). *Clin. Chim. Acta* **3,** 179.	0.5–1.25
Huckabee, W. E. (1958). *J. Clin. Invest.* **37,** 244.	1.05–1.25
This study	0.82–1.30

COMMENTS ON NORMAL VALUES

The accepted normal range for fasting serum glucose is 65 to 110 mg per 100 ml, providing the method is specific for glucose. This does not hold true for lactate, pyruvate, and adenosine triphosphate, which are highly variable. Many of the early studies involving the measurement of these metabolites employed indirect colorimetric methods. For example, pyruvate was converted to the 2,4-dinitrophenylhydrazone derivative (Friedmann and Haugen, 1943). This method was both time-consuming and nonspecific. Table 13-4 illustrates some representative normal values for blood lactate which have appeared in the literature. The accepted range of normal values in this study is 9.8 to 15.8 mg per 100 ml, and compares favorably with the ranges cited in the literature.

Table 13-5 lists representative blood pyruvate values. A wide range of values will be noted; however, the accepted range of normals for the present study, 0.82 to

1.3 mg per 100 ml, compares favorably with those established in the studies of Huckabee (1958). In addition to employing a highly specific methodology (that is, immediate transfer of blood to cold 6-percent perchloric acid), precautions must be taken to prevent the conversion of pyruvate to lactate and interfering degradation products.

TABLE 13-6.
Values for Adenosine Triphosphate in Whole Blood Appearing in the Literature

Reference	μ/M100 ml
Parve, E. P. S. (1953). *Biochim. Biophys. Acta* **10**, 121.	110–150
Gottlieb, J. S. et al. (1959). *A.M.A. Arch. Neurol. Psychiat.* **81**, 504.	9.1
Bishop, C. et al. (1959). *J. Biol. Chem.* **234**, 1233.	43.3 female 42.5 male
Yoshikawa, H. et al. (1960). *J. Biochem.* **47**, 635.	43.0
This study (Adam (1963).)	50.0

The assay methods for adenosine triphosphate include the luciferin-luciferase reaction of Strehler and Totter (1954), ion exchange chromatography (Bishop, 1959), paper chromatography (Yoshikawa, 1960), and enzymatic methods (Adam, 1963; Huckabee, 1958; Overgaard-Hansen and Jorgensen, 1960). There is general agreement that the enzymatic methods are the most reliable and are preferred. Table 13-6 lists the ranges of normal values for adenosine triphosphate.

THE GLUCOSE CHALLENGE

Patients in this study were not maintained on a high carbohydrate diet prior to testing, but they were required to fast the night before reporting to the clinic laboratory, where blood and urine specimens were obtained. The patient then consumed a cola-flavored drink containing 100 grams of glucose, regardless of body weight. Additional blood and urine specimens were obtained at 0.5, 1, 2, 3, 4, and 5 hours after ingestion of the glucose.

RESULTS

Control Subjects

Six ostensibly well, non-diabetic individuals were given a 5-hour glucose tolerance test in the outpatient department of a local hospital. The changes effected by the

glucose challenge on serum glucose, blood lactate, pyruvate and ATP, and the lactate/pyruvate ratio are presented in Table 13-7. The range for glucose in the fasting specimen was 70 to 98 mg per 100 ml, with a mean of 84 mg per 100 ml, and

TABLE 13-7.

Whole Blood Glucose, Lactate, and Pyruvate Values Following Glucose Loading of Control Subjects

Substance	Hours Post Glucose						
	0	1/2	1	2	3	4	5
Glucose (N = 6)							
Mean (mg %)	84	127	145	110	93	82	81
Sum of five means				557			
S.D.				4.54			
Lactate (N = 6)							
Mean (mg %)	9.3	12.3	14.5	15.8	12.9	10.7	9.4
Sum of five means				66.2			
S.D.				1.17			
Pyruvate (N = 6)							
Mean (mg %)	0.82	0.97	1.15	1.30	1.09	0.97	0.87
Sum of five means				5.48			
S.D.				0.09			
Lactate/Pyruvate (L/P) Ratio	11.1	12.7	12.6	12.2	11.8	11.0	10.8

a standard error of the mean of 6.2 mg per 100 ml. All subsequent values for the remaining five hours of the test were within normal limits for non-diabetic subjects. Similarly, the blood lactate and pyruvate values were also within normal limits. A fasting lactate/pyruvate ratio of 11.1 is in good agreement with the published values of Friedman et al. (1945), and Stoltz and Bessey (1942).

Psychiatric Patients

GLUCOSE

Table 13-8 illustrates changes in blood glucose concentration in schizophrenic and psychoneurotic patients, with and without anxiety, following glucose challenge.

When compared to control values, hour by hour, there were no significant differences evident in the categories studied. However, by summing the significant five mean values (0.5, 1, 2, 3, and 4 hours after ingestion of glucose) of each group studied, and comparing these cumulative values to similarly summed control

TABLE 13-8.
Whole Blood Glucose Values Following Glucose Loading in Psychiatric Patients

Group	Hours Post Glucose						
	0	1/2	1	2	3	4	5
Schizophrenia without anxiety (N = 20)							
Mean (mg %)	85	135	137	104	86	77	89
Sum of five means				539			
S.D.				31			
Schizophrenia with anxiety (N = 8)							
Mean (mg %)	88	158	172	128	80	69	75
Sum of five means				607			
S.D.				32			
Psychoneurosis without anxiety (N = 8)							
Mean (mg %)	90	150	141	90	68	77	80
Sum of five means				526			
S.D.				23			
Psychoneurosis with anxiety (N = 7)							
Mean (mg %)	89	155	184	89	95	73	68
Sum of five means				596			
S.D.				38			

values, it was found that both psychoneurotics and schizophrenics with anxiety do differ significantly. Those patients classified as schizophrenic or psychoneurotic but without anxiety do not differ significantly from controls. But when the values for schizophrenics and psychoneurotics without anxiety are summed (1,203) the pair of values differ with a high statistical significance.

LACTATE

Table 13-9 depicts data reflecting blood lactate changes associated with the glucose challenge. Lactate concentrations were markedly ($P < 0.001$) elevated during the third, fourth, and fifth hours post-glucose in anxiety-prone schizophrenic and psychoneurotic patients. Patients devoid of the anxiety component, regardless of psychiatric classification, showed no significant changes in blood lactate.

PYRUVATE

Blood pyruvate data, shown in Table 13-10, were markedly ($P < 0.001$) depressed in all patients classified as schizophrenic, beginning at the second hour post-glucose. This finding was also true for all patients classified as psychoneurotic, but to a lesser extent. It is the depression in pyruvate synthesis that is reflected in the lactate/pyruvate ratio. Although all categories of psychiatric patients studied exhibited lower than normal pyruvate concentrations, only the anxiety-prone group showed abnormally high production of lactate in relation to pyruvate.

LACTATE/PYRUVATE RATIO

The lactate/pyruvate ratio was calculated for all patients ($N = 54$) in the study with respect to anxiety ($N = 18$) and non-anxiety ($N = 36$). These calculations are shown in Table 13-11. The L/P ratio for the non-anxiety group fluctuated no more than +4.0, whereas the anxiety prone group increased a maximum of +29.1.

An examination of the schizophrenic group indicates that patients in the non-anxiety category ($N = 20$) revealed a positive shift in the L/P ratio of +6.6, whereas the anxiety-prone group ($N = 8$) changes +29.4. This relationship is graphically illustrated in Figure 13-1.

The L/P ratio calculations for anxiety-prone psychoneurotic patients are also listed in Table 13-11. Although there is a similarity between anxiety-prone patients, whether schizophrenic or psychoneurotic, there was a reversal in the psychoneurotic non-anxiety group; that is, the non-anxiety group ($N = 8$) showed a negative shift in the L/P ratio of −5.8 at the third-hour post-glucose, returning to within 0.5 of the fasting level during the fifth hour. The anxiety-prone group ($N = 7$) showed a positive shift of +35.1. These data are graphically illustrated in Figure 13-2.

ADENOSINE TRIPHOSPHATE

Blood ATP levels were measured in schizophrenic patients with anxiety ($N = 9$), without anxiety ($N = 2$), and in control subjects ($N = 6$). Table 13-12 depicts

TABLE 13-9.

Whole Blood Lactate Values Following Glucose Loading in Psychiatric Patients

Group	Hours Post Glucose						
	0	1/2	1	2	3	4	5
Psychoneurosis without anxiety (N = 8)							
Mean (mg %)	8.1	10.2	13.0	12.1	10.1	9.1	8.2
S.D.±	3.7	4.1	4.7	5.7	4.7	3.5	2.4
$S.E._M$	1.40	1.54	1.77	2.14	1.77	1.43	0.91
P (diff. from cont.)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Sum of five means				54.5			
S.D.				4.5			
Psychoneurosis with anxiety (N = 7)							
Mean (N = 7)	11.1	13.7	16.8	19.1	23.2	27.3	26.1
S.D. ±	3.4	3.1	3.6	4.3	4.0	5.2	4.9
$S.E._M$	1.50	1.26	1.47	1.75	1.63	2.12	2.00
P (diff. from cont.)	n.s.	n.s.	n.s.	n.s.	0.001	0.001	0.001
Sum of five means				100.1			
S.D.				4.0			
Schizophrenia without anxiety (N = 20)							
Mean (mg %)	7.8	9.9	12.1	12.2	11.7	10.6	9.1
S.D. ±	1.9	2.7	4.5	3.1	4.4	4.0	4.3
$S.E._M$	0.10	0.62	1.01	0.71	1.01	0.92	1.00
P (diff. from cont.)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Sum of five means				56.5			
S.D.				3.7			
Schizophrenia with anxiety (N = 8)							
Mean (mg %)	11.0	15.5	18.6	20.7	24.8	24.3	23.8
S.D. ±	2.4	3.5	3.5	4.0	5.4	4.6	4.3
$S.E._M$	0.07	1.32	1.32	1.51	2.04	1.74	1.62
P (diff. from cont.)	n.s.	n.s.	0.05	0.01	0.001	0.001	0.001
Sum of five means				103.9			
S.D.				4.2			

TABLE 13-10.

Whole Blood Pyruvate Values Following Glucose Loading in Psychiatric Patients

Group	Hours Post Glucose						
	0	1/2	1	2	3	4	5
Psychoneurosis without anxiety (N = 8)							
Mean (mg %)	0.40	0.67	0.84	0.79	0.70	0.54	0.42
S.D. ±	0.29	0.61	0.73	0.47	0.30	0.36	0.25
$S.E._M$	0.11	0.23	0.28	0.18	0.11	0.14	0.09
P (diff. from cont.)	0.01	n.s.	n.s.	0.05	0.01	0.01	0.001
Sum of five means				3.54			
S.D.				0.50			
Psychoneurosis with anxiety (N = 7)							
Mean (mg %)	0.69	0.91	1.12	1.03	0.75	0.65	0.51
S.D. ±	0.32	0.51	0.65	0.70	0.26	0.20	0.27
$S.E._M$	0.13	0.21	0.27	0.29	0.11	0.08	0.11
P (diff. from cont.)	n.s.	n.s.	n.s.	n.s.	0.05	0.001	0.01
Sum of five means				4.46			
S.D.				0.46			
Schizophrenia without anxiety (N = 20)							
Mean (mg %)	0.59	0.71	0.81	0.76	0.60	0.52	0.46
S.D. ±	0.46	0.58	0.47	0.41	0.27	0.21	0.23
$S.E._M$	0.10	0.13	0.11	0.09	0.06	0.05	0.05
P (diff. from cont.)	0.05	n.s.	0.01	0.001	0.001	0.001	0.001
Sum of five means				3.40			
S.D.				0.39			
Schizophrenia with anxiety (N = 8)							
Mean (mg %)	0.67	0.89	0.72	0.81	0.65	0.56	0.52
S.D. ±	0.43	0.64	0.61	0.40	0.27	0.21	0.24
$S.E._M$	0.16	0.24	0.23	0.15	0.10	0.08	0.09
P (diff. from cont.)	n.s.	n.s.	n.s.	0.01	0.001	0.001	0.01
Sum of five means				3.61			
S.D.				0.45			

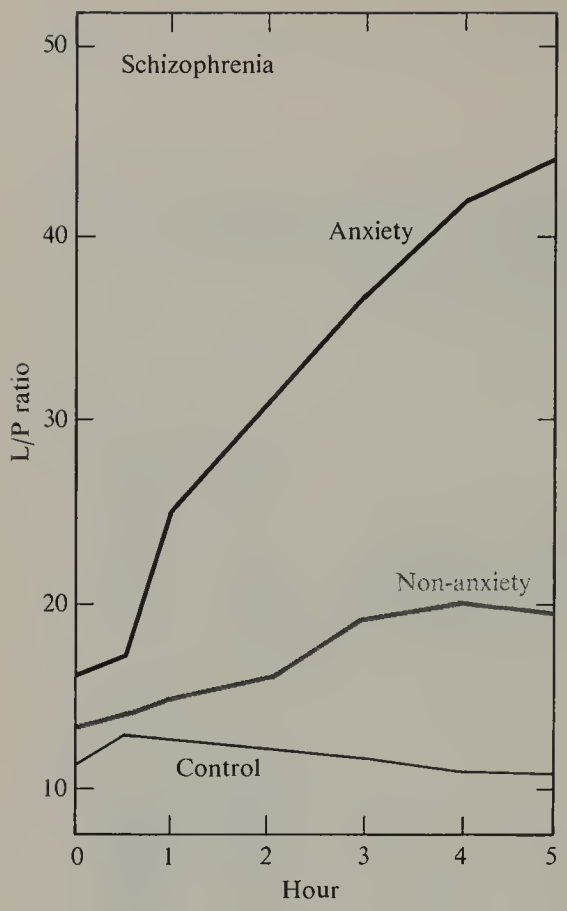


FIGURE 13-1 .
L/P ratio in schizophrenia.

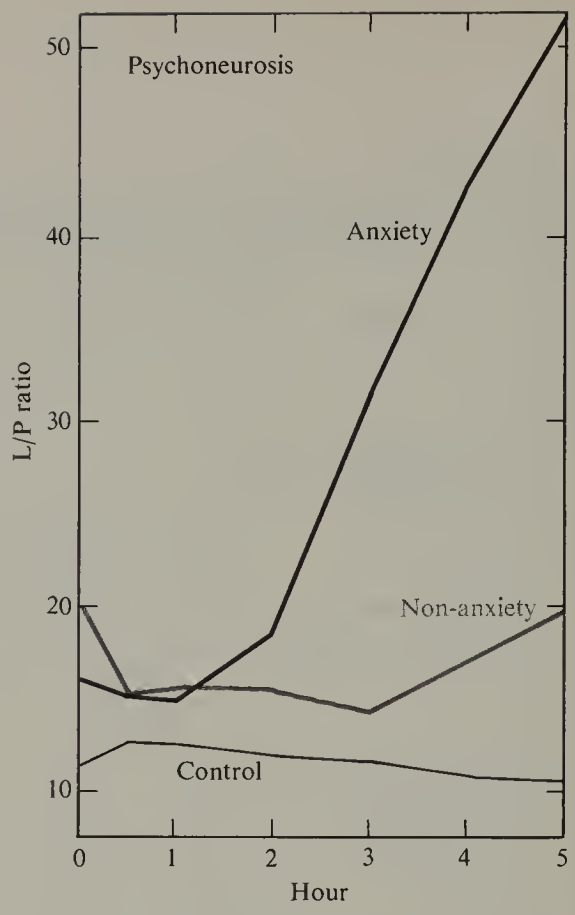


FIGURE 13-2.
L/P ratio in psychoneurosis.

TABLE 13-11.
Lactate/Pyruvate Ratio Following Glucose Loading

Group	Number	Hours Post Glucose						
		0	1/2	1	2	3	4	5
Control	(6)	11.3	12.7	12.6	12.2	11.8	11.0	10.8
All Patients*								
without anxiety	(36)	16.0	15.7	15.8	16.3	19.5	20.0	20.0
with anxiety	(18)	17.3	16.5	17.0	21.8	35.6	43.7	48.4
Schizophrenia								
without anxiety	(20)	13.2	13.9	14.9	16.1	19.5	20.4	19.8
with anxiety	(8)	16.4	17.4	25.8	25.6	38.2	43.4	45.8
Psychoneurosis								
without anxiety	(8)	20.2	15.2	15.5	15.3	14.4	16.8	19.5
with anxiety	(7)	16.1	15.1	15.0	18.5	31.0	42.1	51.2

* Includes psychiatric patients with miscellaneous disorders.

ATP concentrations in relation to time following glucose challenge. Significantly less ATP was measured in the blood of anxiety-prone patients during the first, second, and third hours after glucose loading, whereas no significant changes were found in the non-anxiety group when both were compared to control subjects.

TABLE 13-12.

Blood ATP Levels Following Glucose Loading in Control and Psychiatric Patients*

Group	Hours Post Glucose						
	0	1/2	1	2	3	4	5
Non-schizophrenia (N = 2)							
Mean (mg %)	54.5	74.6	82.3	71.1	56.5	50.6	48.4
S.D. ±	2.4	14.6	18.5	4.2	10.8	4.8	0.6
$S.E._M$	2.4	14.6	18.5	4.2	10.8	4.8	0.6
P	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Sum of five means				336.0			
S.D.				10.6			
Control (N = 6)							
Mean (mg %)	50.0	75.0	82.6	65.0	54.7	48.4	48.2
S.D. ±	7.2	9.3	9.0	4.5	5.5	4.5	1.4
$S.E._M$	3.2	4.2	4.0	2.0	2.5	2.0	0.6
Sum of five means				325.7			
S.D.				6.6			
Schizophrenia (N = 9)							
Mean (mg %)	40.2	50.8	47.5	50.0	40.0	41.5	39.9
S.D. ±	8.8	18.4	7.8	9.8	11.6	10.1	10.3
$S.E._M$	3.1	6.9	2.8	3.5	4.1	4.6	3.6
P	0.05	0.05	0.001	0.001	0.01	n.s.	n.s.
Sum of five means				229.8			
S.D.				11.5			

* Adenosine triphosphate, expressed as micromoles per 100 ml whole blood. Method from Adam (1963).

The relationship between glucose concentration and ATP concentration in control subjects is depicted in Figure 13-3. The coefficient of correlation between the two sets of values was found to be 0.99. A similar plot of data for schizophrenic patients, with or without anxiety, is shown in Figure 13-4. The solid squares of the anxiety group show a great deal of scatter, and thus little correlation, r = 0.16. The non-anxiety group showed a good degree of correlation, r = 0.76.

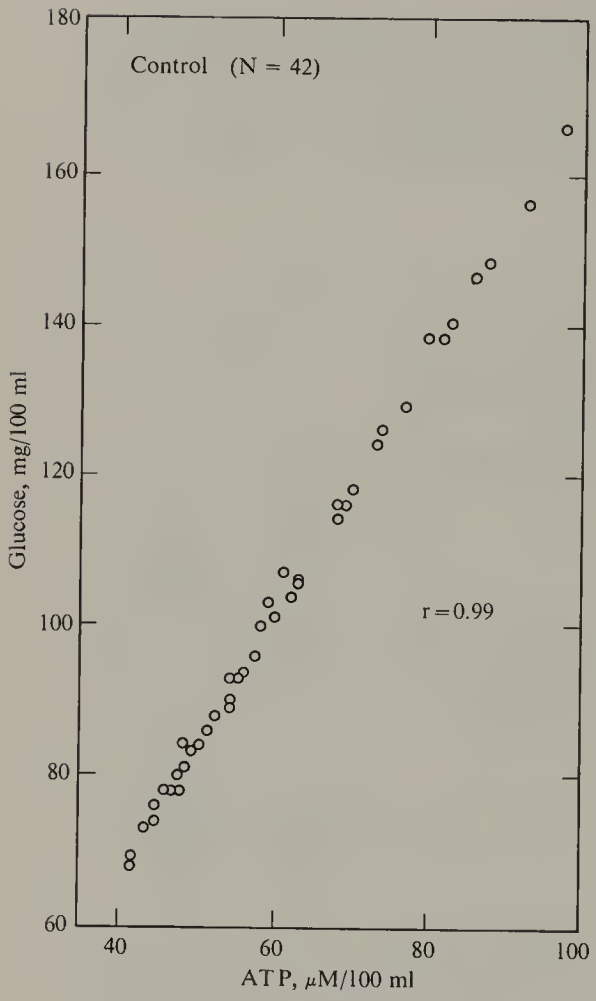


FIGURE 13-3.
Serum glucose as a function of ATP, control subjects.

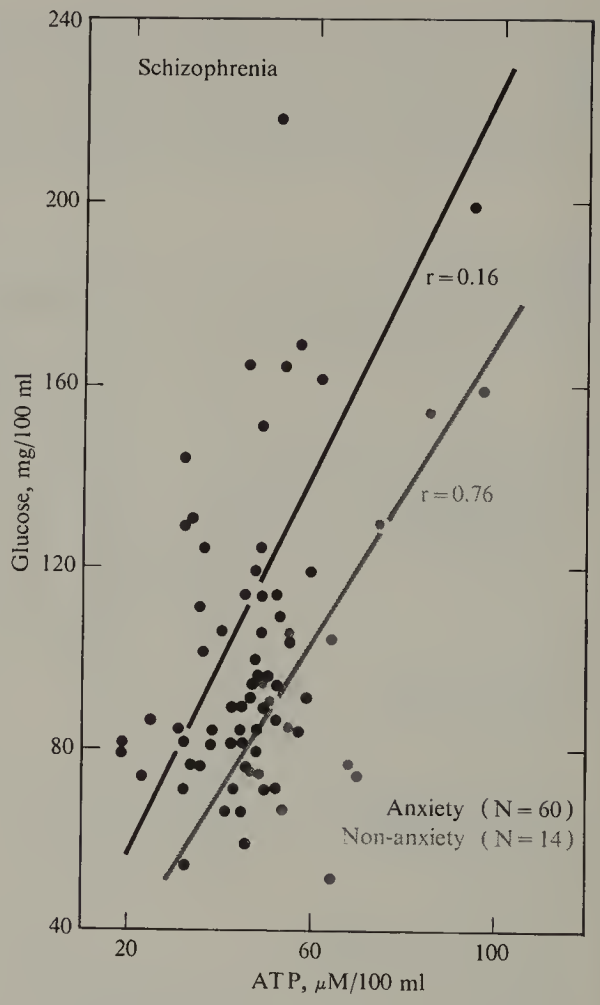


FIGURE 13-4.
Serum glucose as a function of ATP, schizophrenic subjects.

DISCUSSION

Carbohydrate metabolism in psychiatric patients has been the subject of numerous investigations, commencing with studies of fasting blood glucose (Mann, 1925; Mann and Scott, 1929), but only when the subject was challenged with a glucose load were any differences observed. In 1931, McCowan and Quastel (1931) demonstrated that abnormal glucose tolerance is linked with psychosis, and noted that the magnitude of the metabolic abnormality was associated with the "emotional tension of the patient." Tod (1936) confirmed these findings, and further noted that the greatest variations in glucose response were associated with either excessive anxiety or marked depression.

Carbohydrate metabolism in schizophrenics has been the subject of two reviews; one by Richter (1957) and the other by Smythies (1963). On two points there

is agreement with regard to glucose tolerance in psychiatric patients: (1) the fasting blood glucose of psychotic patients is generally within normal limits; and (2) disordered carbohydrate metabolism is frequently observed in psychotic patients.

Investigations of intermediary metabolism of carbohydrates in psychiatric patients has generally been confined to three experimental approaches:

1. A carbohydrate is administered and the absolute change, or rate of change, in metabolic intermediates is measured (Henneman et al., 1954a, 1954b).
2. A metabolic intermediate of carbohydrate metabolism (that is, lactate, succinate, etc.) is administered to the patient, and the absolute change, or rate of change, in concentration of the injected intermediate or related metabolites is measured (Altschule et al., 1956; Arnold et al., 1962).
3. A stressor substance (insulin) or procedure (electroconvulsive shock) is applied to aggravate or stimulate dysfunction of carbohydrate metabolism, and the changes in metabolic parameters are measured (Proctor et al., 1944; Elliott et al., 1941).

In an earlier study, Beebe and Wendel (1968), using a large number of patients (N = 133), observed significant alterations in glucose tolerance response in schizophrenics and psychoneurotics. These findings are consistent with those reported by others (Henneman et al., 1954; Altschule et al., 1952; Freedman et al., 1954; and Klein, 1942).

In the present study mean values of blood glucose showed statistically significant differences between anxiety and non-anxiety patients (Table 13-8).

Alterations in blood lactate, pyruvate and ATP, and the lactate/pyruvate ratio found in the schizophrenic and neurotic patient exhibiting an anxiety component indicate that there is a profound disturbance in the transformation of chemical to kinetic energy. A basic intracellular chemical disturbance in energy formation and utilization, manifested when there is a requirement to mobilize energy rapidly, is consistent with the clinical manifestations of a state of anxiety.

Under aerobic conditions, pyruvic acid metabolism proceeds via oxidative decarboxylation with the formation of acetyl-CoA which enters the tricarboxylic acid cycle. Under anaerobic conditions, pyruvic acid does not accumulate, but undergoes a reaction analogous to the conversion of 3-phosphoglyceraldehyde to 1,3-diphosphoglyceric acid. In this reaction NAD^+ is reduced to NADH, aerobically. The NADH, like pyruvate, is oxidized by the mitochondrial electron transport system. When compared to available carbohydrate, NAD^+ is in short supply. Were the NAD^+ reduced by the oxidation of 3-phosphoglyceraldehyde, not oxidized, glycolysis would cease when all the NAD^+ was reduced to NADH. This is

prevented by the action of lactic dehydrogenase (LDH) which catalyzed the reaction:

$$\text{Pyruvate} + \text{NADH} \leftrightarrow \text{Lactate} + \text{NAD}^+ + \text{H}^+$$

The coupled relationship between these reactions in the coupled glycolytic sequence is:

$$\begin{matrix} P_i + \text{3-Phosphoglyceraldehyde} \\ \text{1,3-Phosphoglyceric acid} \end{matrix} \quad \begin{matrix} \nearrow \text{NAD}^+ \\ \searrow \text{NADH} + \text{H}^+ \end{matrix} \quad \begin{matrix} \nearrow \text{Lactate} \\ \searrow \text{Pyruvate} \end{matrix}$$

The equilibrium of the LDH reaction, as in all reactions involving an alcohol and NAD, strongly favors formation of lactic acid. The glycolytic process proceeds with the net accumulation of two molecules of lactate per mole of glucose. Lactate formation is a blind-alley in metabolism: once formed there is no mechanism for direct utilization other than reversal of the LDH reaction, and the reformation of pyruvate under aerobic conditions. Fortunately, neither lactate nor pyruvate are locked into the cell; this is in contrast to the phosphorylated intermediates of glyceolysis. In vivo, lactic acid diffuses from the cell and enters the circulation. This is a rather slow process, and probably accounts for the delay observed (see Table 13-8).

Studies of lactate and pyruvate production following glucose challenge indicates that anxiety prone schizophrenic and psychoneurotic patients exhibit a marked shift from aerobic to anaerobic metabolism. The highly significant and protracted elevations in blood lactate and the markedly elevated lactate/pyruvate ratio suggest that glycolytic metabolism via the Embden-Meyerhof pathway is being diverted from the aerobic pathway. These findings are consistent with those reported by Altschule and his associates (1952, 1956, 1957), but their tolerance test was of three rather than five hours duration, and no reference was made to subjective symptoms observed.

Anaerobic glycolysis is bioenergetically inefficient. The reaction illustrated in Figure 13-5 yields a relatively small decline in free energy. The equation shown may be considered a statement of two linked systems. In one system glucose is broken down to form two molecules of lactate; in the other, two molecules of ATP are formed from one of adenosine diphosphate (ADP) and phosphate (P_i). These two processes do not take place independently but are coupled. Therefore, glucose breakdown cannot occur without ATP formation, and ATP formation cannot occur without glucose breakdown. In anaerobic glycolysis two facts should be kept in mind: (1) the amount of ATP formed is reduced by a divisor of 19, and (2) NAD^+ is not involved in this sequence of reactions.

The energy yield involved in the aerobic metabolism of glucose should now be considered. Glucose is converted to pyruvate (not lactate), and the following equation illustrates the first or glycolytic phase of glucose metabolism under aerobic conditions:

$$\text{Glucose} + \text{NAD}^+ + 2\,\text{ADP} + 2\,\text{P}_i \rightarrow 2\,\text{Pyruvate} + \text{NADH} + 2\,\text{ATP}. \quad (1)$$

The equation for the oxidation of two molecules of NADH formed in the glycolytic sequence is:

$$2\,\text{NADH} + 6\,\text{P}_i + 6\,\text{ADP} + \text{O}_2 \rightarrow 2\,\text{NAD}^+ + 8\,\text{H}_2\text{O} + 6\,\text{ATP}. \quad (2)$$

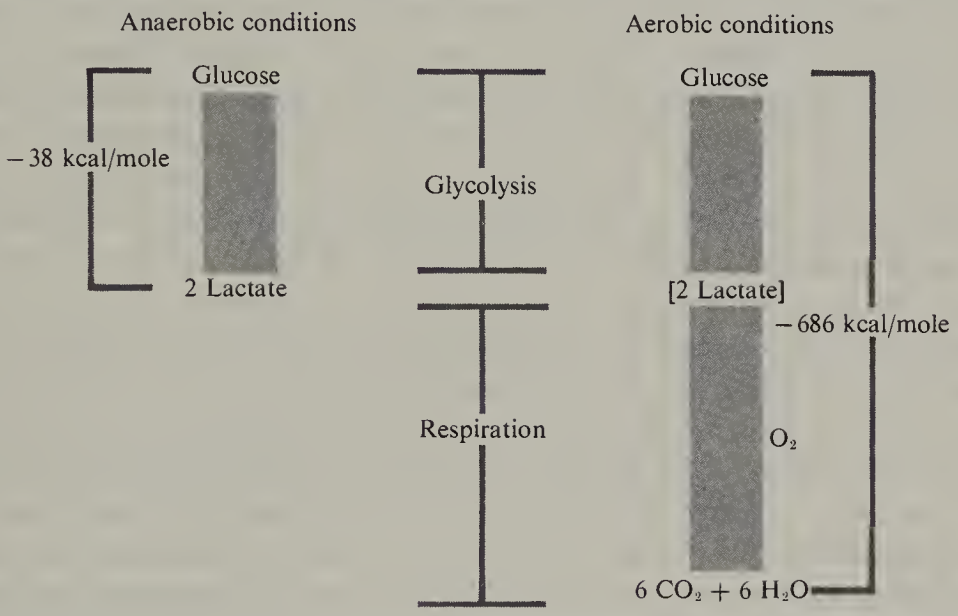


FIGURE 13-5.
Metabolism of glucose under anaerobic and aerobic conditions.

This oxidation proceeds via the respiratory chain and is accompanied by the phosphorylation of ADP.

The equations for the oxidation of two molecules of pyruvate to acetyl-CoA, and the oxidation of the two molecules of NAD^+ are:

$$2\,\text{Pyruvate} + 2\,\text{NAD}^+ \xrightarrow{\text{CoA}} 2\,\text{Acetyl-CoA} + 2\,\text{CO}_2 + 2\,\text{NADH}, \quad (3)$$

$$2\,\text{NADH} + 6\,\text{P}_i + 6\,\text{ADP} + \text{O}_2 \rightarrow 2\,\text{NAD}^+ + 8\,\text{H}_2\text{O} + 6\,\text{ATP}. \quad (4)$$

The overall equation for the oxidation of two moles of acetate, resulting from two revolutions of the Krebs Cycle is:

$$2\,\text{Acetate} + 24\,\text{P}_i + 24\,\text{ADP} + 4\,\text{O}_2 \rightarrow 4\,\text{CO}_2 + 28\,\text{H}_2\text{O} + 24\,\text{ATP}. \quad (5)$$

In each revolution of the cycle four pairs of electrons pass down the chain to oxygen and, on the average, each pair causes formation of three molecules of ATP. Adding all of the equations (1 through 5) and striking the terms appearing on both sides yields the following equation:

$$\text{Glucose} + 38\ P_i + 38\ \text{ADP} + 6\ O_2 \rightarrow 6\ CO_2 + 44\ H_2O + 38\ \text{ATP}.$$

This is the overall equation for the complete oxidation of one molecule of glucose under aerobic conditions; coupled to this process is the formation of 38 molecules of ATP from ADP and P_i.

Anaerobic cells obtain energy from the conversion of glucose to lactate, which leaves the cell by diffusion. The maximum energy available to these cells is only 38,000 cal/mole of glucose, or a little more than 5 percent of the amount available when glucose is oxidized to CO_2 and water, which is 686,000 cal/mole. For the nebulous advantage of being able to extract energy from glucose in the absence of oxygen, the anaerobic cell must waste nearly 95 percent of the total energy potentially available. Because anaerobic glycolysis can extract only a small fraction of the total energy of the glucose molecule, it is a corollary that anaerobic cells must use more fuel per unit of time per unit of weight to accomplish the same amount of cellular work as the aerobic cell.

Because of the knowledge that a shift from aerobic to anaerobic metabolism will directly influence the synthesis of ATP, the relationship between blood ATP and glucose concentrations in schizophrenic patients with and without anxiety was examined. In control subjects there was considerable correlation between ATP and glucose concentrations, but little or no correlation in the anxiety prone group. The relationship between blood ATP and lactate was examined, and a significant degree of negative correlation observed; that is, as the blood lactate concentration increases, the ATP concentration diminishes.

The literature contains several accounts of studies of ATP metabolism in schizophrenics, together with a preponderance of contradictory data. Gottlieb et al. (1959) examined erythrocyte ATP levels and found no significant differences between controls and schizophrenics in the basal state; however, they did discover that following insulin stress the rate of ATP turnover was high in chronic schizophrenics, and concluded that the cells were unable to mobilize ATP.

As a result of additional studies, Frohman et al. (1962, 1968) suggested that (1) the plasma of schizophrenics contains a factor that increases the rate of turnover of ATP in erythrocytes and/or inhibits the reaction where two molecules of ADP are split by myokinase (adenylate kinase) to form ATP and adenosine monophosphate (AMP), and that the plasma factor renders the rate of turnover incapable of being stimulated by the action of insulin; or (2) that the factor causes either an increase in the proportion of glucose passing down the Embden-Meyerhof pathway, or decreases the amount passing down the Warburg-Dickens-Lipmann pathway (the

ribose shunt); or (3) causes an elevation of the lactate/pyruvate ratio, suggesting some inhibition of aerobic metabolism. Considering the shift from aerobic to anaerobic metabolism, niacin therapy may participate in the maintenance of ATP synthesis. Reactions within the cell offer several interesting situations for speculation. A situation arises from bimolecular reactions in which co-substrates are among the reactants and the products, and where a co-substrate is converted to an alternate form in one reaction, and back to the original form in another reaction.

The stoichiometric reaction scheme may appear as follows:

$$A + X \xrightarrow{1} B + X' \qquad B \xrightarrow{2} C \qquad C + X' \xrightarrow{3} D + X,$$

where X and X′ stand for the two forms of the co-substrate or co-enzyme. It is assumed that the constancy of A and C is assured by direct connection with source and sink, respectively.

The regenerated X recycles and is used in the first reaction, and X′ cycles forward to be used in the last reaction. This cyclic character is illustrated in Figure 13-6.

Cyclic systems have interesting properties. To understand the example just schematized, two additional bits of information are needed. If neither X nor X′ is created nor destroyed in the system, this conservation of the total concentration of the co-substrate or co-enzyme can be expressed by the equation $X_t = X + X'$. And, the sum of the net rates of formation of B, C, and X is zero. The rates of reactions 1, 2, and 3 are denoted by v_1, v_2, v_3, respectively, and the net rate of formation of B is represented as $r_b = v_1 - v_2$. Similarly, the net rate for C is $r_c = v_2 - v_3$; and for X is $r_x = v_3 - v_1$. Then $r_b = r_c + r_x = 0$. This implies that $B + C + X$ is constant; that is, $B + C + X = Z$. The system is therefore dependent on Z, since $B + C + X = Z$ regardless of time, and consequently the sum of the initial values must also equal Z. But assume the system could be returned to normal by adding even a trace of A, since it can use A via X and thus regenerate X′. On the other hand, if the system can be stopped in a state where it has no X, but only X′ (that is, by blocking reaction 2), and no B or C, the system would now be unable to metabolize A. But it could be started and returned to normal by adding a trace of B or C (or X). In short, cyclic systems of this kind are capable of existing in states in which they are effectively dead because of a lack of co-substrate or co-enzyme (which, although present in ample amounts, is in the wrong form) and such systems will literally starve in the midst of plenty.

This system was described less for its intrinsic value than to stress the peculiarities of cyclic-containing enzymes. It is characteristic of such systems that the regenerative property which regenerates and, as it were, buffers it, can turn into a trap if pushed beyond the safe limits.

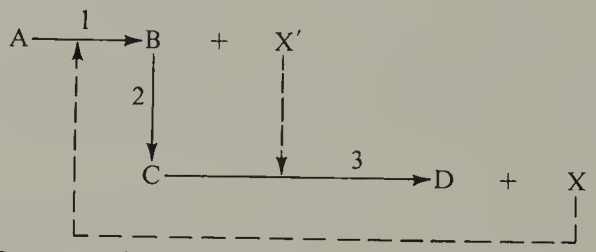
In carbohydrate metabolism two cycles interact; that of hydrogen transfer (NAD^+ and $NADH + H^+$), and that of phosphate transfer (ATP and ADP).

CYCLIC RELATIONSHIP BETWEEN NAD AND ATP

Model System

$$A + X \xrightarrow{1} B + X'; \quad B \xrightarrow{2} C; \quad C + X' \xrightarrow{3} D + U$$

Cyclic Representation



Solving the Rate Equation

Assumptions:

1. If neither X nor X′ is created nor destroyed in the system, then the total concentration of co-substrate can be expressed by

$$X_t = X + X'.$$

2. The sum of the net rates of formation of B, C, and X is zero, for if we denote the rates of reactions 1, 2, and 3 by v_1, v_2, and v_3, then we can write the net rates of formation of each component as follows:

$$r_b = v_1 - v_2$$
$$r_c = v_2 - v_3;$$

and

$$r_x = v_3 - v_1.$$

This implies that B + C + X is constant; that is,

$$B + C + X = M.$$

3. Solving for the steady state

$$\frac{X = k_3 M X_t}{k_1 A + k_3 M}$$

$$\text{Rate} = k_1 A X = \frac{k_1 k_3 M X_t A}{k_1 A + k_3 M}$$

FIGURE 13-6.

They interact because both are essential to metabolism, and also because they contain enzymes which destroy NAD^+. For example, enzymes resynthesize NAD^+ with the help of ATP, so that ATP is needed to maintain the NAD^+ level, and ATP can be generated during carbohydrate metabolism only if NAD^+ is available. This system has a steady state that corresponds to active metabolism, and another that corresponds to death (zero metabolism). The active steady state is stable, and if the system is disturbed it tends to return to the active steady state. The zero-activity "trap" is such that the system can be rescued by priming with ATP or NAD^+, but not by substrate alone. The details of this system can be found in Reiner (1959).

Evidence has been presented which indicates that in the anxiety-prone schizophrenic and psychoneurotic there is a marked shift from aerobic to anaerobic metabolism in the face of a glucose challenge. There is a further indication of a disturbance in ATP synthesis, as reflected in the diminished blood ATP levels of anxiety prone schizophrenic and psychoneurotic patients. The relative productivity and efficiency of aerobic and anaerobic pathways with respect to carbohydrate metabolism have been reviewed. Finally, an attempt has been made to illustrate the close interrelationship between ATP and NAD^+, as shown in the coupled bimolecular cyclic system.

Megadose quantities of niacin may be proving adequate to produce sufficient NAD^+ to effectively serve as a "primer" for the aerobic energy-producing mechanism essential for efficient carbohydrate metabolism.

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14

Ascorbic Acid and Schizophrenia

MARIJAN HERJANIC

The antiscorbutic vitamin, ascorbic acid (vitamin C), was isolated in 1928 and synthesized in 1933. As is usual in science (Mandell and Spooner, 1968), the discovery led to a flurry of interest in the new compound. The amount of literature on ascorbic acid appearing during the next two decades was enormous. (For a summary of the literature, see Sebrell and Harris, 1954 and Stewart, 1953.) In recent years interest in ascorbic acid has decreased and studies using modern biochemical methods are relatively rare, resulting in insufficient understanding of its cellular biochemical action. It is well known that individuals deprived of ascorbic acid will develop scurvy, and that small amounts (10 mg; Bartley et al., 1953) of this vitamin will suffice to prevent the development of the disease. Other reports indicate that extra ascorbic acid, beyond that necessary to prevent scurvy, is valuable in many pathological conditions (Baker, 1967; Goldsmith, 1961; Williams and Deason, 1967).

We shall summarize briefly various physiologic roles proposed for ascorbic acid and in somewhat greater detail various biochemical theories of schizophrenia, not because our knowledge of the latter is greater but because of the context of this book. The bibliography is far from complete; it provides the interested reader with starting points for further reading.

In discussing various functions of ascorbic acid we must distinguish between its physiologic effects and its pharmacologic effects (Graham, 1966). Thus, the use of ascorbic acid to prevent scurvy is a physiologic effect, and its use to acidify the urine is a pharmacologic effect; its use in treatment of patients with infectious diseases is in the controversial area (see, for example, Pauling, 1970). Another word of caution must be said at this time. Animals were used as subjects in most of the studies, thus conclusive evidence for the function of the substance in the human body can rarely be provided.

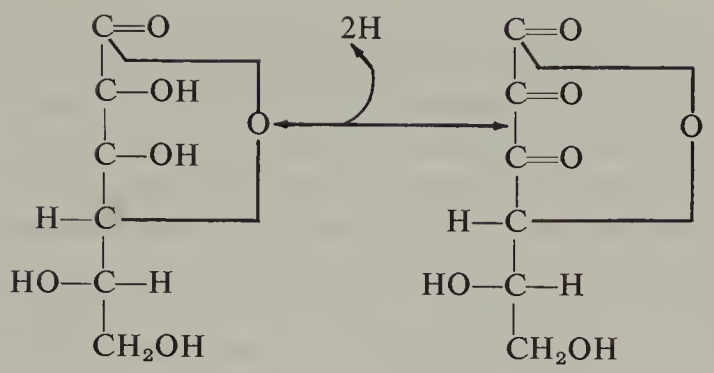
SYNTHESIS

Plants and most animals synthesize their own ascorbic acid. In plants synthesis occurs concomitantly with germination of the seed and proceeds most rapidly in the actively growing regions. It accumulates in certain portions of the plant, especially the fruit. From the time of fruit set to the onset of ripening the ascorbic acid content may increase greatly (Loewus, 1961). All mammals except man, monkey, one species of Indian fruit bat, and the guinea pig manufacture their own ascorbic acid in the liver. Mammals cannot normally contract scurvy, no matter how little ascorbic acid is in their diet, because they synthesize a steady supply of this important substance in fairly large amounts. The mammalian liver produces ascorbic acid from glucose by stepwise synthesis, each step being controlled by a separate specific enzyme (Chatterjee et al., 1961; Isherwood and Mapson, 1961):

$$\text{Glucose} \rightarrow \text{D-glucuronolactone} \rightarrow \text{L-gulonolactone} \rightarrow \text{2-keto-L-gulonolactone} \rightarrow \text{L-ascorbic acid}$$

The animals (including man) that are not able to synthesize ascorbic acid lack the last enzyme in the series, L-gulono-oxidase. The lack of this one enzyme completely blocks the synthesis, even though the human liver contains the other enzymes in the series (Chatterjee et al., 1961).

CHEMISTRY



Ascorbic acid Dehydroascorbic acid

Ascorbic acid possesses two asymmetrical carbon atoms, and is optically active. L-Ascorbic acid and L-dehydroascorbic acid are the only known naturally occurring substances with vitamin C activity. Pure ascorbic acid is a white crystalline solid, freely soluble in water. It is a powerful reducing agent, giving up two hydrogen atoms to become dehydroascorbic acid. This oxidation is reversible in the body (Bell et al., 1968; Harper, 1963). The reducing action of ascorbic acid is the basis for the chemical determination of the compound. In most plant and animal tissues it is the only substance that exhibits this reducing action in acid solutions (Harper, 1963). The stability of ascorbic acid in solution or in food is affected by the *p*H, the temperature, and contact with oxygen in the presence of traces of metals, especially copper. In the presence of light, oxygen, and traces of copper, ascorbic acid is rapidly oxidized at *p*H values above 4, especially if the solution is warmed. Some ascorbic acid is destroyed during the preparation and cooking of many foods. In addition, fruit and vegetables contain an enzyme, ascorbic acid oxidase, which accelerates the oxidation of ascorbic acid in the presence of oxygen (Bell et al., 1968).

DEGRADATION

The pathway of L-ascorbic acid catabolism is essentially unknown except for ready and reversible oxidation of ascorbic acid to dehydroascorbic acid and further irreversible oxidation to diketogulonic acid. Several different pathways from this point on have been proposed (Ashwell et al., 1961).

DISTRIBUTION

Ascorbic acid is probably present in all tissues of higher animals, at least during the developmental stages (Sebrell and Harris, 1954). It is usually found in greater concentrations in the tissues of higher metabolic activity. It is highest in the retina and occurs in decreasing concentrations in the pituitary gland, corpus luteum, adrenal cortex, liver, brain, testes, ovaries, spleen, thyroid, pancreas, salivary glands, lungs, kidneys, intestinal wall, heart muscle, spinal fluid, white blood cells, erythrocytes, and plasma (Sebrell and Harris, 1954). The factors regulating its distribution are poorly understood. One possible explanation is that ascorbic acid has to be oxidized to dehydroascorbic acid prior to penetration into tissues. Kidneys and intestines facilitate the transport of ascorbic acid by oxidizing the vitamin to an un-ionized form that readily penetrates cellular barriers (Martin, 1961).

The total amount of ascorbic acid in the body of a man receiving an adequate diet is about 5 g. Normally some 15 to 30 mg of ascorbic acid is contained in each 100 g of the buffy layer of the blood, half in the leucocytes and half in the platelets. The blood plasma contains from 0.5 to 2 mg per 100 ml (Baker et al., 1966; Bell et al., 1968; Burch, 1961; Goldsmith, 1961; Sebrell and Harris, 1954), but values below 0.5 mg per 100 ml may be found over a long period of time in an individual without any sign of ill health. In subjects deprived of ascorbic acid the plasma level drops to practically zero within two weeks, but at least an additional 15 weeks elapse before the appearance of the first clinical signs of scurvy. On the other hand, the concentration in the buffy layer reaches its lowest value only three to six weeks before the appearance of scurvy (Bartley et al., 1953).

EXCRETION

The urinary excretion of ascorbic acid is dependent on its plasma concentration. Below the level of 1.4 mg per 100 ml in the plasma the urinary excretion of ascorbic acid is almost negligible. Above that level the plasma clearance increases rapidly and approaches the glomerular filtration rate at 6 mg per 100 ml (Burch, 1961).

SCURVY

The classic symptoms of ascorbic acid deficiency have been described many times (see Sebrell and Harris, 1954), from Hippocrates (460–370 B.C.) to Hopkins (1906) and later writers. All descriptions mention the three principal manifestations of scurvy in adults: skin lesions, swollen gums with loss of teeth, and pain and weakness in the lower extremities (Harrison et al., 1966). In human volunteers experimentally

deprived of ascorbic acid (Bartley et al., 1953) the course of the development of scurvy was observed to be fairly uniform. The general sequence is as follows: for about 17 weeks no clinical signs; after 17 to 21 weeks the first sign, hyperkeratosis of the hair follicles; after 26 to 34 weeks perifollicular hemorrhages; and after 30 to 38 weeks swelling and hemorrhages of the gums and exacerbation of acne. Many signs listed as scorbutic in the classical descriptions of the disease, such as abnormal pallor, dryness of the skin, anemia, and night blindness, were not observed in the experiment. It is probable that classical scurvy was often a multiple-vitamin deficiency (Bartley et al., 1953).

Psychiatric symptoms associated with scurvy have been described only rarely, and are usually limited to "listlessness" and "mental depression." No psychiatric syndrome has been associated regularly with overt scurvy (Hoffer and Osmond, 1963).

DAILY REQUIREMENTS

The minimum quantity of ascorbic acid that will prevent scurvy is approximately 10 mg daily (Bartley et al., 1953). However, the recommended daily dose varies from 30 mg (League of Nations Technical Commission on Nutrition, 1938) to 70 mg (United States National Research Council). The latter amount is to allow a margin of safety and to satisfy the ill-defined "additional needs" (Goldsmith, 1961).

FUNCTIONS

The exact links between ascorbic-acid deficiency and the observed scorbutic effects have not been definitely established, but they probably consist of a general inhibition of a series of metabolic reactions for which ascorbic acid is a known cofactor. (1) Ascorbic acid is necessary for formation of collagen (Gould, 1961; Robertson, 1961). In its absence fibroblasts are unable to elaborate collagen, and osteoblasts and odontoblasts do not synthesize osteoid and dentine. The lack of formation of these matrices explains the failure of wounds to heal (Bartley et al., 1953) and changes in the growing bone of infants and children. The underlying biochemical defect concerns the lack of conversion of proline to hydroxyproline. (2) It is also needed for the hydroxylation of tryptophan to 5-hydroxytryptophan (Cooper, 1961). (3) It is necessary for the transfer of plasma-bound iron to the ferritin in the liver (Mazur, 1961). (4) It protects the enzyme *p*-hydroxyphenylpyruvic acid oxidase from inhibition by its substrate (La Du and Zannoni, 1961). (5) It has a pronounced effect upon the peripheral vascular system; deficiency causes increased hemorrhaging, decreased epinephrine response, and increased susceptibility to vascular stress (Dayton and Weiner, 1961; Lee, 1961).

Medical literature contains mention of several other possible functions of ascorbic acid: it may inhibit the formation of pigment from adrenaline (Bell et al., 1968); and it may participate in the conversion of 3,4-dihydroxyphenylethylamine to norepinephrine (Baker, 1967), in the hydroxylation of certain steroids synthesized in the mammalian adrenal gland (Baker et al., 1966), and in the metabolism of cholesterol (Sokoloff et al., 1967). There is a sharp increase in its plasma level in the middle of the menstrual cycle (Mickelsen et al., 1943). The need for ascorbic acid is increased in many pathologic conditions: stress (Baker, 1967), infections, allergies, lead poisoning (Williams and Deason, 1967), and exposure to low temperature (Dugal, 1961). The list could be made much longer, as there are few conditions for which the use of ascorbic acid has not been proposed by at least one investigator, although most of the proposals are based on unconfirmed single observations, and it is impossible to judge how reliable they are. Taking into consideration the distribution of ascorbic acid in the body, it is conceivable that ascorbic acid plays a role in the functioning of practically all tissues, the importance of the role varying with the health of the individual.

ASCORBIC ACID AND SCHIZOPHRENIA

The biochemical theories of schizophrenia are dealt with in a number of excellent texts and reviews (Smythies, 1963; Sourkes, 1962; Wolstenholme and O'Conner, 1958) and are also described fully elsewhere in this book. This review will deal only with theories in which ascorbic acid plays a prominent role.

LABORATORY TEST FOR SCHIZOPHRENIA

Because of the widely divergent clinical criteria and the subjective nature of the symptoms of mental illness there is frequently a disagreement in the diagnosis of schizophrenia. As a result many efforts have been made to establish a laboratory test to differentiate the schizophrenic from other mentally ill patients. Frequently such tests are outgrowths of investigations of biochemical differences: when the procedures are successful and reasonably simple, attempts have been made to adapt them for use as tests (Friedhoff, 1958). Simplicity and ease of duplication probably account for much of the popularity the work of Akerfeldt enjoyed for many years. His test was based on the oxidation of N,N-dimethyl-*p*-phenylenediamine (PPD) by ceruloplasmin (Akerfeldt, 1957). Ceruloplasmin oxidizes PPD enzymatically to a red-colored compound. The color reaction, however, may be inhibited by reducing substances in the serum, including ascorbic acid and certain sulfhydryl compounds. The curve obtained in the test is the net result of various substances acting in concert;

the lag period before the initial rise is believed to result from the action of ascorbic acid; it increases in length as the ascorbic acid concentration increases. The maximum slope of the curve apparently represents the maximum oxidizing effect of ceruloplasmin, while the bend of the curve from the linear represents the effect of sulfhydryl compounds. Akerfeldt found that the lag period in schizophrenics is shorter (low ascorbic acid level), the maximum slope is greater (high ceruloplasmin level), and the bending of the curve away from the linear is more marked (high level of sulfhydryl substances; Friedhoff, 1958).

Akerfeldt's findings were confirmed by other investigators. Positive results, however, were also found in many patients with other conditions, including liver disease, neoplasms, and pregnancy in the last trimester (Abood et al., 1957). In showing that schizophrenic patients had less serum ascorbic acid and more ceruloplasmin and copper than normal subjects, Akerfeldt confirmed the findings of previous investigators (Leach et al., 1956).

In 1940 Lucksch injected mice with cerebrospinal fluid from schizophrenic patients to determine toxicity. He then treated 12 of the mice with ascorbic acid. All cases in which cerebrospinal fluid toxicity for mice decreased during the treatment with ascorbic acid also showed marked clinical improvement (Lucksch, 1940).

Milner (1963) conducted a double-blind trial on 40 male chronic psychiatric patients. He found that adding one gram of ascorbic acid per day to the diet produced significant improvement in many of the patients. Two other studies (Herjanic and Herjanic, 1967; VanderKamp, 1966) also confirmed the previous findings that schizophrenic patients differ significantly in the amount of ascorbic acid required to produce saturation when compared to normal controls (40 and 20 grams in schizophrenics and less than 5 grams in normal controls).

It would be wrong to present these findings as unanimously accepted and unchallenged. Most investigators agree that chronically hospitalized schizophrenic patients show lower serum ascorbic acid levels and/or require very high amounts of ascorbic acid for saturation (Friedhoff, 1958; Hoffer and Osmond, 1963; Kety, 1959; McDonald, 1958). They contend that the difference can be explained by deficient ascorbic acid intake in the diet and perhaps by other unknown factors more related to hospitalization than to schizophrenia (Friedhoff, 1958; McDonald, 1958).

THE EPINEPHRINE HYPOTHESIS

It has been known for many years that epinephrine and norepinephrine are secreted in increased amounts as a result of various stresses, anxiety, and aggressive reactions. Persistent efforts have therefore been made to relate these substances to mental illness in general and to schizophrenia in particular. Their metabolism in normal and in mentally ill patients has been studied persistently for many years. The common

factor in all hypotheses based on such studies is that they postulate disturbed metabolism of epinephrine or norepinephrine. The abnormalities are postulated to occur at various points: abnormal production, utilization, or response, or the production of abnormal hallucinogenic metabolites (Kety, 1959; Smythies, 1963; Sourkes, 1962; Wolstenholme and O'Conner, 1958).

It has been demonstrated that ceruloplasmin is capable of catalyzing the oxidation of a number of substances, including PPD and epinephrine (Abood et al., 1957; Akerfeldt, 1957; Angel et al., 1957; Holmberg and Laurell, 1951; Leach et al., 1956). Leach and Heath (1956) reported the in vitro oxidation of epinephrine in the sera of schizoprenic patients to be nearly twice as high as in the sera of nonschizophrenic subjects. They also reported the serum ceruloplasmin levels of these schizophrenic patients to be approximately twice as high as those of the controls (Leach et al., 1956). The finding that epinephrine is oxidized more rapidly by the serum of schizophrenic patients was confirmed by other investigators (Kety, 1959; McDonald, 1958). It soon became apparent, however, that there is a high correlation between plasma ascorbic acid levels and the rate of epinephrine oxidation (Kety, 1959; McDonald, 1958). McDonald reported that he had been able to produce wide fluctuations in the epinephrine oxidation phenomenon, from normal to highly abnormal rates in both normal subjects and schizophrenics, by altering the level of ascorbic acid in the blood with diet, and that this had no effect on the mental processes of either group (as quoted in Kety, 1959). The very interesting results of previous investigations were attributed to the dietary deficiency of ascorbic acid in chronically hospitalized schizophrenic patients (McDonald, 1958). It was also noted (Angel et al., 1957) that ascorbic acid inhibits the in vitro serum oxidation of epinephrine and that ascorbic acid loading of schizoprenic and nonschizophrenic subjects causes the rate of oxidation to decrease markedly.

The interesting hypothesis that links the pathogenesis of schizophrenia to the faulty metabolism of epinephrine and the production of adrenochrome or adrenolutin (Smythies, 1963) and the mechanism of in vitro reduction of adrenochrome by ascorbic acid (Mattok, 1965) is reviewed extensively elsewhere in this book.

DISCUSSION

Taking into consideration the wide distribution of ascorbic acid in the human body, the multiplicity of functions attributed to it, and the variety of conditions that influence the blood levels, it would be surprising if in such a serious illness as schizophrenia we should not be able to detect changes in one of the parameters of ascorbic acid in the body—blood level, saturation, distribution, or excretion. On the other hand, because of the profusion of functions attributed to ascorbic acid, it is impossible at present to determine if the changes in ascorbic acid parameters are

causally connected with schizophrenia, if they reflect only the much broader general disturbance of the schizophrenic patient, or if they are unrelated to the illness.

It has been suggested (Baker, 1967; Urbach et al., 1952) that "almost any disturbance of the mind or body will cause significant changes in vitamin C levels in plasma." Respiratory infections and fever sometimes decrease ascorbic acid levels to zero; emotional stress and strain decrease the levels considerably; schizophrenic and control subjects have lower plasma ascorbic acid levels when anxious than when not anxious; severe physical exertion reduces the levels drastically (Maas et al., 1961). Suffering from schizophrenic illness is probably a stress in itself. The emotional reactions of schizophrenic patients to outside stimuli are unpredictable and frequently different from those of control subjects: events accepted calmly by controls may produce excessive anxiety or violent outbursts in schizophrenic patients. It is exceedingly difficult, if not impossible, to control the influence of emotional stress on the levels of ascorbic acid, even in controlled studies. When we also take into consideration other parameters (for example, illnesses and even minor physical exercise) that influence ascorbic acid levels, the difficulties of any attempt to interpret the results of different studies are compounded.

The validity of Akerfeldt's test for schizophrenia and the significance of the low levels of ascorbic acid or the increased amounts of ascorbic acid required for saturation reported by various investigations (Herjanic and Herjanic, 1967; Leach et al., 1956; Leach and Heath, 1956; VanderKamp, 1966) apparently stand or fall on acceptance or rejection of the claim that the changes in blood level are caused by dietary deficiencies in chronically hospitalized patients or dietary peculiarities of schizophrenics (Kety, 1959; McDonald, 1958).

Reports from different investigators are often contradictory. Yuwiler et al. (1961), as a prelude to an investigation of their own, reviewed the contradictory results reported in the literature and thought that they are probably due to "such critical factors as age, nutritional state, activity level, concomitant medical treatments, etc." In their study they examined the serum oxidase activity in schizophrenic patients, other psychiatrically ill patients, prison inmates, and hospital personnel, under a variety of conditions. Group A consisted of subjects on the research ward maintained on a controlled diet supplemented with daily multivitamin tablets: it included schizophrenics, nonschizophrenic psychiatric patients, and a group of physically healthy prisoners. Group B was also on the research ward, on regular hospital diet and no vitamin supplement; it consisted of schizophrenic and nonschizophrenic patients. Group C comprised both male and female subjects on the hospital wards on an ordinary hospital diet; it included schizophrenics, patients with neurologic and organic diseases, and hospital personnel. Yuwiler et al. interpreted their results as showing that

> under conditions of dietary and environmental control no differences were found between schizophrenic and non-schizophrenic subjects or between acute and chronic

schizophrenics. Serum oxidase activity decreased with increasing environmental and dietary control. An increase in activity was found following imipramine medication but this increase did not correlate with the degree of reactivation of the psychotic process or any behavioral alteration. There was a strong correlation between serum oxidase activity and liver damage.

Unfortunately, instead of settling the question, this study proved only how difficult it is to study adequately a substance as versatile as ascorbic acid, which has many functions. The design of the study, even though better than most, is still open to criticism. (1) The Groups A, B, and C are not strictly comparable; the only common subgroup consists of schizophrenic patients. (2) We do not know the amounts of ascorbic acid intake, or the ascorbic acid levels, for any of the groups. (3) The results can be interpreted differently (Hoffer and Osmond, 1963). In the best controlled group, A, the normal subjects had less oxidase activity than either the schizophrenic or nonschizophrenic patients, although they were on similar diets and therefore on similar ascorbic acid intakes. If we remember that both schizophrenia and stress or anxiety can decrease ascorbic acid levels, though possibly for different reasons, it is not surprising that the oxidase activity of the two subgroups of psychiatric patients was similar. Group B cannot be further assessed since no normals were compared, but the values for schizophrenic and nonschizophrenic patients were almost the same as in Group A. In Group C the oxidase activity was significantly higher in schizophrenics and organically sick patients than in hospital personnel. Thus we can conclude that normal subjects have less oxidase activity than schizophrenics, that organic and psychiatrically ill nonschizophrenic patients have as much oxidase activity as schizophrenics, and that improving the diet lowers oxidase activity in both normals and schizophrenics—findings that agree with those of many other investigators (Abood et al., 1957; Akerfeldt, 1957; Angel et al., 1957; Leach et al., 1956; Leach and Heath, 1956; Mattok, 1965).

It has been argued that the plasma level of ascorbic acid is a poor index for evaluation of the state of vitamin C nutrition (Bartley et al., 1953; Burch, 1961; Kyhos et al., 1945). The level of ascorbic acid in the whole blood has been suggested as more truly representative of the general body status, since the cell content does not fluctuate as rapidly as does the plasma content (Bartley et al., 1953). It must be remembered, however, that the ascorbic acid is not evenly distributed throughout the body tissues (see Distribution, p. 306), the concentrations in different organs vary enormously. If we are correct in supposing that ascorbic acid in the plasma is mainly transported to various tissues (including white cells), which take up the amounts necessary for optimal functioning, the amount in the plasma fluctuates widely, depending upon the demands of various organs and the dietary intake. Very little is known about the variations in the ascorbic acid content of various organs of the body during a developing hypovitaminosis. Do they follow a linear curve or are there organs that become depleted earlier than others? It has been proposed, therefore,

that the amount of administered ascorbic acid retained by the body may be a better indication of the state of depletion in the tissues (saturation test; Kyhos et al., 1945). It must be remembered, however, that the saturation test is also not a perfect index. At least two factors may affect the results: (1) the amount of ascorbic acid in the diet (hypervitaminosis or overt scurvy); and (2) the body requirements (relative hypovitaminosis). Increased need of the body in certain pathologic conditions may lead to a picture of relative hypovitaminosis in spite of the average dietary intake (Kyhos et al., 1945).

Hospitalized chronic schizophrenic patients may require up to 70 g of ascorbic acid to reach saturation, as compared to 4 g for controls (VanderKamp, 1966). This finding was confirmed by another study (Herjanic and Herjanic, 1967), where the amounts of ascorbic acid required for saturation were highest in a group of chronic hospitalized schizophrenics, and then, in decreasing order, acute schizophrenics, patients with depression, and normal controls. These studies did not, however, control the diet or report on the plasma levels of ascorbic acid. It is of interest to note the tremendous discrepancy between the recommended daily ascorbic acid intake and the amounts required for saturation in medically ill (Kyhos et al., 1945) and schizophrenic (Herjanic and Herjanic, 1967; VanderKamp, 1966) patients. Also, the amount of ascorbic acid which reportedly produced improvement in schizophrenic patients was 1 g per day or more (Lucksch, 1940; Milner, 1963). One has to wonder if these large amounts were still physiologic. The amount of ascorbic acid, 10 mg per day, necessary to prevent scurvy is well established for man (Bartley et al., 1953; Stamm et al., 1944). How much beyond this minimum is necessary for optimal functioning is still controversial. If we turn for the answer to animals who synthesize their own ascorbic acid, we see that the unstressed normal rat synthesizes ascorbic acid at the rate of 70 mg/kg of body weight per day (Sebrell and Harris, 1954), and the stressed rat increases this to 215 mg/kg per day (Conney et al., 1961). This is equivalent to the production of 4.9 to 15 g of ascorbic acid per day calculated to the 70 kg weight of an adult human. It would be interesting to see if and in what way man would benefit by being supplied with ascorbic acid in amounts comparable to that produced by the rat (Stone, 1966). It is also possible that individual needs vary greatly. Intakes of ascorbic acid that might be regarded as adequate for one person could be far below those necessary to prevent deficiency in another individual. Williams and Deason (1967) have studied the variability of individual needs in guinea pigs. They concluded that there is at least a 20-fold range in the ascorbic acid need of individual animals.

CONCLUSION

It is clear from the presented evidence that lack of ascorbic acid is not "the cause" of schizophrenia. It is probable, however, that the need for ascorbic acid in

schizophrenia, as well as in many other illnesses, is increased. The individual variation of the need for ascorbic acid may turn out to be one of the contributing factors in the development of the illness. Ascorbic acid is an important substance necessary for optimum functioning of many organs. If we desire, in the treatment of mental illness, to provide the "optimum molecular environment," especially the optimum concentration of substances normally present in the human body (Pauling, 1968), ascorbic acid should certainly be included. The amounts required for saturation, as we have seen, vary enormously and should be established on an individual basis.

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15

Should the Science-based Food Industry be Expected to Advance?

ROGER J. WILLIAMS*

In spite of improved infant feeding which has been made evident by some increase in stature, it has seemed to me that the food industries in general tend to remain static (or even be regressive) with respect to providing the public with better and better food. My apprehension with respect to this problem has increased immeasurably during the past eighteen months when, with library help of S. Rodman Thompson, I surveyed critically the current medical and scientific literature which bears directly or indirectly on the relationship of nutrition to disease.

My apprehension was further increased as a result of the following experiment, which was designed to find out how serious the lag may be in the crucial milling and baking industry, which provides the public with its "daily bread."

Weanling rats of four different strains were placed on two bread diets. Sixty-four rats, 16 of each strain, were given commercial "enriched" bread still produced essentially in accordance with the practices of about 30 years ago; matched groups

* With the technical assistance of Charles W. Bode.

were given the same bread supplemented in accordance with more up-to-date nutritional knowledge by the addition of small amounts of minerals, vitamins, and one amino acid, lysine.[1] The supplementation was limited; no attempt was made to make the bread the best possible. The actual wholesale cost of the supplement was about 70 cents per 100 pounds of flour, and the modified bread could not be distinguished in appearance from the commercial bread.

After about two weeks on these diets the rats in all the strains showed strong contrasts. The average rates of gain for the four strains were 4.8, 6.1, 6.5, and 9.5 times as great for rats on the improved bread as for those on commercial bread (Figures 15-1 to 15-4).

After 90 days on the commercial bread diet about two-thirds of the animals were dead of malnutrition and the survivors were severely stunted, whereas practically all the animals on the improved bread were alive and growing.

We were not surprised that commercial white bread appeared severely deficient, because we had previously found that weanling rats lived on the average only about 60 days on a bread diet (Williams and Pelton, 1966). We were, however, surprised that the deficiencies of bread could so easily be corrected.

From these experiments it appears that an extremely serious situation exists with respect to the manifold products made from "enriched" flour, and that similar questions arise with respect to many other foods. The seriousness of this problem cannot be underestimated. From the evidence we have gathered, poor nutrition—prenatally, and during youth and adulthood—is a probable cause of a large number of important and highly prevalent diseases (Williams, 1971). "Enriched" products, whether they be bread, bakery goods, or cereal breakfast foods, for example, are nutritionally *far below* what scientific advance should demand. Furthermore, the same disregard of nutritional value that is observed in the milling and baking industry is carried over into the production of many other foods.

One reason for this disregard of nutritional values in the milling and baking industry is evident: "Enrichment" as now practiced is nearly 30 years old and is antiquated. During the intervening years there has been instituted no nutritional advance or improvement whatever. No cognizance has been taken of the other nutrients, or of the newer knowledge about them; vitamin B6, pantothenic acid, vitamin B12, vitamin A, vitamin E, folic acid, the amino acids, and the minerals, particularly magnesium.

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[1] To each pound of "enriched" flour was added pyridoxine, 2 mg; pantothenate, 4.5 mg; cobalamine, 2.2 μg; vitamin A, 2160 μg; vitamin E, 20 mg; folic acid, 0.5 mg; L-lysine, 0.5 g; calcium, 300 mg; phosphate, 713 mg; magnesium (oxide), 150 mg; manganese (sulfate), 20 mg; copper (sulfate), 4 mg.

As the experiment progressed supplementation with vitamin D was also included. Under the conditions of our experiment this seemed to make no substantial difference. We look upon the particular formulation used as primarily illustrative. Undoubtedly, the nutritional value could have been increased further by adding more lysine, but under prevailing conditions this would have increased the cost.

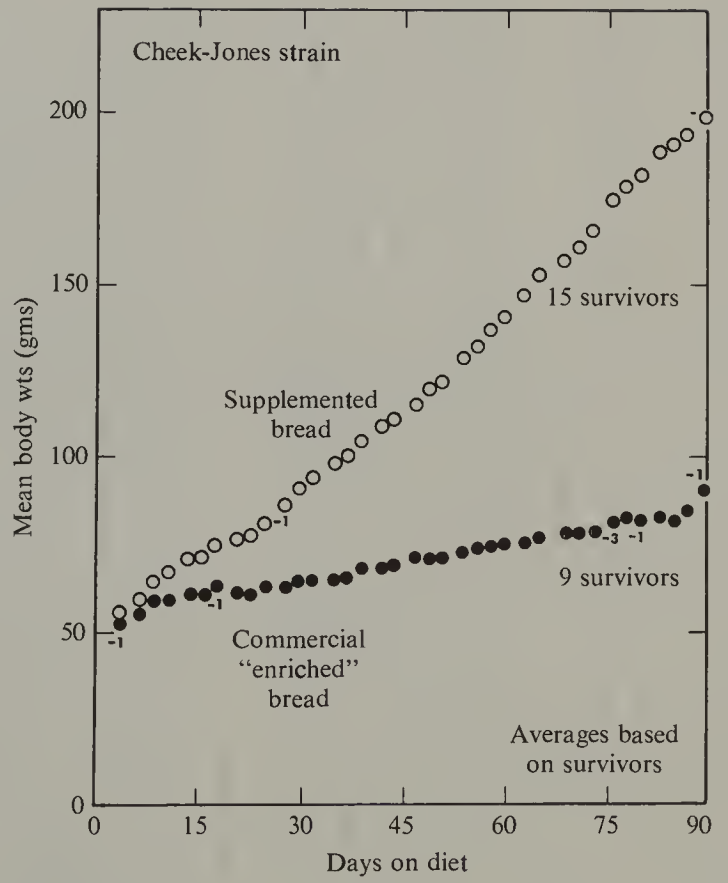


FIGURE 15-1.
Rate of gain in body weight for rats receiving commercial "enriched" bread and rats receiving supplemented bread, Cheek-Jones strain.

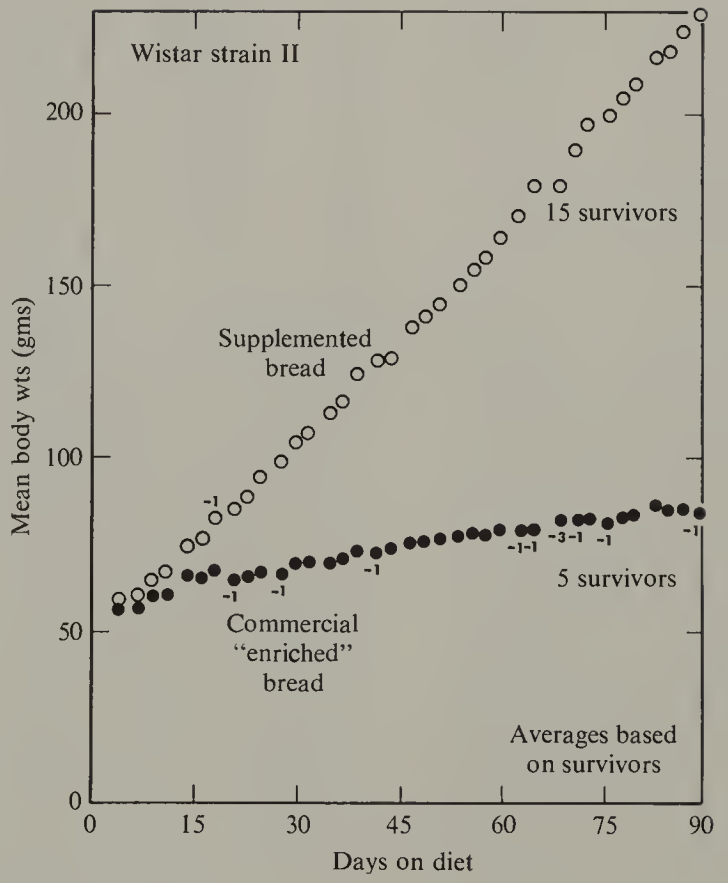


FIGURE 15-2.
Rate of gain in body weight for rats receiving commercial "enriched" bread and rats receiving supplemented bread, Wistar strain II.

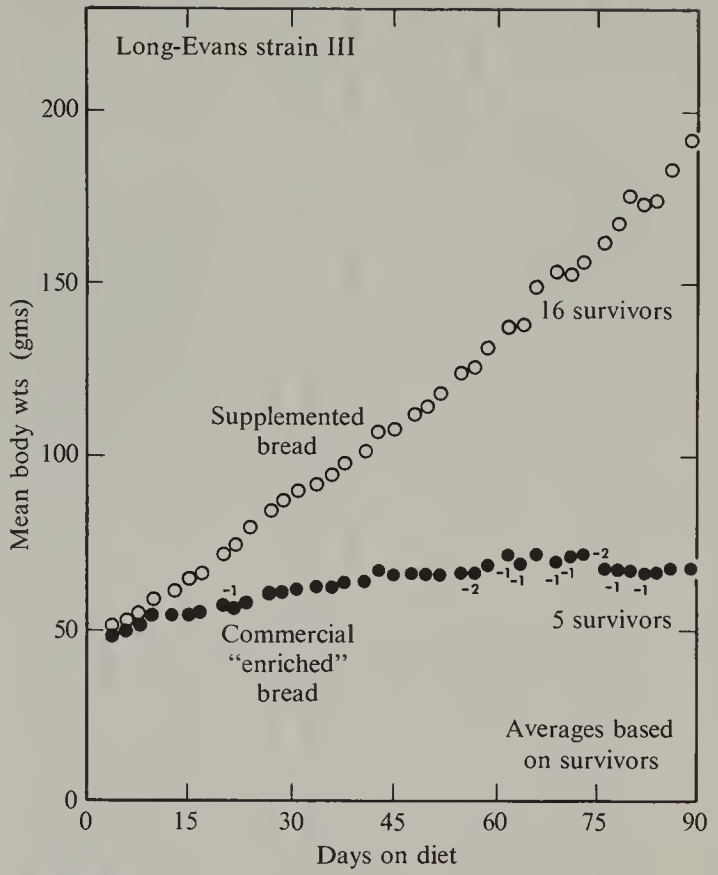


FIGURE 15-3.
Rate of gain in body weight for rats receiving commercial "enriched" bread and rats receiving supplemented bread, Long-Evans strain III.

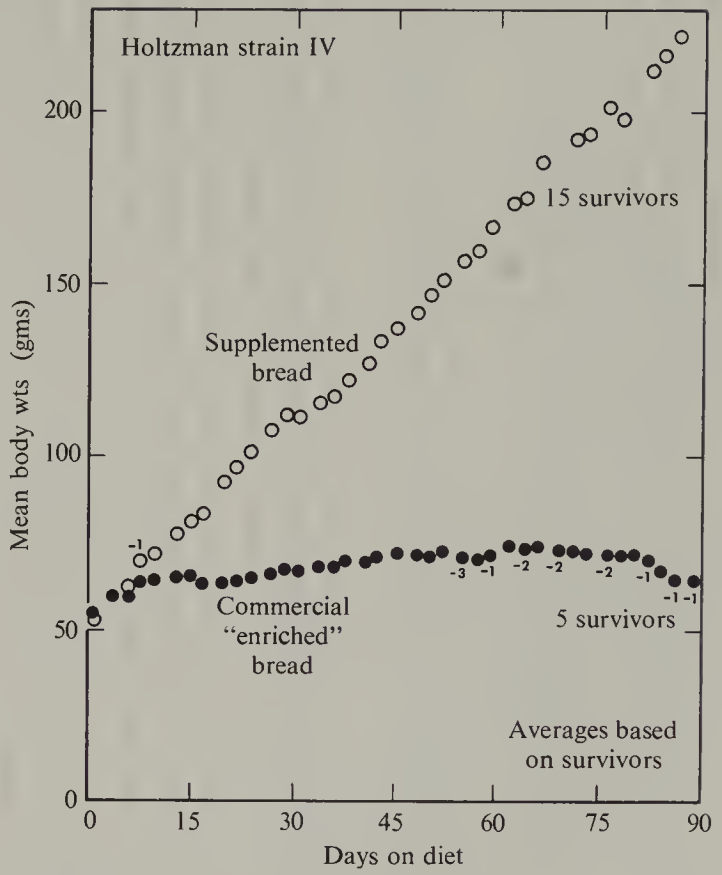


FIGURE 15-4.
Rate of gain in body weight for rats receiving commercial "enriched" bread and rats receiving supplemented bread, Holtzman strain IV.

What would we think of the communications industry if year after year and decade after decade there were no substantial advances in printing and duplicating, in radios, telephones, and television, or in voice and musical reproduction? In recent decades the textile industry has been revolutionized, the lighting industry has advanced rapidly, ultra-advancement has come in transportation, the paint industry has completely changed, computers have been developed and improved almost beyond belief. But while food technology has made some advances, there has been no comparable advance in the nutritional values.

Should there not be marked progressive improvements in the quality of our food? Is it that nutritional science is backward, or has there been a failure to apply what is scientifically known?

One defense which the baking and milling industry may cite is the fact that bread is not customarily consumed alone. Bread is eaten, for example, with butter or milk or in sandwiches. There is no doubt that the rats in our experiment would have fared better if the bread diets had been supplemented with milk, meat, or cheese. These are superior foods, as can be demonstrated by feeding them to experimental animals. The fact that bread accompanied by these good foods would produce passable results proves nothing with respect to bread. Sawdust when accompanied by good foods such as milk, meat, and cheese can yield acceptable results, yet sawdust is known to be almost without nutritional value. The proper way to test the nutritional value of bread is to test it alone, as we have done. That the commercial bread is so deficient is intolerable in light of the fact that it can so easily be vastly improved.

A more valid defense, which the baking and milling industry might put forward, is based upon the restrictive activities of the Food and Drug Administration, which tend to hold "enrichment" at a static level. Bakers and millers are not allowed by this governmental agency to modify the flour and bread as they may wish.

One concept that has influenced the flour and bread enrichment program is that ideally white bread and flour should approach whole wheat bread and flour in nutritional value. I see no reason why in an age of scientific advance the product of a modern bakery should not *far surpass* whole wheat bread. We suspect that the supplemented bread used in our experiment was much superior to whole wheat bread. In any case, it would be easy with our modern knowledge to produce a bread that is vastly superior. Why not?

If we look for more deep-seated reasons for the nutritional backwardness of the milling and baking industry, we can readily trace this high regard for the *status quo* back to the apathy, if not antagonism, exhibited by classical medical education toward nutrition. It is no secret that medical education is deficient with respect to nutrition, and that it does not foster rapid advancement in this field. Without appreciating the consequences of the action, traditional medical education has for decades been disregarding the pleas of nutrition enthusiasts (and experts). It has been saying

to them in effect, "You can say what you wish, we're not interested. Quackery is outside our province."

In an earlier publication (Williams and Deason, 1967) we called attention to the psychological attitude that has developed in the medical profession, an attitude that militates against the members being interested in or well-informed about nutrition. These comments were reprinted with approval in Britain, and the related suggestions have been the basis for favorable articles and editorials in the medical press (*Medical News*, 1967; *Medical Tribune*, International Edition, 1967).

The status is briefly this: Nutrition enthusiasts, who include some faddists and charlatans, are prone to make unwarranted generalized claims (for specific vitamins, for example) and are often masters of publicity. Rather than become embroiled with these enthusiasts and to avoid disputation or association of any kind with them, official medical education has said, in effect, "Ignore them." In ignoring them they have regretfully tended to ignore *bona fide* nutrition also.

In a time when we hear so much about environments, and the crucial need for preserving them, medical education has failed to stress the tremendous importance of the environment which we desperately need to provide continuously to the cells and tissues of our bodies. Without a suitable environment the liver cells cannot effectively perform their many tasks, which include the detoxification of many harmful substances; without a suitable environment the cells and tissues of the heart and blood vessels cannot do their crucial work effectively; without a suitable nutritional environment the brain cells cannot develop and perform, decade after decade, their manifold regulatory and other functions.

How are these environments provided, and where do the essential environmental factors come from? They come mainly from nutrition. If we furnish through our open mouths an adequate assortment of the approximately three dozen nutritional elements which are indispensable to the environments of cells, they will function well and health will result. If any link in the chain is missing or weak the environments are correspondingly unfavorable, and the cells malfunction, producing disease.

We have assembled abundant evidence from the scientific and medical literature that points strongly to the conclusion that *aside from infection, the most important potential cause of disease is the poor nutritional environment of cells and tissues.* Medical education has ignored this possibility.

It is true, of course, that some physicians are interested and well-informed about current nutritional thinking. But in general they have become well-informed by special study and research which has been done *in spite* of rather than *because of* their medical training. Physicians have told me that many of their number will heartily welcome what is written here, because they know that nutrition has been sadly neglected.

The failure of medical science to take nutrition seriously is the basic cause of the

backwardness of the baking and milling industry and the ineptness of the Food and Drug Administration with respect to nutrition. This failure has had far-reaching effects. Although individual medical scientists may have interests along this line, it can be said that there is no organization or institute anywhere in the world which even purports to study any disease (atherosclerosis, arthritis, mental disease, cancer, or whatever) *thoroughly* from the standpoint of the role of nutrition and nutritional environments.

Two broad and crucially important facts which underlie the whole problem of noninfective and infective disease have largely escaped medical science because of its lack of attention to the science of nutrition.

The first fact is that living cells, wherever they occur in nature, are *always subject to limitations* in their nutritional environments.

Single cells rarely if ever encounter culture media that are optimal—not subject to improvement in any way. The cells in our bodies are not automatically furnished with a perfect environment from which nothing is lacking or is in short supply. The kind of environment these cells are furnished depends upon what we eat. Limiting nutritional factors are the rule, not the exception. Many people eat so carelessly that their liver cells, for example, never, over the years, get a really "square meal." As a result, liver cells (and other cells in the body) limp along as best they can in a poor environment, just as does corn or cotton growing in a poorly fertilized or sparsely watered field. "Limping along" in an inadequate environment is certainly prevalent in the world of nature. It is just as common in the world that is inhabited by our body cells. When the limp becomes severe, overt disease results. Fully adequate nutrition is a continuing question mark for every one of us. This, medical education has not taught.

The second comprehensive fact which encompasses all attempts to apply nutritional knowledge and which has been overlooked in medical education is this: *nutritional factors always work as a team.*

In testing the efficacy of a drug we simply administer the drug. If it brings the desired result, the answer is "yes," if not, the answer is "no." In testing the efficacy of a mineral, amino acid, or vitamin, however, the principle of *teamwork* needs desperately to be recognized. If it is not, as has usually been the case, the results are erroneous. No nutritional factor can do anything *by itself.* It is like a nut, bolt, spindle, or gear in a complicated machine; unless the rest of the machine is there (which biologically may *sometimes* be the case), it is completely useless.

This important principle has been largely overlooked because medical education has not seriously explored nutrition. Let us consider the following broad question: Is *n* (one of the essential nutrients) effective in preventing heart disease, arthritis, obesity, alchoholism, mental disease, or cancer? The obvious answer to the question appears to be "no," since there is no known nutrient whose simple administration will bring about these results. But the testing on which this obvious and far-reaching

answer is based has been seriously at fault. Indispensible teamwork has been ignored; the experiments have been designed to answer the wrong questions, and the conclusions are worse than useless.

The scientific question whether or not *n* can prevent heart disease, arthritis, obesity, alcoholism, mental disease, or cancer remains an open one until *n* has been tested under conditions such that all other parts of the metabolic machinery can be functional. *Teamwork must be involved.* If *n* is tested under conditions that make it impossible for it to function, of course the results will be negative.

Especially in the light of the extensive evidence we have gathered, there is a strong presumption that careful scientific handling of the teamwork in the nutritional environment of our body cells will not only prevent the onset of numerous diseases but will also prevent the production of malformed and mentally retarded babies. Medical science needs to explore these possibilities extensively and intensively. In view of the present public mood, the importance of cellular environments cannot be denied or brushed aside.

This is a matter which should be of maximum public concern and there should be many public servants engaged in exploring these cellular environments and what can be done to improve them. On the basis of present knowledge it appears certain that health can be vastly improved in every direction if the quality of our food is improved.

The baking and milling industry is crucially important in this regard because products made from "enriched" flour are consumed in enormous quantities, especially by those with lower incomes. Breads, crackers, cakes, pastries, and other "enriched" and processed foods are consumed in quantity by children whose body and brain cells as a consequence continuously limp along in a poor environment. Current "enrichment" disregards the teamwork that is essential, and physical and mental ills arise as a consequence. If the nutritional value of flour, bread, and related products can be brought up to a respectable level by any means whatever, it will be a tremendous forward step.

I am not the first American scientist to entertain what some may regard as an extravagantly optimistic view of the possibilities residing in the field of nutrition. Henry C. Sherman of Columbia in writing the book *The Nutritional Improvement of Life* revealed a belief that vast benefits can be derived from better nutrition. From correspondence with Elmer V. McCollum I know that he too held what may be regarded as extreme views. I am confident that my brother, R. R. Williams, who had much to do with the original enrichment program, would, if he were living, heartily applaud what I have to say.

Perhaps the clearest enunciation has come from Frank G. Boudreau, M.D., formerly a member of the Food and Nutrition Board. He wrote (1959)

> If all we know about nutrition were applied to modern society, the result would be an enormous improvement in public health, at least equal to that which resulted when

the germ theory of infectious disease was made the basis of public health and medical work.

He was calling for a revolution in medicine as important as that following the recognition of infectious disease! I echo this call, and I believe on the basis of extensive evidence hitherto not available, that there is vast reason for hope.

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SECTION II

CLINICAL DIAGNOSIS

16

The Hoffer-Osmond Diagnostic Test

H. KELM

During the past two decades experimental and clinical evidence has shown that perceptual disturbances are common in schizophrenia. Autobiographies of recovered schizophrenics clearly indicate that they lived in an unstable or constantly shifting experiential world. Written accounts of hundreds of normal subjects who had taken various psychotomimetic substances also show that they experienced numerous perceptual changes. Recovered schizophrenic patients who read these accounts indicated that these were the same type of perceptual disturbances that they had experienced, and those who had been given LSD reported that the drug created an unstable world that was similar in many ways to the one in which they lived when they were ill (Hoffer, 1966a; Hoffer and Osmond, 1961a).

The realization that there was a great need in psychiatry for simple and reliable tests to diagnose and monitor treatment prompted A. Hoffer and H. Osmond to construct the Hoffer–Osmond Diagnostic Test, known as HOD (Hoffer and Osmond, 1961a). The test consists of 145 True–False questions, read and answered by the patient, which are designed to measure visual, auditory, olfactory, touch, taste, and

time perception, as well as thought and mood disturbances (Hoffer and Osmond, 1961a, 1962, 1966a, 1966b; Kelm, 1967; Kelm, Hoffer, and Osmond, 1967; Seidler, 1969). A complete description of the test is provided in the HOD kit.[1]

Underlying this work was the assumption, now supported by substantial experimental evidence, that there is a genetic predisposition in schizophrenics which under certain conditions leads to errors in metabolism, resulting in the formation of chemicals that may interfere with the functions of the central nervous system that are responsible for maintaining perceptual stability (Hoffer, 1966a, 1969a; Hoffer and Osmond, 1962a, 1963, 1966a, 1966b; Huxley et al., 1964; Kelm, 1967; Kelm, Hoffer, and Osmond, 1967; Seidler, 1969). There is also some evidence that suggests these functions of the nervous system are affected by diet (Cott, 1967; Green, 1969; Green, 1970; Pauling, 1968).

Two terms have recently been introduced to refer to these perceptual changes: *metabolic dysperception*, and *subclinical pellagra.* Kowalson (1967) introduced the term metabolic dysperception, which refers to "people who suffer from varying degrees of abnormal perception, with corresponding changes in thought, mood, and behavior, who respond favorably to megavitamin B3 and allied therapy, if treated before irreversible damage has developed." Subclinical pellagra, which results from a deficiency of or an increased demand for niacin, is defined as a "deficiency syndrome characterized by the presence of perceptual changes, affecting any or all of the five senses, associated with neurasthenia" (Green, 1970). The HOD, and related tests, can measure the degree of perceptual abnormality and changes in thought and mood.

DIAGNOSIS

Although the test was originally designed to help identify the schizophrenic patient, assist in monitoring treatment, and establish a rough index of prognosis, many studies have shown that it is also capable of identifying schizophrenics and assisting in the early detection of perceptual, thought, and mood changes, thus reducing the time between the onset of the disorder and its diagnosis and subsequent treatment (Paolucci, 1969; Seidler, 1969; Chiossone et al., 1969; Hawkins, 1968; Hoffer, 1965, 1969; Hoffer and Kelm, 1970; Hoffer and Osmond, 1961a, 1961b, 1962a, 1966a, 1966b; Kelm, Chambers, and Hall, 1966; Kelm, Hoffer, and Osmond, 1967; Kelm, Callbeck, and Hoffer, 1967; Irvine, 1965; Marjerrison et al., unpub. data).

The HOD is being used increasingly as a rough screening instrument in a variety of disciplines, such as general medicine, school counselling, and social work. A

[1] Available from Modern Press, Saskatoon, Saskatchewan.

general practitioner, for example, can administer it to patients who have a history of mental illness, unaccountable symptoms, or unusual attitudes and behavior, as well as to family members of patients with high HOD scores, those consuming large quantities of alcohol, delinquents, and those who have difficulty adapting to physical or psychological stress (Kowalson, 1967). Another physician has used the test with many elementary grade students who are underachieving and have various physical complaints, such as sore throat or eyes, headaches, stomach or leg aches, with no clear physical basis for their ailments (Green, 1969; Green, 1970). He reports that most of those who score high on the test suffer from fatigue and malaise. Invariably they have a poor diet and the physical examination is usually normal. A few weeks after being on a high protein–low carbohydrate diet with megavitamins their perceptual world begins to stabilize, other symptoms disappear, and their school performance improves. Other physicians are using the HOD and find that it is a valuable aid in their medical practice.

Many adolescents are diagnosed and treated for a variety of illnesses which may be approached more effectively by measuring their perceptual world. Often the test reveals disturbances which can be stabilized, thus relieving many individuals of one of the major sources of their problems (Hoffer and Osmond, 1966b; Kehoe, 1969; Paolucci, 1969). A school counsellor (Paolucci, 1969) reports that perceptual problems in adolescents may interfere with their physical and emotional performance, making it difficult for them to cope with reality. He suggests that the HOD will assist in the early detection of such problems. A social worker (Kehoe, 1969, p. 8) suggests that the HOD "may prove a boon to developing adolescent diagnostic profiles as well as profiles for the pregnant-out-of-wedlock adolescent."

Overlapping Diagnostic Categories

As with other diagnostic tests, concern has been expressed over the considerable overlap of the distributions of HOD scores for schizophrenic and nonschizophrenic patients (Buros, 1965). Approximately 70 percent of adult schizophrenics and 30 percent of nonschizophrenics score above the established cut-off points. Two findings may be mentioned regarding this problem. First, a study was carried out in which the HOD was given to patients on admission to an intensive psychiatric treatment hospital and again before they were discharged. The HOD scores were then correlated with the initial clinical diagnosis made soon after admission, and the final clinical diagnosis which was made on each patient when more information was accumulated. The results showed that the agreement of the HOD with the final clinical diagnosis was higher than the agreement between the clinical diagnosis made on admission and the final diagnosis (Chiossone et al., 1969). The authors con-

cluded that "the HOD test proved to be an efficient and reliable tool for establishing the diagnosis of schizophrenia, and it proved to be more reliable than the initial psychiatric diagnosis" (Chiossone et al., 1969, p. 241; see also Kelm, Hoffer, and Hall, 1967). It has also been reported that patients diagnosed as neurotic or with personality disorders, for example, who have high HOD scores and are treated on the basis of these high scores, frequently improve rapidly (Hoffer, 1966a; Ward, 1967).

Secondly, another study examined the diagnostic discriminative power of the HOD in a sample of psychiatric patients whose diagnoses had been established by one psychiatrist. The usual sizeable overlap in scores between schizophrenic and non-schizophrenic patients was evident. The investigators then asked another psychiatrist to make an independent diagnosis of each patient. Only those patients on which both experts agreed on the diagnosis were retained. An analysis of the HOD scores on this sample showed that the overlap of scores between schizophrenic and non-schizophrenic patients was significantly reduced (Marjerrison et al., unpub. data).

Other Psychotic and Toxic States

It has been reported that toxic and organic psychotics, senile confusional patients, and LSD users obtain HOD scores which are similar to those of schizophrenic patients (Hoffer and Osmond, 1961a; Kelm, Hoffer, and Osmond, 1967; Seidler, 1969). The scores of toxic psychotics tend to drop quickly when the toxin is removed. The HOD scores of recovering schizophrenics do not drop as quickly, therefore the rate of decrease in scores may be used to differentiate toxic psychotics (for example, alcoholics) from schizophrenic patients. When the scores begin to increase after admission to a hospital, one of the consequences of alcoholism, usually delirium tremens, can be suspected.

Chronic schizophrenic patients tend to score higher than acute cases. In one sample it was found that schizophrenic patients who had been ill for more than ten years obtained Total Scores (TS) 50 percent higher than acute patients (Hoffer and Osmond, 1961a).

HOD users are cautioned against giving the test when a patient is receiving ECT (Hoffer, 1966a) because results are usually erratic and rather meaningless. It is recommended that HOD testing be resumed approximately one week after the last ECT session.

In 1963 a study carried out on female patients in a psychiatric institution was reported to have shown that the HOD in its then present form could not discriminate between schizophrenic and nonschizophrenic patients (Stewart and Mahood, 1963). A re-analysis of the data of this investigation revealed that the test could differentiate

schizophrenic from neurotic and character-disorder patients, but could not discriminate schizophrenic from other psychotic patients (Kelm, Grunberg, and Hall, 1965). An attempt was made to overcome this deficiency by introducing a new score (Ratio Score or RS) that seemed to be particularly effective in differentiating schizophrenics from other psychotic patients, excluding toxic and organic cases (Kelm, Grunberg, and Hall, 1965; Kelm and Hoffer, 1965).

Retrospective and Prospective Method

While the HOD was being constructed it was found that the only way a volunteer subject could adequately complete the test when he was given LSD was in retrospect (Hoffer and Osmond, 1961a). That is, he would answer the questions after the LSD experience subsided and in terms of what he experienced during its height. This retrospective technique has since been found to be particularly useful when a clinician sees a patient for the first time and has little or no information about him. The patient is first asked to do the test to indicate his *present* experiential world. When this is completed he is asked to do the test as he was during the *height of his illness.* This technique enables the clinician to determine where the patient is in his illness, whether he is getting worse, improving, or staying the same. It may also provide information regarding the risk of suicide or homicide and thus alert the clinician to such dangers (Osmond, personal commun.).

An extension of this technique is the prospective method, in which the patient, after doing the HOD to indicate his present condition, is asked to do the test as the *best he has ever been* or *the best he can imagine or hope to be.* This method may indicate whether the patient was ever perceptually stable and where he is now in relation to his best condition. Such information may also be used to encourage patients to start or maintain treatment when they feel that they do not need any treatment (Osmond, personal commun.).

MONITOR TREATMENT

A substantial body of evidence indicates that the HOD is capable of measuring a patient's response to treatment (Chiossone et al., 1969; Cott, 1967; Hawkins, 1968; Hoffer, 1966a, 1966c, 1969b; Hoffer and Osmond, 1961a; Hoffer and Osmond, 1966b; Kelm, Hoffer, and Osmond, 1967; Seidler, 1969; Sugerman and Williams, 1965; Tobin, 1967; Ward, 1967). Since high HOD scores are pathological and low scores indicate an absence of perceptual, thought, and affective pathological phenomena, the *rate* of decrease in the scores can be used as a measure of the rate of improvement

(Kelm, Hoffer, and Osmond, 1967). If the test is given at regular intervals while the patient is being treated, the test scores may be plotted on a graph. At a glance this graph will indicate whether the patient is improving, remaining stationary, or getting worse.

The test is also used to guide therapy. Assuming that the best therapy is the one which reduces perceptual, thought, and mood disturbances most quickly, the results of the HOD have been used to increase or decrease medication or change to different therapies (Hoffer, 1966a; Kelm, Hoffer, and Osmond, 1967; Seidler, 1969). For example, it has been reported that HOD scores may increase if the dose of a tranquilizer is too high (Hoffer, 1966a). If the TS and Perceptual Score (PerS) are decreasing much faster than the Depression Score (DS), the use of a suitable antidepressant drug may be indicated (Osmond, personal commun.).

It has also been reported that the HOD may be effective in detecting a relapse, sometimes even before the patient or physician notices it (Hoffer and Osmond, 1966b; Kelm, Hoffer, and Osmond, 1967; Seidler, 1969). Frequently, a patient who is receiving treatment will forget to take his medication or feel that he no longer needs it. The test has been found very useful in detecting an early change in his condition, especially if he has been improving while taking medication.

Some clinicians discuss each HOD protocol with their patients and find that it encourages patients and accelerates their rate of recovery (Hoffer, 1966a; Kelm, Hoffer, and Osmond, 1967; Ward, 1967). Sometimes they are discouraged because of what they think is a lack of progress even though the HOD may be indicating steady improvement. Knowledge of improvement on the test can help the patient to continue treatment and reinforce hope and thereby aid recovery. Another practice that is being developed is to have follow-up personnel administer the HOD to a patient at regular intervals, or teach the individual to self-administer a simplified version (Hoffer, 1966a; Kelm, Hoffer, and Osmond, 1967; Seidler, 1969). If the scores begin to increase this may indicate that the disease is returning and that the patient's doctor should be consulted.

PROGNOSIS

Early in the development of the HOD it was found that it could be used to establish prognosis. In 1961 Hoffer and Osmond reported that patients who obtained HOD scores *below* certain cut-off points immediately before they were discharged from hospital were less likely to require readmission within a six month period than patients with discharge scores *above* these cut-off points (Hoffer and Osmond, 1961a). In another study they found that when the TS at the time of discharge was 40 or less, one in ten patients had to be readmitted within six months of discharge. When TS was 41 or more, 12 in 21 required readmission within six months. They concluded

that "high HOD scores in patients awaiting discharge suggest that they are not as well as patients with low scores and so less likely to stay out of hospital" (Hoffer and Osmond, 1962b, p. 841, 1966a; Kelm, Hoffer, and Osmond, 1967).

In psychiatry today there is a great need for improved measuring devices or methods for determining when a patient is ready to be discharged from the hospital. The HOD data suggest that this test can assist the clinician in making decisions regarding discharge. As one reviewer notes, "So many of the senseless crimes that are paralyzing our cities with fear are committed by people who have been discharged from mental hospitals—ostensibly ready for life in society. The HOD test can determine if a patient is indeed ready for discharge. . ." (Seidler, 1969, p. 118).

HOD AND OTHER TESTS

Malvaria

In 1961 Hoffer and Osmond and their colleagues introduced a chemical test (referred to as a test for malvaria) which they found useful for making psychiatric diagnosis, monitoring treatment, and indicating prognosis, and which was significantly correlated with the HOD (Hoffer, 1965, 1966b, 1966c, 1966d, 1967; Hoffer and Mahon, 1961; Hoffer and Osmond, 1961b, 1962a, 1963, 1966a, 1966b; Irvine, 1961, 1963, 1965; Helm, Hoffer, and Osmond, 1967). It was found that malvariacs obtained higher HOD scores than nonmalvarian patients. When a patient with malvaria recovered from his or her illness, the chemical disappeared and the HOD scores decreased. When both tests were used together prognosis could be more accurately established. One study showed that the higher the HOD scores obtained by a patient when he is admitted to a hospital, the longer he will have to be hospitalized (Kelm, Hall, and Hoffer, 1968). The best relationship with the length of hospitalization was obtained, however, when the test for malvaria and the HOD were used together. The investigators found that malvarians with considerable perceptual disturbances required a significantly longer period of treatment in hospital than nonmalvarians with less perceptual instability.

It is reported that the test for malvaria determines which illness is present, and the HOD may indicate which patients require hospitalization (Hoffer, 1966b). Hoffer and Osmond have suggested that their chemical test may represent "end-products of toxins which impede the working of parts of the brain; perhaps those which govern stability of perception" (Hoffer and Osmond, 1962a, p. 645). Continued research on both tests indicates that the biochemical abnormality may precede the perceptual, thought, and mood disturbances (Hoffer, 1965). Hopefully, such tests may be used for the early detection of disorders, thus permitting appropriate treatment before the disease fully manifests itself.

Figural After-Effect (FAE)

The HOD was recently compared with a refined laboratory measure of perceptual distortion—the visual figural after-effect (Kelm and Hall, 1967). In the visual FAE a figure appears distorted as a result of the subject's previous fixation on another figure. The exact magnitude of this distortion is accurately measured and has been assumed to reflect metabolic and cortical events, and found to be related to psychiatric diagnoses (Kelm, 1962; Kelm, 1968; Prysiazniuk and Kelm, 1963, Wertheimer, 1954; Wertheimer and Jackson, 1957; Wertheimer et al., 1955). The FAE was shown to be significantly correlated with both the HOD (Kelm and Hall, 1947) and Hoffer and Osmond's test for malvaria (Kelm et al., unpub. data). The data suggest that the FAE, HOD, and the test for malvaria may each be measuring aspects of the same disease.

Inpatient Multidimensional Psychiatric Scale (IMPS)

In a sample of first-admission patients to a mental hospital it was found that the HOD was significantly correlated with the IMPS. The authors noted that the relationship between these two tests had "particular clinical validity implications when it is recalled that the HOD is a self-rating done by the patient, while the IMPS is a rating completed by the psychiatrist after interview" (Marjerrison et al., unpub. data).

Minnesota Multiphasic Personality Inventory (MMPI)

Very little work has been done using the MMPI and HOD together. In one study both tests were administered to a group of Canadian Indian and Causasian high school students (Milner et al., unpub. data). As might be expected, the HOD correlated significantly with the Sc scale of the MMPI. When each test was correlated with various criteria, such as school achievement and behavioral problems in the school, the HOD showed the more significant and consistent relationships.

SCHOOL ACHIEVEMENT AND AGE

A number of studies have shown that there is a relationship between HOD scores and achievement in school (Green, 1969, 1970; Hoffer, unpub. data; Hoffer and Osmond, 1966b; Kelm, Hoffer, and Osmond, 1967; Milner et al., unpub. data). A sample of

15-year-old students in an urban center in Saskatchewan showed that those in grade 8 obtained a mean TS of 52; grade 9, 40; grade 10, 33; and grade 11, 25 (Hoffer, unpub. data; Kelm, Hoffer, and Osmond, 1967). In another investigation students 15 and 16 years of age who were in grades 9, 10, or 11 had a median TS of 31 compared with students of the same age in grades 8 or less, who had a median TS of 102 (Milner et al., unpub. data). TS and I.Q. were not significantly correlated in this study.

A general practitioner has reported that many students referred to him who are underachieving in school have unstable perceptual worlds (Green, 1969; Green, 1970). The HOD test and related inquiries permit him to detect these cases and take remedial action which often involves an improved diet and megavitamin intake. He reports that these children usually feel better within a few weeks and their school performance improves.

In another study, adolescents referred by teachers to the school psychologist or nurse with various behavioral problems were found to have a median TS of 94 compared with a TS of 27 in an equivalent group without such problems (Milner et al., unpub. data). A school counsellor has found the HOD useful for the early detection of perceptual problems in adolescents, thus permitting him to make appropriate referrals which can lead to early treatment and the possible prevention of progressive problems for the student (Paolucci, 1969). In a study conducted by Hoffer (in prep.), all the results of which have not yet been completely analyzed, the data indicate that the HOD could detect potential school-achievement and psychiatric problems *before* they occurred. All students in grade 9 in a number of schools were given the HOD at the beginning of the school year. Later in the same year, without knowledge of the test results, a number of students were referred by their physicians for psychiatric attention, and another group failed grade 9 at the end of the year. An examination of the HOD test given at the beginning of the year showed that a significantly higher proportion of the students in these two groups scored above established cut-off scores than all the other students who were not referred for psychiatric help and who passed grade 9.

Soon after the HOD test was published it was found that the scores of normal teenagers decreased as a function of age (Hoffer, 1963, and unpub. data; Hoffer and Osmond, 1962a, 1966a, 1966b; Kelm, Hoffer, and Osmond, 1967; Milner et al., unpub. data). Relatively high scores were obtained by 13-year-olds, but decreased and seemed to level out at approximately 18 to 19 years of age. These studies suggest that if a student's perceptual world is considerably more unstable than the average for his age group, then he seems to experience problems in trying to cope with his world. This may manifest itself in reduced school performance and various behavioral problems in the school and home.

A study of teenage psychiatric patients showed that they also scored significantly higher on the HOD than adult psychiatric patients (Kelm and Hoffer, 1967). It was found that higher cut-off points must be used for patients 13 to 17 years of age than

for older patients (Kelm, Hoffer, and Osmond, 1967). The HOD is usually not given to subjects under the age of 13.

ANTISOCIAL BEHAVIOR

Mounting HOD test data are suggesting increasingly that perceptual, thought, and mood disturbances may be involved in many cases of antisocial behavior. In one study several hundred delinquent boys were given the HOD and approximately 35 percent seemed to have relatively unstable perceptual worlds (Seidler, 1969). Many individuals who had committed various crimes and were referred by the courts to a psychiatrist had elevated HOD scores and showed marked improvement when treated with the megavitamins.

How many crimes are committed by individuals whose unstable perceptual experiences are involved in episodes of uncontrolled behavior? What about our prison systems? Are our prisoners screened for these disturbances, treated and followed-up? Are they released from prison when their perceptual worlds are still unstable?

A test which measures the degree of perceptual distortion and is correlated with the HOD and malvarian test was given to a group of prisoners in a penal institution. Without knowledge of the test results, the staff familiar with each prisoner was asked to make an evaluation of each inmate in terms of the possibility of successful rehabilitation. The data showed that those prisoners given a poor prognosis for rehabilitation had significantly more perceptual distortion than those with a good or doubtful prognosis (Kelm, Pringle, and Njaa, unpub. data). The former group displayed a characteristic type of perceptual distortion found in schizophrenic patients and in alcoholics while they are under the influence of LSD (Kelm, Jensen, and Ramsay, 1963).

Some police officers are beginning to use the HOD with offenders whom they suspect to be mentally ill. For example, one young man who had been in and out of jail and mental hospitals for petty thievery and attempted suicide was given the HOD by a policeman and consequently referred for psychiatric treatment. His condition was treated and he is now leading a productive life in society (Seidler, 1969).

Data also suggest that the HOD may be used to help determine the risk of suicide and homicide, not only in patients receiving psychiatric treatment, but also among students in high school and college, where the suicide rate is particularly high (Hoffer and Osmond, 1968; Kelm, Hoffer, and Osmond; 1967; Osmond and Hoffer, 1967; Seidler, 1969). In these cases the DS and its relationship to other parts of the test is very important. Clinical impressions suggest that various combinations of test items may indicate the danger of suicide and homicide (Osmond, personal commun.).

More research is required to work out possible test patterns that may be useful in such situations.

PSYCHOACTIVE CHEMICALS

Since knowledge of the effects of various psychoactive substances was used to help derive many of the HOD questions, it is not surprising that the test can be used to measure the effects of these chemicals. It has been shown that the HOD protocols of normal subjects who have taken LSD are similar to those of severely disturbed schizophrenic patients (Hoffer and Osmond, 1961a; Hoffer and Osmond, 1966a). It has been suggested that if the dose of LSD is adjusted appropriately, a state similar to early schizophrenia can be induced (Hoffer and Osmond, 1961a). Naturalism Inc. of Chicago has administered the HOD to over 1,000 drug users and found that marijuana smokers had average TS's of 50 to 60, LSD users 70 to 90, and amphetamine users 150 (Peters, 1970). They have suggested that, starting at a TS of approximately 70, most of their subjects reported "being an outsider." They called this the "breakoff point" (Peters, 1970). Experience indicates that the HOD may be extremely useful in detecting individuals who might be particularly susceptible to a "bad trip" should they take a psychotomimetic substance. The test has also been used to monitor the effect of trifluoperazine and trifluperidol, and to indicate when the dose of a tranquilizer may be too high (Hoffer, 1966a; Sugerman and Williams, 1965).

Since we live in a society which uses and depends upon such a variety of pharmacological substances, many of which produce considerable perceptual, thought, and mood changes, tests like the HOD given before and while these chemicals are being taken may help to better regulate their use and reduce the risk of "accidents" (Osmond, personal commun.).

MENSTRUAL CYCLE

A considerable fund of evidence has established that the menstrual cycle is associated with a variety of behavioral problems. It has been shown that a few days before menstruation and during menstruation there are increases in psychiatric illnesses and their severity, increased accident rates, a rise in general hospital admissions, more alcoholic bouts, suicide attempts and crime, a higher failure rate in the writing of examinations, and so forth (Dalton, 1964; Dalton, 1968; Janowsky et al., 1969). A study on the HOD test on first-year university students showed that TS, PerS, and DS were significantly higher on the first day of menstruation than on the day immediately after menstruation ceased (Fischer et al., 1969). Another study with high school students and nurses showed that TS, PerS, and DS were highest just before

and at the beginning of menstruation (Kelm, Pringle, and Njaa, unpub. data). It is recommended that the menstrual cycle be considered when interpreting the HOD protocols of female subjects.

EXPANDING USES AND ADVANTAGES

It has been pointed out that the HOD may save time in taking a patients history and provide information that might not be otherwise obtained (Green, 1970; Kelm, Hoffer, and Osmond, 1967; Ward, 1967; Whieldon, 1966). A social worker has reported that the test has virtually eliminated a waiting list in his agency because of the time saved in quickly detecting cases that require referral (Kehoe, 1969).

Clinicians who have used the HOD point out that important perceptual disturbances which may not be detected in the interview are frequently discovered by the test. Some patients may be unaware that they have perceptual disturbances, or have learned to cope with their unstable perceptual world. They may think these phenomena are quite unimportant and so do not mention them in an interview. When the test results are later discussed with the patients, they will often admit to disturbances and will freely talk about them (Green, 1970; Hoffer and Osmond, 1966a; Kehoe, 1969; Kelm, Hoffer, and Osmond, 1967).

An experienced user of the test reports that it seemed to increase confidence in his patients and staff members that the illness was being understood, measured, and monitored objectively (Hawkins, 1968). The HOD has also been recommended for use in training physicians, psychiatrists, psychologists, social workers, nurses, and hospital attendants. After they have become familiar with the patient's condition, they may do the test for the patient and compare it with the patient's own test. Much may be learned from this simple exercise (Osmond, personal commun.). Many clinicians who have patients with high HOD scores ask the members of the patients' family and even relatives also to take the test. This practice has led to the early detection and treatment of disorders and may thus prevent many serious behavioral problems (Green, 1970; Hoffer and Osmond, 1966b; Kowalson, 1967; Osmond, personal commun.). Siblings and parents of a patient have also been asked to do the test for the patient and then compare their understanding of the patient with the patient's HOD. This may give the family more insight into the patient's condition or provide an "empathy index," and show that the patient is suffering from a "real" illness (Osmond, personal commun.).

Preliminary experience indicates that results of HOD testing seem to be reasonably well received by judges, lawyers, and juries (Osmond, personal commun.). Evidence showing that the accused was having considerable perceptual, thought, and mood disturbances, and that his overt behavior was dependent upon these events, can provide important data worthy of consideration by the courts.

FAKING OR DENIAL

There is no doubt that a patient can falsify the test results or deny the existence of experiences which the test attempts to probe. Rather than complicate the test with so-called "validity scales" with their doubtful effectiveness, the authors of the test stress the importance of establishing a trustworthy patient-doctor relationship before the test is administered. One experienced user of the test gives the following instructions to his patients:

> This is a very broad test covering all the possibilities from quite sick to only minor nervousness. There are some pretty wild questions on the test—don't let that bother you. If you have a particular pattern on the test, there is something that can be done about it easily. (Ward, 1967, p. 141).

He reports that this approach has produced fewer denials and has reduced the number of patients who are offended by the test.

To guard against denial by some patients, clinicians also compare the HOD test results with the clinical state of their patients. When there is a marked discrepancy, the possibility of denial may be raised (Kelm, Hoffer, and Osmond, 1967). When a patient answers all the items *false*, then the record is quite obviously invalid.

Medicine has many tests of which the results depend heavily upon the cooperation of the patient. Examinations of all orifices, the chest and the abdomen, and neurological tests, to name a few, use the patient's subjective report. As one test user states: "Questions regarding perceptual changes are no more leading than questions about bowel habits or weight loss" (Green, 1970, p. 71). So in medicine as in HOD testing we must depend upon the patient to indicate whether it hurts a little, much, not at all, or whether he is experiencing certain perceptual, thought, and mood changes. Unless it has been proved otherwise, we may assume that we have a reasonably accurate picture of the patient's experiential world. When the HOD is used in court cases, in prisons, or in testing large groups where the level of cooperation and rapport may be marginal or nonexistent, then the problem of faking will be more important. As the above review indicates, HOD testing of thousands of subjects in a variety of situations has yielded encouragingly valid and useful results. In the final analysis, however, any human being can fool another, for the only way we can know another person's experience is through his telling us.

SUMMARY AND CONCLUSIONS

As the above review has shown, the HOD can be used to make psychiatric diagnosis, monitor and help guide therapy, and establish prognosis. It is being used by an increasing number of professionals, including general practitioners, social workers,

school psychologists and counsellors. The test may prove to be very useful for detecting those individuals who might have a "bad trip" should they take a psychotomimetic substance. In view of the widespread use in our society of various chemicals which affect perceptual, thought, and affective processes, the HOD may help to better regulate the use of such substances and minimize the risk of physical and psychological damage. The HOD and related tests may also prove to be useful in helping to establish "safe" levels of perceptual stability required in a variety of psychomotor tasks, such as driving an automobile or flying an aircraft (Osmond, personal commun.).

One of the most important conclusions suggested by the above review is the indication that the HOD facilitates the *early detection* of behavioral problems. The relationships between HOD scores and various forms of antisocial behavior, and the indication that the test can detect underachievement and other problems in school *before* they occur, suggest areas of investigation which must be pursued with greater vigor.

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17

The Experiential World Inventory in Clinical Psychiatry and Psychopharmacology

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INTRODUCTION

In diagnosing patients as psychotics or schizophrenics, psychiatrists rely on major disturbances such as frank delusions, hallucinations, bizarre thoughts, and peculiar behavior. They often overlook the minor symptoms of perceptual distortions with all their richness, variety, and multiplicity.

Among these disturbances are an infinite variety of sensory illusions which change the appearance of objects, people, and space. Changes also occur in modes of perception. Psychologists speak, for example, about perceptual constriction, failure to filter sensory input, over-inclusion, and the like. Phenomenologists have brought to our attention a host of changes in time sense, not only in schizophrenia but also in the depressions and other psychiatric conditions.

These phenomena occur in varying degrees and constellations in almost all mental disorders. They have been noted in normal subjects under stressful conditions—for example, sensory deprivation or prolonged isolation. Indeed, young

people who experiment with drugs are also familiar with such phenomena. In serious mental disorders, such as schizophrenia, "minor" disturbances (sensory illusions and changes in time sense or body image), are often more crippling than the major ones (delusions or hallucinations). They occur more frequently, they develop much earlier in the course of the disease, and they may remain unnoticed for a long time. Furthermore, while patients may hardly be aware of them, they suffer from their consequences. They endure the uncertainty of day-to-day living where time and space, people, and things are constantly changing. A sustained effort of courage and will is required to undertake the smallest activities. It is this battle of attrition which saps patients' energy and may lead them to give up the struggle. Additionally, in the course of trying to control their perceptual anomalies, schizophrenic patients may lose control of their fantasies and thus be deprived of one of their few pleasures. And yet, drug therapies are aimed only at the major disturbances such as anxiety, delusions, agitation, and depression. Their effects on the minor symptoms are almost completely unknown.

Impressive as they appear, major symptoms of schizophrenia are not necessarily more damaging than the less dramatic malperceptions. It does not take more than a glance through a few autobiographies of schizophrenics to realize how pervasive such malperceptions are and what disastrous effects they can have on mood, thought processes, motor behavior, and interpersonal relations.

A schizophrenic patient gave up driving because the wheel changed its diameter and felt like rubber in his hands. Another could not talk because his own voice did not sound like his anymore and because of failure to synchronize his thinking with his speech. Much will have to be done in relating the many little-explored and less-understood aspects of perception to behavior.

Often social living becomes impossible for schizophrenics because of malperceptions—sometimes gross ones such as seeing people as puppets, robots, two-dimensional figures, animals, or monsters, and also subtle ones due to disturbances in space-time which distort the schizophrenics' sense of territoriality and temporal reality. This may lead schizophrenics to feel that they are being invaded, encroached upon, threatened, and hurried, or it may make them feel spurned, neglected, and ignored, to name a few possibilities.

These experiences, real enough to the schizophrenic, cause him to behave in a manner which others cannot comprehend; thus with growing uncertainty and mutual misunderstanding, interpersonal relations are disrupted.

Such experiences are not likely to be detected by laboratory procedures used to measure circumscribed perceptual reactions of the "stimulus-response" variety. Useful as they are, laboratory procedures are not suitable for exploring the "life-size" phenomena of the type we have just enumerated. Similarly, psychological tests,

designed to quantify behavioral manifestations of pathology, fail to show what such manifestations mean in terms of the patient's experience of himself in relation to the world.

It would, therefore, appear that changes in the perceptual world brought about by mental illness, biochemical agents, or prolonged environmental stress call for an instrument aimed at understanding the subject's immediate experience of himself in relation to the world about him.

It is for this purpose that the Experiential World Inventory (EWI) has been developed. As the name indicates, the Experiential World Inventory is a self-rating diagnostic instrument whose main objective is to measure parameters of experience which we consider essential for the evaluation of the patient's mental condition.

By measuring these parameters, we can construct a *map*, so to speak, of the patient's *experiential world*; that is, the world as experienced by him at a given time. The map enables us to answer a number of important questions. Does the patient perceive the world about him as most people do? If not, how distorted does it appear to him? Are the distortions circumscribed or pervasive? Are they limited to physical surroundings such as objects and spatial relationships, or do they extend to the appearance of people about him, or to his own body image?

With regard to temporality, does the patient live more or less in social time, or does he appear marooned in his own personal time? Does he experience time passing as most of us do with minimal disruptions or fluctuations in its rate? How does he relate to past, present, and future?

With regard to *I-world relations*, what is the extent of change in his personal identity? Does he maintain an adequate degree of self esteem in spite of the changes which have transformed his physical surroundings? What are the characteristics of his stance toward people?

The map also helps us evaluate the patient's affective life. What is the extent of his depression? How emotionally labile does he appear? How certain is he of his own autonomy and control?

As for thinking, the map enables us to assess the intensity or poverty of the patient's ideational activity. It answers such questions as: How intense are the patient's thoughts? Does he maintain a balance between ideational activity and emotional reactivity? Does he feel in control of his thoughts or do they overpower him and sap his energy?

In brief, the EWI brings to focus the perceptual phenomena long overlooked by diagnostic procedures. Yet it does not neglect non-perceptual phenomena such as ideation, affectivity, and impulse regulation. Finally, and most importantly, the EWI enables us to determine the dynamic interaction between perceptual and non-perceptual phenomena and the relative contribution of each category of disturbance to the overall pathological condition.

CONSTRUCTION OF THE INVENTORY

The EWI is a paper and pencil test which can be administered individually or in groups. There is no time limit, but administration time is usually between 25 and 50 minutes. For screening purposes, normal subjects can be tested in groups as large as practicable. Psychiatric patients who are relatively intact, such as dried-out alcoholics and outpatients, can be effectively tested in small groups.

The Inventory consists of 400 statements to be answered true or false by the examinee. The statements represent authentic experiences of real people. They have been compiled from a variety of sources: (1) personal document such as autobiographies of mental patients (Schreber, 1955; Sommer and Osmond, 1960; Kaplan, 1964; Landis, 1964); (2) verbal reports of patients examined by the authors; (3) verbal reports of normal subjects about their experiences with hallucinogens; and (4) from phenomenological and existential literature (Jaspers, 1963; Camus, 1942, 1947, 1952; Sartre, 1943; Schilder, 1950; Dostoyevsky, 1951).

The statements are divided into eight categories, which constitute the principal scales of the Inventory. Each scale consists of two equivalent halves. All scales are scored in the pathological direction: higher scores indicate greater abnormality and lower scores indicate lesser abnormality. Individual items are weighted according to the degree of abnormality they imply. Thus some are given a weight of 2 while others are given a weight of 1. The weights have been determined empirically (El-Meligi and Osmond, 1970).

The area of perception is covered by the first five scales: (1) sensory perception; (2) time perception; (3) body perception; (4) self perception, and (5) perception of others. The area of thinking is covered by scale 6, ideation. Depressive affect is measured by scale 7, dysphoria. Scale 8, impulse regulation, is devoted to problems of emotional control; for example, affective lability, excitability, or emotional arousal.

It should be borne in mind that dividing one's experiential world into such areas is merely a methodological procedure. In reality there are no such sharp divisions. An experience is usually a complex structure in which a given component (perceptual, affective, or ideational) may predominate. More detailed definitions of the scales are given below.

Scale 1—Sensory Perception

This scale includes all sorts of abnormalities pertaining to various sense modalities. They range from minor illusions to flagrant distortions. Also included are disturbances which are not specific to a single sense modality, such as hyperesthesia (increased sensory impressions), hypoesthesia (diminished sensory impressions),

synesthesia (fusion of sensory impressions such as hearing bright colors or tasting sound), general disorientation, and the like.

What does it mean when a person obtains a high score on this scale? It means that the world about him is somewhat chaotic, that he cannot bring order to his sensory impressions, and that he cannot rely on external cues in guiding his behavior. A high score may also indicate that he no longer perceives the world in the same way healthy people perceive it. Among psychiatric patients, schizophrenics and drug abusers obtain the highest scores. Normal subjects under the influence of hallucinogenic substances may score as high as acute schizophrenics.

Scale 2—Time Perception

The statements in this scale are all related directly or indirectly to time. They fall roughly into three sub-categories:

1. Statements describing how a person experiences time passing, whether speeded up, slowed down, or not moving at all:

   "Time seems to stop altogether; everything is suspended and dead quiet."
   "I am constantly in a hurry for no particular reason."
   "Time seems to slow down at night."

2. Statements related to attitudes toward past, present, and future:

   "I wish I had lived in ancient times."
   "I don't brood over the past."
   "I do not belong to this century."
   "I am afraid of the future."

3. Statements related to age-consciousness:

   "I sometimes feel I am becoming younger."
   "My age does not seem to change."
   "I feel I have always been old."
   "I cannot visualize myself older than I am now."

The scale of time perception includes several syndromes which may or may not be interdependent. Therefore, a global score does not do justice to the richness and complexity of experiential time. Each area of experiential time requires an independent scale if we want to explore fully modes of existence in time. Within the context of the EWI, a rough index of abnormality is sufficient to reflect the patient's overall experience of time. Global as it is, the scale has proved helpful in the detection of

altered states of consciousness in schizophrenia, toxic conditions, and intracranial dysfunction. Less dramatic forms of disorders of consciousness, such as mild dissociative tendencies, may also be detected by this scale.

Scale 3—Body Perception

This scale comprises three categories of bodily experiences:

1. Somatic complaints:

   "Now and then I feel that my body is being pierced with needles."
   "My brain is bothering me."
   "I am exhausted."
   "My body feels numb."

2. Affective attitudes toward one's physical appearance, such as shame due to perceived defects, anxiety over bodily integrity or physical contact:

   "Somebody may cut off my genitals."
   "I often dream about losing my teeth."
   "I am bothered by the color of my skin."
   "I do not like to touch my own body."
   "I loathe people who touch me."

3. Strange sensations and distortions in body image:

   "I am rotten inside."
   "My blood is polluted."
   "I feel turned to stone."
   "I am shrinking."
   "There are insects under my skin."

Scale 4—Self Perception

The following categories of experience are included in this scale.

1. Deterioration in self-esteem:

   "I hate myself."
   "I am not the kind of person my mother wanted me to be."
   "I do not like my voice."
   "I have nothing to be proud of."

2. Experiences of depersonalization, identity diffusion, internal disorganization:

"I hardly realize that I have a name."
"I get puzzled as to who I am."
"I don't know whether I am a man or a woman."
"My reflection in the mirror looks strange."
"My voice seems unlike my own voice."

This scale is helpful in determining the effect of the illness on the patient's self esteem and/or ego integration and also in the detection of suicidal tendencies.

Scale 5—Perception of Others

The term "others" is intended to underscore the fact that one's personal world extends beyond human individuals to encompass social groups, social roles, cultural institutions, animals, and inaminate objects that tend to be invested with personal and cultural meanings. Thus, experiences included in this scale reflect one's perception of, and attitudes toward whatever is "not-self." The statements covered by this scale can be divided into five sub-categories.

1. Statements that reflect a tendency to perceive people in a way that detracts from their humanness:

"Most people move and act as puppets do."
"People do not look alive any more."
"People are dirtier than pigs."
"I can easily recognize animal features in people's faces."

2. Statements reflecting paranoid anxiety:

"People look through me."
"People look fierce and dangerous."
"People smile strangely at me."
"I wonder why people are so grim."

3. Statements reflecting ideas of reference, doubts, or paranoid convictions about people.

"People want to see my genitals."
"People often laugh at me."
"My enemies are everywhere."
"Most people hate each other."

4. Statements describing morbid or deviant attitudes toward people:

"I often have love affairs with persons I do not care for."
"Old women turn my stomach."
"Old men are indecent."

5. Statements suggestive of anthropomorphic perception of animals:

"Cats tease me."
"Dogs make fun of me."

The above classification is based on the content of the statements. We could also classify these statements on the basis of their emotional significance—whether they imply fear, suspicion, puzzlement, anger, spite, repugnance, hatred, or alienation. For this reason, it would be inaccurate to say that this scale is a pure measure of perceptual distortion. As we mentioned earlier, it is impossible to isolate a perceptual anomaly from its emotional components. Similarly, an emotional experience aroused by a person or an event has an immediate effect on one's perception of the person or event.

Thus, this scale combines the perceptual and affective components which determine the nature of a person's orientation toward his environment.

The sensitivity of this scale to paranoid tendencies in mental illness, delinquency, and drug abuse has been demonstrated empirically (El-Meligi and Osmond, 1970).

Scale 6—Ideation

This scale focuses on pathologic changes in thought processes. Five types of aberrations are represented.

1. Indications of interference with thinking processes:

"My memory has gotten much worse."
"I cannot make sense of what I read now."

2. Indications of thought disorganization. This includes such serious disturbances as loss of boundaries between the world of objects and the world of ideas, or fluidity of concepts:

"The moon affected my mind."
"As I think, ideas fuse into each other."

3. Indications of experienced change in intellectual orientation:

   "Everything has special meaning for me now."
   "I have new ideas about religion and the world entirely different from anything I have ever thought before."

4. Indications of change in productivity of ideas:

   "Thoughts crowd into my mind too rapidly for discussion."
   "My thoughts are slow and dull."

5. Indications of pseudo-intellectualization and bizarre ideation:

   "I am trying to solve the riddle of life and death."
   "I cannot help thinking of reasons for everything that is said or done."
   "I feel that my ideas may turn into insects."
   "I have become invisible."

Scale 7—Dysphoria

This scale provides a measure of depressive feelings. It consists of four sub-categories.

1. Somatic complaints which we often encounter in depressive conditions, such as reduced initiative, depletion of energy, and restlessness:

   "I am losing my vitality."
   "I have difficulty in getting to sleep."
   "I am so weary of myself that life seems a burden."

2. Dysphoric feelings such as disillusionment, loneliness, despair, grief, feelings of guilt, and self-deprecatory attitudes:

   "I feel lonesome most of the time."
   "I do not feel needed any more."
   "I am beginning to think that I am losing out everywhere."
   "My conscience gives me no rest."

3. Cynicism, sinister thought content, and loss of a forward outlook:

   "My dreams are often depressing."
   "Life is a stupid drama."
   "I cannot forget the mess I have made of my life."
   "I have no plans for the future."

4. Death wishes and suicidal thoughts:

"The lights of life seem to be going out one by one."
"Life would not be worth living if things were always as they are now."

This scale measures the degree of depression, not only in depressive conditions, but also in other mental disorders. Together with Self Perception, it alerts us to suicidal tendencies.

Scale 8—Impulse Regulation

The main objective of this scale is to assess affective lability and determine the extent to which a patient feels overwhelmed by excitation, whether caused by environmental impact, breakthrough of primitive impulses, or emotionally toned ideation.

The rationale of this scale derives essentially from Rorschach's discovery that the prevalence of crude color responses to the chromatic blots reflects a tendency to overreact to environmental impact and, consequently, to be lacking in affective control (Rorschach, 1951; Schachtel, 1960; Alcock, 1963). Thus, we included in this scale statements about reactivity to color, fire, and other emotionally charged situations. Roughly, the scale contains three types of experiences:

1. Excitability or emotional arousal in reaction to external or internal stimulation:

"Bright colors excite me."
"My dreams are often in colors."
"Fire excites me."
"I often feel that I could go out and lick the world."

2. Experiences of loss of command over one's thoughts, impulses or actions:

"I cannot think in a concentrated fashion."
"Sometimes I do not know whether I am talking or not."
"I do not know what my hands will do next."

3. The threat of being overpowered by primitive urges:

"I like torturing people."
"I enjoy watching car accidents."
"I have a strong urge to disfigure women."
"I have a desire to burn things."

Our expectation that the Impulse Regulation scale would serve as a non-projective counterpart for Rorschach *color dynamics* has been fulfilled. This scale, for example, helps differentiate between schizophrenic excitement and neurotic emotional arousal. Overstimulated catatonics obtain the highest scores, followed by hysterical neurotics, while apathetic patients usually score even lower than normal subjects.

It would appear that the relation between this scale and dysfunction is curvilinear; namely, that both high and low scores are indicative of abnormality, while medium scores (between 40 and 50 T-scores) are indicative of optimal excitation (or emotional arousal).

RELIABILITY OF THE SCALES

Split-Half Reliability

Split-half reliability coefficients for each scale were obtained from twelve samples of subjects: six samples of psychiatric patients, one sample of prison inmates, and five samples of normal subjects. The total number of subjects was 1,865.

For a given scale, the reliability coefficient was obtained by correlating the scores on the two halves and then correcting the resulting correlation using the Spearman Brown formula (Ferguson, 1966). The reliabilities are presented in Table 17-1.

To facilitate inspection, separate means and ranges of the reliability coefficients within the psychiatric samples and within the normal samples have been calculated from Table 17-1. These are presented in Table 17-2, which also contains reliability coefficients for the sample of prison inmates. Thus, Table 17-2 provides a means to compare the reliability of the scales in different types of populations.

A number of findings emerge from the inspection of Table 17-2.

1. Generally speaking, the reliability coefficients using the split-half method are quite satisfactory. Indeed, they are remarkably high in the psychiatric population in particular, where the lowest coefficient is .76 on time perception scale. The correlations of other scales range from .88 to .95.
2. The coefficients are highest in the psychiatric groups, followed by normals, whereas the prison inmates obtained lower correlations. However, even the lowest correlation, which is .50 on time perception scale, is still statistically significant.
3. Time perception scale yielded the lowest correlations in all groups and yet all of the correlations are statistically significant. It is understandable that time perception would have the lowest correlations because, as mentioned earlier, its content is the most complex.

TABLE 17-1.

Corrected Split-Half Reliability Coefficients of EWI Scales for Psychiatric, Prison, and Normal Samples

Sample	N	Sex	1 Sens.	2 Time	3 Body	4 Self	5 Others	6 Idea.	7 Dysph.	8 Impulse
Schizophrenics	45	M	0.96	0.82	0.92	0.94	0.88	0.86	0.92	0.91
Schizophrenics	86	M	0.95	0.77	0.91	0.92	0.90	0.89	0.95	0.88
Schizophrenics	96	F	0.96	0.77	0.89	0.93	0.88	0.88	0.94	0.84
Psychotics	83	M & F	0.96	0.75	0.85	0.93	0.81	0.84	0.78	0.95
Neurotics	39	F	0.96	0.66	0.88	0.94	0.94	0.90	0.96	0.95
Alcoholics	115	M	0.90	0.80	0.91	0.90	0.86	0.91	0.94	0.73
Prison inmates	260	M	0.84	0.50	0.77	0.77	0.77	0.75	0.83	0.62
College students	263	M	0.87	0.57	0.73	0.77	0.76	0.81	0.87	0.80
College students	184	F	0.90	0.76	0.79	0.91	0.90	0.86	0.92	0.85
Attendants	285	F	0.87	0.62	0.65	0.82	0.77	0.76	0.83	0.65
Adult normals	181	M	0.85	0.60	0.66	0.63	0.80	0.76	0.83	0.61
Adult normals	228	F	0.79	0.57	0.86	0.90	0.79	0.78	0.92	0.77

Source: Adapted from El-Meligi and Osmond (1970).

What the split-half reliability coefficients indicate is that the EWI scales have a high degree of internal consistency and that psychiatric patients, in particular, respond to the two halves of the test in a highly consistent manner.

TABLE 17-2.

Means and Ranges of Split-Half Reliability Coefficients of EWI Scales in Psychiatric and Normal Samples Compared to Reliability Coefficients in a Sample of Prison Inmates

Scale	Psychiatric		Normal		Prison
	M	Range	M	Range	M
1 Sensory	0.95	0.90–0.96	0.86	0.79–0.90	0.84
2 Time	0.76	0.66–0.82	0.62	0.57–0.76	0.50
3 Body	0.89	0.85–0.92	0.74	0.65–0.86	0.77
4 Self	0.93	0.90–0.94	0.81	0.63–0.91	0.77
5 Others	0.88	0.81–0.94	0.80	0.76–0.90	0.77
6 Ideation	0.88	0.84–0.91	0.79	0.76–0.86	0.75
7 Dysphoria	0.92	0.78–0.96	0.87	0.83–0.92	0.83
8 Impulse	0.88	0.73–0.95	0.74	0.61–0.85	0.62

Agreement of the Two Halves of the Test with the Full Test

As a further test of the internal consistency of the scales, scores on each half of the scales were correlated with full-scale scores in various psychiatric samples.

Mean correlations and range of correlations of Part 1 and Part 2, with total scores on EWI scales in psychiatric male samples, are provided in Table 17-3. The corresponding values for psychiatric female samples are shown in Table 17-4. The values of these tables are derived from more detailed tables in the *Manual for the Clinical Use of the Experiential World Inventory* (El-Meligi and Osmond, 1970).

Inspection of Table 17-3 shows that the lowest mean correlation of any part with the full scale is .85 (between Part 2 of impulse regulation and the full scale), and yet this value is highly satisfactory. All other mean correlations fall between .87 and .96.

The values pertaining to the female groups are equally impressive (see Table 17-4). Two mean correlations are .86 and .89, while the rest range between .92 and .98.

Therefore, it would be safe to state that for all practical purposes, either part of the EWI is as adequate as the entire test.

TABLE 17-3.
Mean Correlations (and Range of Correlations) of Part I and Part II with Total Scores on EWI Scales in Psychiatric Male Samples

Scale	Part I		Part II	
	M	Range	M	Range
1 Sensory	0.95	0.90–0.98	0.92	0.83–0.97
2 Time	0.87	0.78–0.93	0.87	0.76–0.97
3 Body	0.93	0.86–0.97	0.90	0.66–0.96
4 Self	0.93	0.87–0.97	0.94	0.85–0.98
5 Others	0.94	0.92–0.97	0.94	0.89–0.96
6 Ideation	0.92	0.87–0.95	0.94	0.91–0.97
7 Dysphoria	0.96	0.94–0.97	0.95	0.88–0.98
8 Impulse	0.93	0.90–0.97	0.85	0.49–0.96

Test–Retest Reliability

In order to assess the reliability of EWI scales, three groups of subjects were given the entire test on two occasions with varying intervals between tests. Test and retest scores on each were correlated for each group independently.

The groups used in this study were:

1. 47 psychiatric in-patients at the New Jersey Neuro-Psychiatric Institute (23 schizophrenics, 23 neurotics, and one organic patient). The subjects' ages ranged from 15 to 54 years with an average of 33. The time lapse between test and retest ranged from one to 146 days with an average of 34 days.

TABLE 17-4.
Mean Correlations (and Range of Correlations) of Part I and Part II with Total Scores on EWI Scales in Psychiatric Female Samples

Scale	Part I		Part II	
	M	Range	M	Range
1 Sensory	0.97	0.96–0.98	0.97	0.95–0.98
2 Time	0.89	0.85–0.95	0.86	0.84–0.89
3 Body	0.94	0.89–0.97	0.94	0.90–0.95
4 Self	0.96	0.95–0.98	0.96	0.94–0.97
5 Others	0.95	0.90–0.97	0.94	0.91–0.97
6 Ideation	0.92	0.88–0.95	0.93	0.86–0.95
7 Dysphoria	0.97	0.96–0.98	0.98	0.97–0.99
8 Impulse	0.93	0.87–0.98	0.92	0.83–0.97

2. 51 chronic male alcoholics, inpatients at the Alcoholic Center of the New Jersey Neuro-Psychiatric Institute. The subjects' ages ranged from 20 to 59 years with an average of 45. The time lapse between test and retest ranged from 6 to 22 days, with an average of 10 days.
3. 76 normal male college students at Rutgers University. Ages ranged from 17 to 23 years with an average of 19. The time lapse between test and retest was 95 days for all subjects.

Test–retest reliabilities are shown in Table 17-5. The values for the psychiatric patients range from .59 to .73. These values are quite satisfactory, bearing in mind the long interval between test and retest and the fact that patients used in this study received varying treatment modalities which are bound to minimize the stability of the scores over a period of time.

TABLE 17-5.
Test-Retest Reliability Coefficients of EWI Scales for Different Groups

Scale	Psychiatric patients	Alcoholics	College Students
Number	47	51	76
Sex	M & F	M	M
1 Sensory	0.64	0.87	0.64
2 Time	0.73	0.74	0.68
3 Body	0.61	0.84	0.61
4 Self	0.59	0.78	0.54
5 Others	0.67	0.79	0.66
6 Ideation	0.61	0.88	0.66
7 Dysphoria	0.70	0.92	0.23
8 Impulse	0.71	0.85	0.74

The corresponding values for the alcoholic group range from .74 to .92, which is highly satisfactory.

It is interesting to note that the values for the normal group are consistently the lowest. This is to be expected since the test measures pathological phenomena that rarely occur in normal subjects. This tends to minimize the variance and so reduces the size of correlations.

VALIDITY OF THE SCALES

Several studies have been conducted which provide evidence of the validity of the EWI as an instrument for the assessment of psychiatric illness (El-Meligi and

Osmond, 1966, 1970). We shall not describe these studies in detail, but shall give a brief summary of the findings. Special emphasis will be given to the agreement of EWI scales with various neurophysiological measures.

The validity studies fall into three categories:

1. Studies which showed that the EWI agrees with psychiatric judgment. Using raw scores as the basis for differentiation between groups, the EWI scales differentiated between clinical and normal groups at a very high level of significance in both male and female groups.

   Most of the scales significantly differentiated male schizophrenics from either male alcoholics or male neurotics. Female psychotic patients were significantly differentiated from nonpsychotic female patients by all scales.

2. Studies of score configurations as the basis for differentiation between groups. By transforming raw scores into standard scores (as we will show later) ratios between individual scales or between combinations of scales could be used.

   Thus, it has been shown that schizophrenics tend to obtain higher (that is, more pathological) scores on the perceptual scales than on the dysphoria scale (a measure of depressive affect). Conversely, depressive patients, whether neurotic or psychotic, tend to obtain higher scores on dysphoria than on the perceptual scales (El-Meligi, 1967; El-Meligi and Osmond, 1970).

   Another configuration differentiates between schizophrenics and depressives—the ratio of self perception to perception of others. Schizophrenics tend to score lower on the former, and the reverse is true for the depressives. This implies that, typically, schizophrenics develop distorted perceptions of people more often than of themselves while depressives develop distorted perceptions of self more than of other people (El-Meligi, 1967).

   Configural analysis was also helpful in differentiating between two groups of delinquents—those with a history of violence and those with a history of drug abuse (El-Meligi and Johnston, unpub. data). The areas of disturbance most frequently found in violent delinquents are sensory perception and perception of others. In the drug abusers, ideational disturbances and affective lability (as measured by the scale of impulse regulation) are the most prominent features.

   A third configuration characterizes LSD-induced psychosis in relation to time perception and ideation. El-Meligi (1968d) has shown the prominence of these two scales in the profiles of patients who developed psychosis subsequent to experimentation with LSD.

   The findings cited above suggest that configural analysis of the EWI may provide a means for meaningful classification of psychopathological conditions.

3. Correlational studies relating certain scales to other psychological tests. Tests that can be used include the questionnaire type, such as the Minnesota Multiphasic Personality Inventory (MMPI), the rating scale, such as Self Cathexis and

Body Cathexis (Secord and Jourard, 1953), or Essential-Reactive Alcoholism (Rudie and McGaughran, 1961), or the projective variety, such as Witkin's Body Sophistication, which is based on drawing a human figure (Witkin et al., 1954).

Many correlational studies providing evidence of the validity of the EWI scales have been outlined by El-Meligi and Osmond (1970). On the basis of such studies, the following statements can safely be made: (1) The perceptual scales measure essentially the psychotic aspects of illness, especially in schizophrenia. (2) Self perception and dysphoria scales measure the severity of depression, whether in schizophrenia or psychoneurosis, and can therefore provide an index of suicidal risk. (3) Body perception measures body image disturbances brought about by sensory anomalies. (4) Perception of others is the best indicator of the paranoid stance, whether in schizophrenics or in assaultive delinquents.

THE USE OF THE EWI TO DETECT BIOCHEMICAL CHANGES

The previous studies provided evidence of validity based on the agreement of EWI scales with psychological measures of relevant variables and with psychiatric judgment of psychopathological conditions. This section provides a different type of evidence derived from correlations between the EWI scales and biochemical measures. Three studies will be outlined.

First Study: Increase in EWI Scores Due to the Menstrual Cycle

The inventory was adminstered to 29 female college students one to three days before menstruation or during menstruation. All subjects were normal volunteers. Their scores were compared to scores obtained from a control group of 184 normal college females. It was hypothesized that the menstrual group would score significantly higher than the normal group, and that the so-called menstrual tension is not simply a mood change, but is also a function of perceptual alterations. Means, standard deviations, and t-test of significance of differences between means of the menstrual group and the control group are given in Table 17-6.

Inspection of Table 17-6 will show that the menstrual group obtained higher scores on all scales than the control group, the differences being highly significant throughout. Not only does the inventory detect the widely known components of the menstrual tension syndrome, such as mood changes and body discomforts, but also

TABLE 17-6.

Means and Standard Deviations of EWI Raw Scores for the Menstrual Group (N = 29) and a Sample of College Females (N = 184), t-Values for Significance of Difference between Means and Levels of Significance

Scale	Menstrual Mean	Group S.D.	College Mean	Group S.D.	t	Sig.
1 Sensory	16.6	13.1	7.4	8.4	3.47	0.002
2 Time	10.2	6.1	7.6	4.4	2.24	0.025
3 Body	6.7	5.7	3.7	5.0	2.17	0.025
4 Self	11.7	7.9	5.3	6.7	4.08	0.001
5 Others	9.0	7.5	5.2	5.9	2.54	0.010
6 Ideation	9.4	6.4	4.2	4.8	4.10	0.001
7 Dysphoria	6.8	7.7	3.0	4.7	2.58	0.010
8 Impulse	7.8	4.6	4.2	4.2	3.84	0.001

suggests alterations in sensory and time experiences which would otherwise have remained unrecognized.

Second Study: EWI in Relation to Drug-Induced Biochemical Change

Studies cited by Pfeiffer et al. (1968) had shown that chronic male schizophrenics have a lower blood histamine level than the nonhospitalized controls and that certain anti-psychotic drugs increase the mean blood histamine levels of chronic male patients to a normal level. To gain a better understanding of the role of histamine and the polyamines spermidine and spermine in the biochemical processes of the human body, Pfeiffer et al. (1968) undertook a series of longitudinal studies to determine the correlation of histamine levels with changes in the mental state of schizophrenic patients.

Serial EWI measures and various neurophysiological measures were obtained simultaneously from 72 chronic schizophrenics (39 males and 33 females). Various drug therapies were administered to all subjects over differing periods of time. Subjects were seen at one to four week intervals for periods of at least four months. The two halves of the EWI, given alternately, served to assess the change in mental status. This study provided a unique opportunity to find out the capacity of the EWI to detect biochemical changes in schizophrenic patients.

Table 17-7 summarizes the correlation coefficients between the pairs of blood histamine levels and the corresponding EWI scores for various groupings of the 72 patients. It should be mentioned that the EWI scores used in this study are the sum of raw scores on the eight scales of the EWI. All correlations are significant and

in the predicted direction, namely that improvement in the patients' mental state as evidenced by the decrease in their global EWI scores is associated with increase in their blood histamine level. It is interesting to note that the therapeutic successes obtained a higher negative correlation coefficient than any other group. Pfeiffer and his associates (1969) concluded that "combining the EWI measures with polyamines provides a new and potent tool for the study of schizophrenia."

In more recent studies, significant correlations were obtained between EWI individual scales and various neurophysiological variables. In one of these studies,

TABLE 17-7.
Correlation Coefficients between Blood Histamine Level and EWI Global Scores (Schizophrenic Outpatients)

Groups	N	Pairs of observations	r	Sig.
Paranoids	27	109	−0.24	0.05
Non-Paranoids	45	174	−0.22	0.05
All Patients	72	283	−0.23	0.05
Therapeutic Successes	22	136	−0.28	0.01
Therapeutic Failures	50	147	−0.20	0.05

Source: Adapted from Pfeiffer et al. (1969).

Pfeiffer and his associates obtained successive measures from 102 chronic schizophrenic patients over a period of approximately 20 months. Throughout this period, the patients were tested on an average of 7.7 occasions, each time for all variables, including the EWI scales. Thus, a large number of observations were obtained and intercorrelated.

The main objective of the study was to compare schizophrenic patients having a low histamine level to those with a high histamine level. Male and female patients were dealt with separately.

The male groups provided a considerable number of significant correlations between EWI scales and the neurophysiological measures. These correlations are reproduced in Table 17-8 for both the low and high blood histamine groups of the male schizophrenics. To facilitate inspection, we include in the table only the correlations which are statistically significant at the .05 level of confidence or better.

A number of interesting results emerge from this table.

1. The level of histamine in the blood determines the degree of correlations between EWI scales and neurophysiological measures. For example, various EWI scales correlate significantly with Mean Energy Content (MEC), spermidine, and histamine, only within the low histamine group. On the other

TABLE 17-8.

Significant Correlations between EWI Scales and Biochemical Measures in Male Schizophrenics with Low and High Blood Histamine Levels

	Scale	Mean energy content		Spermine		Spermadine		Serum uric acid		Histamine	
		Low	High	Low	High	Low	High	Low	High	Low	High
1	Sensory	+0.27			+0.26				+0.17	−0.21	
2	Time	+0.16				+0.72					
3	Body	+0.19			+0.26	+0.16				−0.20	
4	Self				+0.31	+0.56				−0.14	
5	Others	+0.20				+0.50					
6	Ideation				+0.30	+0.68			+0.16		
7	Dysphoria		−0.14		+0.35	+0.64					
8	Impulse	+0.29			+0.35	+0.30		−0.14		−0.16	
	Total EWI	+0.22								−0.16	

Source: Adapted from Pfeiffer et al. (1970).

Low histamine subjects = 28; number of observations = 215. High histamine subjects = 30; number of observations = 170.

hand, the correlations between EWI scales and spermine are significant within the high histamine group, but not within the low histamine group.

2. The pattern of correlations between the EWI scales and the biochemical variables is congruous with Pfeiffer's predictions. For example, histamine level has an inverse relationship with various EWI scales, while Mean Energy Content, spermine, and spermidine are positively related to EWI scales.
3. Among biochemical variables, spermidine is the most closely related to psychopathological phenomena measured by the EWI scales.

Just what these correlations mean to the student of the biochemistry of schizophrenia is beyond the scope of this paper. What we are interested in is what the correlations imply regarding the value of the EWI as an instrument for the evaluation of illness in schizophrenia or other mental conditions. Pfeiffer's studies demonstrate the relevance of the variables measured by EWI scales to biochemical phenomena underlying schizophrenia. They also point to the suitability of the EWI in psychopharmacological studies.

Third Study: EWI in Relation to Drug-Induced Changes in Electric Activity of the Brain

In a longitudinal study of acute schizophrenic patients, Goldstein and Pfeiffer (1968) used the EWI measures to determine the degree of improvement with various drug therapies and to compare it with an EEG measure of variability.

The subjects (24 males and 27 females) were seen over periods of time varying from 3 to 18 months. The age range was 18 to 68 with a median of 32 for male patients, and 18 to 60 with a median of 29 for female patients. The therapies used included neuroleptics, lithium, vitamins, and other drugs.

Repeated EEG's and EWI scores were obtained simultaneously from all subjects at varying intervals. The EEG was directly monitored and processed at the same time through electronic integrators. The on-line quantitated data were computed so as to yield, for each patient-session, an estimate of the time-course variability of the EEG as manifested in 30 successive "epochs," each of 20 seconds duration.

The coefficients of variation (CV: standard deviation expressed as a percentage of the mean) were used throughout to express the levels of EEG variability. Significance levels, in case of change, were ascertained from F-ratios of the variances. The methodological and practical aspects of such an approach to EEG quantification have been discussed in a number of publications (Goldstein et al., 1963; Goldstein and Beck, 1965; Goldstein et al., 1965; Pfeiffer et al., 1968).

The patients were classified as "therapeutic success" when EWI global scores on

TABLE 17-9.
Levels of Variability in the EEG (Left Occipital) of Acute Patients

Sex	N	EEG Coefficient of variation	
		First recording	Last recording
Females			
Success	14	10.5	15.2*
Failure	13	9.6	10.5
Males			
Success	16	10.9	15.1*
Failure	8	11.4	10.8

Source. Goldstein and Pfeiffer (1968).
* Statistically significant difference (F-ratios) $P < 0.01$.

the eight scales dropped significantly, and as "therapeutic failure" when no significant change occurred in EWI global scores. It should be noted that the base-line of EWI scores was the same for the "success" and "failure" groups. Moreover, there was no significant difference between males and females with regard to the initial or final EWI scores.

The results of this study are summarized in Table 17-9 (Goldstein and Pfeiffer, 1968). The values show quite clearly that the changes in EEG variability were related to changes in EWI global scores. In the cases of therapeutic success, EEG variability increased by 38 percent in male patients and by 45 percent in female patients, whereas in therapeutic failures no change occurred.

Previous studies (Goldstein et al., 1963; Goldstein and Beck, 1965; Goldstein et al., 1965) had shown that schizophrenics' brain waves are typically *hyper-regulated*, that is, lacking in variability, and that *hyper-regulation* is a function of arousal. The concept of arousal is most helpful in interpreting the EWI scales. In the light of this concept, the EWI scales may be considered to reveal three major types of arousal.

SENSORY AROUSAL

By sensory arousal we mean the experience of being flooded by sensations or being unable to inhibit sensory stimulation. Such experience interferes with the individual's efforts to achieve an optimal level of perceptual organization. The scales of sensory perception and body perception contain many items which are pertinent to sensory arousal.

IDEATIONAL AROUSAL

By this we mean overproductivity of ideas and images, increased cerebration, and the like. The scale of Ideation deals essentially with this category of arousal.

EMOTIONAL AROUSAL

This category of arousal includes such traits as excitability, affective lability, and the tendency to overreact to emotional situations. The scale of impulse regulation covers such phenomena. The dysphoria scale is limited to depressive feelings. Self perception and perception of others include a variety of affective reactions toward self and others.

STANDARDIZATION

Norms

Separate norms were derived from two reference groups of psychiatric male patients (N = 739) and psychiatric female patients (N = 367) (El-Meligi and Osmond, 1970). Norms have also been derived from normal populations, 612 males and 882 females (El-Meligi, unpub. data). However, it has been our practice to compare patients' scores to norms derived from psychiatric rather than normal populations. The reason for this is that the greatest majority of EWI items represent peculiar experiences which are very rarely admitted by normal subjects. It follows that the scores of disturbed patients often fall above the upper limits of normal population norms. This would limit the usefulness of profiles based on norms derived from a normal population. While such norms may be useful in the assessment of normal subjects or of patients in remission, they yield little information about psychiatric patients. Much more meaningful information is gained by comparing patients' scores to norms derived from patients representing a wide spectrum of psychiatric disorders.

The patients used in the development of the final psychiatric norms were taken from various psychiatric centers and private offices in New York, New Jersey, Connecticut, Michigan, and Saskatchewan (Canada). Both inpatients and outpatients were represented. Detailed information about the normative samples is provided elsewhere (El-Meligi and Osmond, 1970).

Standard Scores

Raw scores on each scale within each standardization sample were converted to *normalized* T-standard scores with a mean of 50 and a standard deviation of 10

(Ferguson, 1966). We cannot here go into the actual statistical operations whereby raw scores are expressed in terms of T-standard scores. What is important is to have an idea of the rationale of this procedure, aptly described by Senders (1958):

> To summarize this method briefly, each individual is assigned the standard score which *would* correspond to his percentile rank *if* the distribution were normal. . . . T-scores can be treated like measurements on an interval scale, and they are, by their very nature, normally distributed. Both of these facts make them convenient measures to use as the basis of later calculations [p. 223].

It should be noted that while raw scores on different scales are not comparable due to differences in their distribution, T-scores are. It should be mentioned that the person administering the test does not have to do any transformation himself, since each profile chart contains both the raw scores and their T-standard score equivalents. Separate profile charts are available for male and female patients.

Detailed instructions about how to plot the profile and how to interpret it will be given in the following section.

METHOD OF INTERPRETATION

In this section, we shall try to demonstrate how we interpret test findings and how we arrive at conclusions regarding the patient's mental condition and personality functioning. Ideally, the process of interpretation includes the following procedures.

Description of the Patient's Reaction to the Testing Situation

It should be borne in mind that the test constitutes but one component, albeit the most important, of an entire situation involving at least two people, the patient and the examiner. Very often, other people may be included such as the psychiatrist who referred the patient for testing, or a parent or spouse who may have been involved in the situation.

It is therefore important to find out the patient's general attitude toward the whole situation and, in particular, toward the test itself. A talk with the patient before and after the test can often elicit reactions that will help to assess his cooperativeness, trust, suspicion, or defensiveness. Observing his test behavior and listening to his comments during the test further facilitate our task. Furthermore, consistency in responding to the test can be assessed by comparing the scores obtained on the two parts of the test. As previously noted, these are equivalent parts. Therefore, any

marked discrepancy between the scores on the first and second parts of a given scale should raise the issue of a shift in attitude, and an explanation of this shift should be sought.

Quantitative Analysis

In this phase, we find out to what extent the patient's scores deviate from the mean of the distribution, whether the scores deviate in the direction of illness (above the mean) or in the direction of normality (below the mean), and whether the scores lie within psychotic, neurotic, or normal range.

The profile is a visual representation of the distribution of scores in the psychiatric population. Understanding how it is constructed is essential for interpretation of test scores.

The profile chart (see Figure 17-1) is constructed in two separate parts. The part on the left is for plotting the profile of the eight basic scales. The smaller one on the right is for later use in plotting three additional scales[1] (to be published later).

T-standard scores are shown in the left and right margins of the chart. They indicate how much the score obtained on any scale deviates from the scores obtained by the reference group, namely the psychiatric sample used in the standardization of the test.

Scale names appear at the top and bottom of the chart, in their standard order from 1 through 8. The range of raw scores for each scale appears in the column headed by the scale name, from the lowest score to the highest. For example, the lowest score in scale 1 (sensory perception) is 0, which is equivalent to about 31 T-score. The highest score that has ever been obtained is 115, which is equivalent to 82 T-score. Note that raw scores are spaced according to their T-score equivalents.

Configural Analysis

Here we examine relationships between scales and the occurrence of recognizable configurations. We make inferences about what these relationships and configurations mean in terms of severity and type of pathology or in terms of their behavioral correlates.

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[1] Three additional scales have recently been derived by El-Meligi from the EWI: hyperesthesia, hypoesthesia, and euphoria. The first measures the tendency to be overwhelmed by environmental impact, the second measures the opposite tendency which seems to give rise to feelings of unreality, and the third measures disturbed affect in the direction of elation.

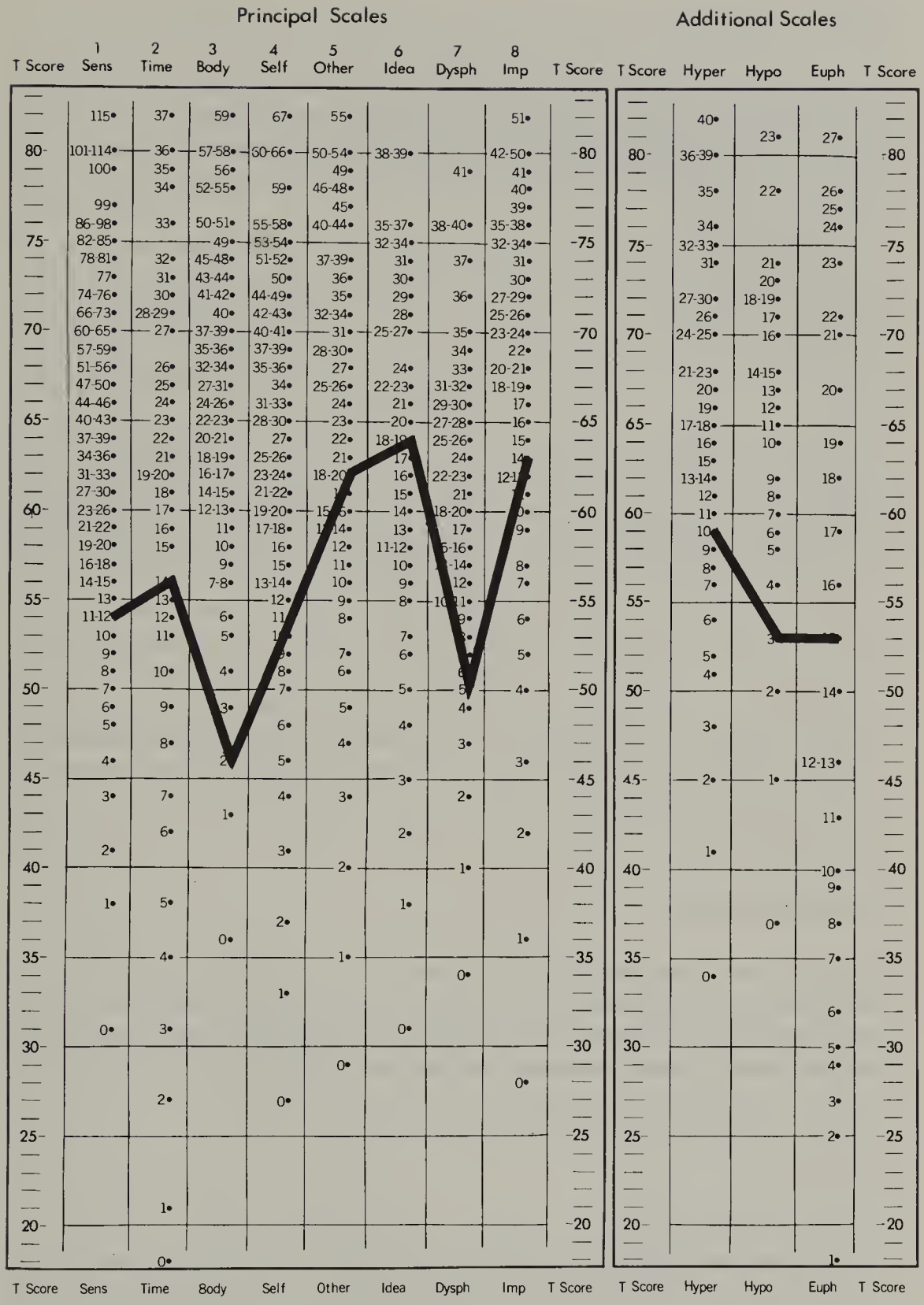


FIGURE 17-1.
EWI profile of Mr. Stanley, a schizophrenic.

Content Analysis

This phase consists of examining the actual test items which have been answered by the patient in the pathological direction. This enables us to find out the patient's idiosyncrasies, and what is unique in his pathological condition. This complements the nomothetic outlook provided by quantitative and configural analysis by an idiographic outlook.

The importance of content analysis becomes evident if we consider the example of two patients with equal scores on a given scale. Equal scores simply mean that they deviate to the same extent from a given norm. This, however, does not necessarily mean that they have similar meanings, because the items answered by one patient may be totally different from those answered by the other. For this reason, content analysis is used to personalize the statistical description.

In content analysis, one of the things we look for is the frequency of serious disturbances which are typical of severely disturbed patients. The items weighted 2, which we designate as "critical items," indicate such experiences. Two patients may have equal scores on a given scale, yet the contribution of critical items to the score in one case may be greater than in the other. This indicates that the former is more seriously disturbed than the latter. Also, a schizophrenic patient in remission may have a score within neurotic range, yet the score may be made up largely of critical items. Therefore, inspection of the items serves to complement and sometimes modify the statistical findings.

We have found content analysis to be particularly useful in later interviews with patients. They usually can elaborate upon their experiences, thus revealing areas of experience not represented in the EWI item pool.

Inferential Analysis

Inferences are made at each of the stages outlined above concerning the severity of illness, the type of illness (for example, the most likely diagnosis) personality functioning, and the likelihood of certain behavioral patterns such as drug abuse, suicidal attempts, violent outbursts, and the like. The role of inference in psychodiagnostic testing is aptly outlined by Hutt (1969).

Integration of Findings

The inferences made on the basis of the EWI are then compared to findings from psychological or neurophysiological tests, clinical interview material, and biographical data.

The EWI findings may be augmented by retests and/or other tests if the psychologist considers them insufficient for formulating definite conclusions.

We shall limit ourselves in the following case demonstrations to the procedures concerning the interpretation of the EWI, occasionally checking the results against general findings from psychiatric interviews or other test results. Although we will skip the sixth procedure, integration of findings, we recommend it very strongly in routine practice.

CASE DEMONSTRATIONS

First Case: Mr. Stanley, a Schizophrenic

This 21-year-old patient was referred to one of us (H.O.), who interviewed him and gave him the EWI. The EWI answer sheet was then submitted to the first author (A.M.E.) for scoring and blind interpretation. The only information made available to the interpreter at the time was the patient's age, sex, and educational status.

TEST BEHAVIOR

The psychologist assigned the task of blind interpretation of a test protocol is at a serious disadvantage, because he is deprived of the opportunity to interact with the patient and, consequently, to observe his attitudes toward testing and his reactions to the test situation as a whole. It is for this reason that we discourage blind interpretation as a routine procedure in clinical evaluation. We use it only for the sake of demonstration or for validation of test findings. Understanding the patient's attitudes and reactions in the course of testing is often crucial in interpreting test scores, profile configurations, or content of responses.

For example, an excessively elevated profile obtained by a patient who is known not to be psychotic could easily be explained if we had the chance to witness his histrionic reactions during testing, his tendency to dramatize or exaggerate. On the other hand, a male patient might have been pressured into taking the test by a wife with whom he was in conflict. His better than normal scores would make sense had we observed his resistance, negativism, and suspiciousness during testing. Thus, observations of patients' attitudes can modify the meaning of test scores and provide safeguards against misinterpretations.

Irrespective of whether we have had the chance to observe the patient, we can still find indications in the test itself about the patient's test attitudes. For example, we may note whether he has completed the test or omitted some items. Inspection of the omitted items might tell us a good deal about him. We may also examine the way he

marked his answers on the sheet. He may have marked certain items both true and false or he may have revealed certain rituals such as answering true and false alternately. The latter would invalidate the test.

There is also the question of consistency referred to earlier. Since the EWI has two equivalent parts for each scale, comparing the two sets of scores allows us to assess the patient's consistency in responding to the test items.

Now, going back to our patient, some striking features pertinent to test attitudes will be noted:

First, he did not omit any items.

Second, he marked his answers on the IBM sheet with much pencil pressure and rarely exceeded the space provided for marking the answers. From this it appears that he took the task in earnest, followed instructions rigidly, and made a successful attempt to contain his nervous energy, that is, to control the motor discharge of impulse.

Several inferences may be made at this point. It would appear that the patient is extremely tense, anxious, and susceptible to episodes of exhaustion as tension accrues. There is also the possibility of loss of control when tension becomes unbearable.

Third, the patient did not erase any answers. This implies that he deliberated sufficiently before responding and/or that he felt no uncertainty about any of the items. It further implies that he felt the test items to be neither ambiguous nor equivocal and to be relevant to his immediate experience.

CONSISTENCY

In order to assess the patient's degree of consistency, let us have a look at his raw scores in Table 17-10. Obviously, the two sets of scores are highly correlated, indicating a high degree of consistency. However, there is a definite tendency toward lower scores on the second part of the test. The sum of scores on the second part of

TABLE 17-10.
Raw Scores for Mr. Stanley, a Schizophrenic

	Scales	Part I	Part II	Total
1	Sensory	9	2	11
2	Time	9	5	14
3	Body	2	0	2
4	Self	8	2	10
5	Others	14	6	20
6	Ideation	12	7	19
7	Dysphoria	5	0	5
8	Impulse	8	6	14

the test is 28, compared to 67 on the first part. This indicates a definite shift. The tendency to have lower scores on the second part of the test is in itself quite common but the discrepancy in this case seems unusual.

One possible explanation is that, as testing progressed, the patient became more guarded. It is likely that at one point he came to realize that he had gone too far in admitting abnormal experiences and therefore began to censor himself.

It is also likely that, as he became more familiar with the task, he became more discriminating and began to interpret test items too carefully. Our experience shows that cognitive styles influence the way we respond to test items. For example, an obsessive subject has trouble seeing any item, relevant as it might be, as corresponding exactly to his personal experience. In contrast, a carefree person readily endorses items which, upon careful scrutiny, would not appear to correspond exactly to his experiences.

With the information available so far, it is not possible to decide which hypothesis applies, but the fact remains that while the configuration of scores did not change significantly from Part 1 to Part 2, sharp drops in scores did occur.

The drops are particularly sharp on scale 1, sensory perception, and on scale 7, dysphoria. The drop on the latter may suggest that the patient's mood improved significantly with his involvement in the test. The improvement of mood may itself account for the drop in scores on the latter part of the test and, in turn, may be due to the fact that the patient's initial anxiety had subsided. This is a common phenomenon in schizophrenic patients.

QUANTITATIVE ANALYSIS

As we mentioned earlier, the second step in interpretation is to assess the severity of illness by comparing the patient's score on each scale to the distribution of scores in a reference group. This can be done through the profile (see Figure 17-1).

With the exception of body perception, all scales fall above the mean of the psychiatric norms. Three scales exceed 60 T-score: ideation, impulse regulation, and perception of others. Thus, the patient presents himself as a severely disturbed young man. He admits abnormal experiences, both neurotic and psychotic. This is a further indication of the patient's truthfulness. It would appear that he neither tried to place himself in a good psychological light nor to exaggerate his illness.

PROFILE CONFIGURATION

Ideation peaks the profile and forms together with impulse regulation and perception of others, a conspicuous configuration far higher (that is, more pathological) than other scales and about 1.5 standard deviation above the mean of the psychiatric norms. This configuration suggests a mental condition which is more severe than

mere neurotic symptomatology. It raises the issue of a psychotic condition or a schizophrenic process.

In order to understand this configuration, it is important to recall what each of its three components mean. A moderately high score on Ideation indicates increased productivity of ideas and may be correlated with intellectual interests, enthusiasm, and drive. When too high, as in this case, it indicates a lack of ideational organization and shows that the patient is prevented from engagement in practical pursuits by mental activity too impelling to direct. It also means that the patient relies too much on his own intellect and interprets external situations in terms of inner cues, with minimal consideration of external ones. We might infer from this that intellectualization of an aggressive type (such as argumentativeness) is a dominant feature in this patient.

Impulse regulation scale provides a measure of affective lability, excitability, or failure to control and integrate affect in adaptive action. The patient's score reflects severe failure in affective control, indicating susceptibility to diffuse excitement and a tendency to express affect crudely or explosively.

Perception of others measures the degree of misperception of the social environment and the tendency to rely on internal cues in interpreting people's behavior, motivations, and intentions. It reveals the paranoid stance in an individual.

This constellation reflects a state of ideational and affective arousal beyond the patient's control. Clinically, he might appear hypomanic and for this reason might be seen as elated. Because of the tendency to be over-ideational, he might entertain many ambitious plans but fail to actualize any of them. Restlessness and lack of concentration would prevent him from making adequate use of his creative potential.

There is an obsessive quality to his thinking. Furthermore, he tends to get excited by his own thoughts. It is therefore likely that he manifests pressure of speech and is quite irritating to people around him.

His score on perception of others suggests the presence of negative attitudes toward people and susceptibility to a distorted perception of them. He is likely to be impoverished in empathy.

There is a marked discrepancy between the scores on self perception and perception of others (T-scores are 53 and 62, respectively). The discrepancy indicates that in his mode of adjustment the patient is more inclined to be extrapunitive than intropunitive, and to see fault more with other people than with himself. What this means is that the patient's stance in life is essentially paranoid.

With this in mind, one would expect the patient's excessive ideation to have a paranoid flavor. One can make another inference with regard to his affective reactions. Having established the fact that his affectivity is crude and explosive, one would expect the paranoid stance to favor acting-out against the world. This danger increases in the aftermath of rage. Since he is inclined toward intellectualization, he may resort to rationalization in order to rid himself of guilt feelings.

Let us now examine another feature in the profile. The time perception scale is moderately elevated, suggesting that the way the patient organizes himself in time is far from being optimal. One doubts if the patient could adapt to the rhythm of life around him. Peculiar experiences of time are likely to occur. For example, there may be episodes of dissociation, or having the feeling of being unable to catch up with others, or the feeling that people are irritatingly slow.

Inspection of the item content of this scale should help us determine the nature of his time disturbances. However, since we have established that he is hypomanic and overly aroused, chances are that his subjective time is pathologically speeded up, and that he is therefore likely to be demanding and impatient. Hypomania makes it hard for him to deploy his energies in time in a smooth and regular manner. Therefore, his productivity is likely to be episodic or erratic.

Disturbances in sensory perception are present to a moderate degree. There is no evidence of sensory distortion. His trouble seems to reside in sensory overloading which lowers the level of perceptual organization. While he sees the world around him as most people see it, he tends to overreact to external stimulation (T-scores on hyperesthesia, impulse regulation, and euphoria are 59, 63, and 53, respectively). This is likely to minimize perceptual sharpness and may lead to perceptual constriction. It is reasonable to infer that the patient feels the encroachment of the environment upon him and that, as his condition worsens, the environment becomes increasingly threatening. The development of paranoid delusions may serve the purpose of maintaining body boundaries and personal identity.

It is interesting to note that body perception is relatively intact. It would appear that the patient's body esteem is preserved. He is much more sensitive about his self-esteem, which he seems to preserve by assuming an offensive strategy against the environment.

CONTENT ANALYSIS

The items answered by the patient in the pathological direction are listed in Table 17-11.

Starting with the sensory perception scale, we note that three of the items are critical and that they all relate to visual illusions. Changes in perception of space or depth are indicated by "Stairs look very steep" and "Straight edges look curved at times." Item 46 suggests failure in focusing: "Sometimes when I read, the lines of print zig-zag up and down." Item 18, "Music I used to like does not sound harmonious any more," suggests some failure in organizing auditory stimuli.

Generally speaking, the items in time perception scale suggest increased personal tempo, anticipatory anxiety, and, probably, a tendency to cling to a youthful image of himself, indicated by "My age does not seem to change."

Only two items in the area of body perception are endorsed by the patient. However,

TABLE 17-11.

Items Answered in the Pathological Direction by Mr. Stanley, a Schizophrenic. Critical Items are Marked with an Asterisk

Sensory

16.* Stairs look very steep.
18. Music I used to like does not sound harmonious any more.
30. Sunlight often seems dazzling.
34.* Straight edges such as those of walls and floors look curved at times.
46.* Sometimes when I read, the lines of print zig-zag up and down.
196. I feel at home in the world. (answered false, F)
203. I can judge distances easily. (F)
360. When depressed, my body feels so heavy that moving becomes particularly tiresome.

Time

1. Bad times will pass. (F)
13. I am afraid of the future.
14. I am constantly in a hurry for no particular reason.
47.* I do not belong to this century.
137. I cannot visualize myself older than I am now.
185. I usually know what will happen next.
197.* I often feel like a child.
202. I look forward to each new day. (F)
206. I feel as if I am waiting for something to happen.
224. I feel younger than my real age.
228. My age does not seem to change.
239. I seem to have lived another life before.

Body

93. My skin is very sensitive.
103. Now and then I feel as if my whole body is being pierced with needles.

Self

24. I am made up of two opposite characters.
54.* I sometimes leave my body.
57. I would like to escape from my body.
70. I love to see my name in print. (F)
164. I get puzzled as to who I am.
194.* My reflection in the mirror looks strange.
247.* I hardly realize that I have a name.

Others

38. I wonder why people are so grim.
86. People generally have good reasons for most of their deeds. (F)
89.* I often have love affairs with persons I do not care for.
90. Everyone seems to have changed lately.
94. Old women turn my stomach.
95.* Cats tease me.
111. I have been sexually attracted to men (or women) for whom I have little respect.

117.* People smile strangely at me.
143. People are parasites.
156. Most people move and act as puppets do.
183. There is a lot of good in all of us. (F)
212. My feelings about my family have changed.
234. People do not look alive any more.
283. People never say what they mean, now.
323. I often think about my enemies.
358. It is easy to forgive people. (F)
375. I am as happy in company as alone. (F)

Ideation

4. I have new ideas about religion and the world entirely different from anything I have ever thought before.
39. Strange ideas come into my head from nowhere.
66. Thoughts crowd into my mind too rapidly for discussion.
87.* The terrors of hell approach.
91. Everything has special meaning for me now.
124. Order is a basic quality of nature. (F)
147.* I often do not know whether I am awake or asleep.
167.* The moon affected my mind.
179. I sometimes think other people's thoughts.
243. There is always a simple explanation for everything.
324.* All of the problems of the universe crowd into my mind, demanding instant discussion.
355. Lots of funny things that I do not understand are going on these days.
371. As I think, ideas fuse with each other.
382. I can read people's thoughts in their eyes.
387. Honesty is practical in the long run. (F)

Dysphoria

3. I have difficulty in getting to sleep.
97. Life is a stupid drama.
134.* I am so weary of myself that life seems a burden.
168. My conscience gives me no rest.

Impulse

92. I cannot think in a concentrated fashion.
101.* I am bothered by murderous ideas.
102. I sometimes feel an urge to bite somebody
114 I would like to burn things.
146. I often imagine scenes of torture.
162. I have full control of myself. (F)
175. Bright colors excite me.
205. I wake early in the morning.
211. My dreams are very vivid.
241. I often feel I could go out and "lick the world."
348. Fire excites me.
349. I often imagine scenes of mutilation.
386. I am responsible for almost everything I do. (F)

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skin sensitivity may suggest that he has allergies of some kind (see item 93). Item 103 reflects experiences of diffuse physical pain. Further inquiry may add to our knowledge of the patient's physical complaints.

Self perception scale shows that seven abnormal experiences are admitted by the patient, three of them critical items. Two main conclusions can be drawn from this scale. First, that the patient has unusual experiences such as out-of-the-body experiences and ambiguous change in the perception of his own face: "My reflection in the mirror looks strange." Second, problems of identity may be present: "I hardly realize that I have a name."

Seventeen items contribute to this patient's score on the scale of perception of others; however, only three of them are critical. The following inferences can be made. First, the patient's interpersonal relations are quite disturbed. He reports changes in feelings toward his family and anxiety in interpersonal situations: "I wonder why people are so grim," "People never say what they mean, now." There is a paranoid flavor to item 117, "People smile strangely at me." There is also a tendency to dehumanize people or a failure to see them as totally human: "People are parasites," "Most people move and act as puppets do." A depressive view of the world around him is suggested by item 234, "People do not look alive any more."

On the scale of ideation, fifteen items contribute to the patient's score, including four critical items, the greatest number of such items on any scale. Here the patient complains of intrusive ideas, puzzlement, poor concentration, religious and philosophical preoccupations, and bizarre thoughts. One gets the impression that his mental activity is far from being organized or goal-directed. Item 371 supports this hunch: "As I think, ideas fuse with each other."

The patient endorses only four items on the dysphoria scale. One of these is item 134, "I am so weary of myself that life seems a burden." The items indicate that the patient is moderately pessimistic and tends to blame himself, but there are no indications of suicidal preoccupations.

There are thirteen items endorsed by the patient on the impulse regulation scale, which suggests a number of features. First, he has general excitability and probably a tendency to seek excitation: "I would like to burn things," "Fire excites me," "Bright colors excite me." Second, fantasy life is probably intense but does not seem to be of a gratifying nature. Morbid images such as scenes of torture and murderous impulses are frequent. It may well be that the patient has phobias which interfere with his smooth functioning and affect his sleep.

The conclusions drawn from analysis of content support the conclusions drawn from quantitative analysis of scores and profile configuration. The patient emerges as a high-strung, fearful, excitable, and insecure individual. He is threatened by people. His perception of them reflects suspiciousness, guardedness, and a sense of alienation. He has unbridled fantasies, and his emotional reactions and ideation are

intense. He tends to overreact to environmental stimuli and may get so emotionally aroused that he cannot behave in an organized fashion.

Intellectualization may be one of his main defensive measures against disintegration, but is not sufficiently effective since morbid and impractical preoccupations interfere with his problem solving activities.

DIAGNOSTIC IMPLICATIONS

The following features favor a diagnosis of schizophrenia rather than neurosis or affective disorder. (1) Ideation scale is within psychotic range and is much higher than dysphoria, which implies that dysphoria is secondary to problems of thought organization. Ideation is one of the most frequent peaks in schizophrenic patients' profiles and in those of drug-induced psychotic conditions. (2) Perceptual scales are more prominent than dysphoria. The average T-score on the former is 54.2 compared to 50 on the latter. What this implies is that perceptual disturbances in this case contribute to the pathological condition more than does affective disorder as measured by the dysphoria scale. It should be noted in this regard that El-Meligi (1967) has shown this feature to characterize 60 percent of the profiles of schizophrenic patients, compared to only 20 percent of the profiles of depressive patients, neurotic or otherwise. (3) Perception of others is significantly higher than self perception and exceeds the neurotic range. As we have pointed out in the manual, this feature is one of the most potent indices of social maladjustment, whether associated with schizophrenia or psychopathy.

PSYCHIATRIC FINDINGS

It is not possible to include the entire psychiatric report. We will limit ourselves to the following excerpts which are pertinent to evaluation of pathologic features.

> Mr. Stanley is a rather vague, verbose, circumstantial, self-centered, preoccupied young man. He told me that he was in a difficult situation because he was facing military induction and had a college thesis due; he said he was consequently a "bundle of nerves."
>
> He has apparently been taking Librium and has managed to keep up with his grades, although periods of depression in the last year have "knocked him out" for weeks, and given him a nightmarish feeling. He does not seem to have been suicidal, although he sometimes drove furiously in his sports car. He married his childhood sweetheart six months ago and claims that they are very happy.
>
> In college, he used to have many conflicts with his teachers but now feels that they are coming around to his views. He believes that he will finish successfully and would then like to get away from things because he has been "deeply wounded by events," and they have an uncanny way of affecting him. He tells me he does not read newspapers because they affect him so much, and he sometimes feels as if he is in a "minor kind of trance."

He would like to find suitable employment, perhaps something manual like being a carpenter's apprentice. This sounded quite unrealistic to me, but apparently he is good at these things. He and his wife have furnished a home themselves; he makes things and she sews. He agrees that he will probably do something like teach, since he likes children.

His personal history indicates that he fell out of a car when he was small, seems to be accident prone, has had two operations on his eyes to correct a squint, at first "a real source of mental anguish." He was also hit by a car and suffered a fractured wrist. He describes his moods as being changeable; when music is played, he has thoughts which run to ecstasy and violent crying. His mother seems to be a gentle and competent person. His father, a teacher, is "moody and has violent outbursts" but gets on well with children, particularly with his sons. Of his five siblings, three seem to be "moody and freaky." A brother is seeing a psychiatrist. Mr. Stanley feels that they are a happy family and get along fairly well.

He has taken LSD, mescaline, etc., on a number of occasions. He feels they generally help him, although he has had paranoid experiences. He has also had a number of "flash-backs" several weeks after taking drugs, some of which have frightened him.

I believe this patient is a rather sick young man who must be very intelligent to have kept going in spite of an illness with so many perceptual anomalies. I would certainly expect the strain of his thesis to make him somewhat sicker, and the prospect of going into the army to further exacerbate things. I would diagnose this condition as a schizophrenic illness, difficult to recognize because his thinking is intact, there is a lack of depression, and paranoid features are relatively low compared to substantial perceptual changes.

COMMENTS

The following findings may be considered the highlights of the psychiatric report. First, fluctuations in consciousness. The patient himself indicates that he is sometimes in a "minor trance." Second, fluctuations in mood with prominence of depression which "knocked him out" for weeks. Third, the patient is currently unable to cope with reality demands, not so much because of a withdrawal tendency as because he experiences the environment as overwhelming. For example, he is "deeply wounded by events." It would appear that he is prone to episodes of uncontrollable excitation. This is borne out by the patient's experiences of music. When it is played, he has "thoughts which run to ecstasy and violent crying." He is trying to reduce stimulation. He does not read the newspaper and longs for a simple job such as a carpenter's apprentice.

It is important to point out that he has had experiences with LSD during which he experienced paranoid feelings. Furthermore, flashbacks occur.

All these features are remarkably consistent with the EWI findings. The question now arises as to the particular contribution of the EWI to the psychiatric evaluation. Relying on subjective evaluation and guided by the patient's overt behavior during the interview, the psychiatrist missed the subtle disturbances in thinking and the

paranoid feelings, thus indicating that the patient's thinking was intact and that paranoid features were relatively low compared to substantial perceptual changes. Apparently, the patient was able to express his thoughts clearly during the interview and did not show the major thought disturbances which usually lead to a diagnosis of schizophrenia. However, the EWI revealed that the patient was unable to concentrate, that he was over-ideational and flooded by imagery.

These features were not likely to be apparent in the clinical interview. In fact, some patients who are over-ideational (like those who take brain stimulants) or of superior intellect, are likely to impress the psychiatrist by their verbal ability. The EWI seems to be able to cut through the halo effect and thus correct the errors caused by it.

The EWI has also shown that, even though the patient did not have frank delusions, his stance toward people was essentially paranoid in nature. This also was not evident in the interview because the psychiatrist based his judgment about the presence or absence of paranoid features on major paranoid symptoms such as delusional thinking It would appear that the major contribution of the EWI in this case comes from the fact that, rather than focusing on major disturbances, it provides a survey of a wide range of disturbances undetectable by the interview.

Second Case: Mr. Arthur, a Schizophrenic with History of Behavior Disorder

This 19-year-old patient was tested by the first author (A.M.E.), who also interpreted the EWI. The psychiatric interview was conducted independently by the second author (H.O.). The interpretation of this case will be outlined more briefly than the first case. Various phases of interpretation will be combined to demonstrate a faster way of arriving at conclusions from the EWI. A busy psychologist would handle the case in this way.

Inspection of the EWI profile (see Figure 17-2) shows that none of the scores lie below 60 T-score, and that they range from 60 to 75 T-score. This implies that the patient presents himself as seriously ill.

He readily admits various sensory anomalies pertaining to spatial relationships: "Buildings often look as if they are crumbling," "Straight edges such as those of walls and floors look curved at times." Problems of auditory organization are also indicated by the item: "Voices of people have changed."

In addition to discrete sensory anomalies, it seems that feelings of estrangement have crept in: "I am in the far, far distance." A tendency to project shows in the item "Pictures seem to come alive when I look at them." Equally important is the fact that the patient experiences synesthesia, that is, hearing bright colors and tasting sound.

With regard to experiences of time, the patient seems quite muddled. In the first place, he feels alienated in time: "I wish I had lived in ancient times," "I hardly pay

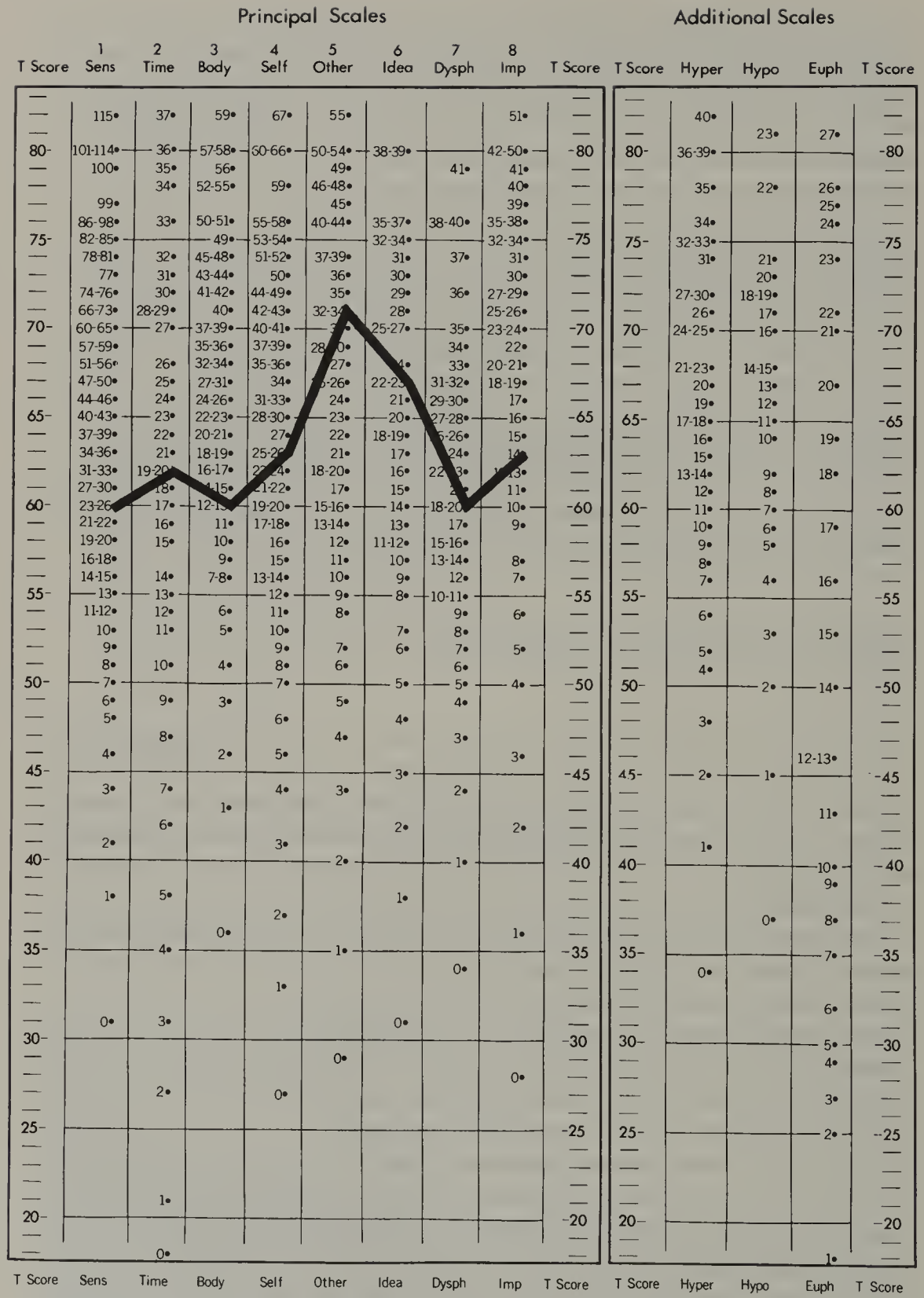


FIGURE 17-2.
EWI profile of Mr. Arthur, a schizophrenic with history of behavior disorder.

attention to the sequence of day and night." The latter item should raise the issue of fluctuations in level of consciousness and the possibility of dissociative experiences. He does not seem to be well anchored in the present and reveals past orientation, particularly preoccupation with reincarnation: "I seem to have lived another life before." He lacks the experience of progressing in time. This is demonstrated by the following items: "My age does not seem to change." "I feel I have always been old." "Time seems to stop altogether; everything is suspended and dead quiet." This feature is characteristic of young schizophrenic patients. Our experience shows that it gives rise to despair, particularly in young patients who were ambitious, intelligent, and active premorbidly.

Somatic complaints suggestive of disturbed body image are present: "I have a sense of extraordinary looseness in my muscles," "I am rotten inside," "I do not like to touch my own body," "There is absolute silence in my head," "My reflection in the mirror looks strange." The last item suggests that changes in body image are associated with changes in experiences of personal identity.

This is supported by a high score on self perception. It is higher than his score on body perception, indicating that, subjectively, the patient feels that the problem is essentially one of personality disorganization and only secondarily a problem of body integration.

Perception of others represents a conspicuous peak and is well within psychotic range. T-score is 75. Item content strongly suggests the presence of distortion assuming paranoid proportions. This distortion facilitates destructive acting-out: "People deceive me all the time," "People smile strangely at me," "People look fierce and dangerous," "Most people hate each other," "My enemies are everywhere." One gets the impression that the patient's affectivity is quite intense. That perception of others is higher than self perception indicates that the tendency to act-out against people is much more likely than the tendency to act-out against himself. Since the scales are high, one would also expect that, in acting-out, the patient might also be hurting himself indirectly. Therefore, rash behavior, accident proneness and cynicism are likely to influence his overall behavior.

The elevated dysphoria scale indicates dysphoric affect, and muddled thinking is suggested by the ideation scale. Bizarre thoughts are present:

44. I seem to have discovered the secrets of the universe.
147. I often do not know whether I am awake or asleep.
275. I have strange thoughts much of the time.
278. People eventually will turn into animals.
396. I live in a dream world.

Combined analysis of the profile and item content reveals that the patient is much more likely schizophrenic than psychopathic. Sensory anomalies, muddled thinking, and inappropriate engagement in time strongly suggest that behavior problems are secondary to a serious mental illness, probably schizophrenia, characterized by

excitation, sensory overloading, depression, paranoid ideation, and destructive acting-out.

PSYCHIATRIC REPORT

Space limitations confine us to a few excerpts from the psychiatric findings.

> As a small child, this patient was fascinated by fire and nearly burned down two different houses. Later he was inclined to steal and was always in trouble in school for this. He has a history of skin trouble. Case history indicates that as his behavior gets worse, his skin condition gets better. For the last six years, his skin has been much better than at any time during his life, and his behavior, according to his family, has gotten steadily worse. Three years ago, he was advised to see a psychiatrist.
>
> He has often stolen from his parents, sisters, and friends, taking items such as cameras and money. He is a great liar. He seems to have frequent car accidents. Following one of these, he spent three days in jail for disorderly conduct. However, the police felt that he was not a typical delinquent. At their suggestion, he was hospitalized.
>
> In the interview, he was rather quiet and, although unwilling to talk at first, was persuaded to do so. He feels that he has been unwell recently because it seems that he is "in a dream." He believes that he must be held responsible for the things he has done. He is not, however, completely sure how these actions came about, and this apparently puzzles and concerns him.

FOLLOW-UP

The conclusions based on the EWI were borne out by subsequent events. A few days after testing, the patient was apprehended by the police and sent to a mental hospital. Not being able to detect the usual signs of schizophrenia, his psychiatrist discharged him. A few weeks later he was again arrested while breaking into a house, and sent to a reformatory. However, the reformatory authorities, impressed by his odd behavior, sent him to a mental hospital where he received the usual psychiatric treatment. His improvement was so remarkable that he was able to continue his studies in the hospital and even after he was returned to prison.

Third Case: Mrs. Roberts, Neurotic Depressive

This 27-year-old patient was independently diagnosed as neurotic depressive. We include her case to provide a contrast with the previous cases of schizophrenics.

Her EWI profile, shown in Figure 17-3, is typical of this diagnostic category. The peak of the profile lies on the dysphoria scale, with self perception as the second highest peak. The dysphoria scale is significantly higher than the rest of the scales, indicating that depression is primary in this case. Sensory perception is relatively

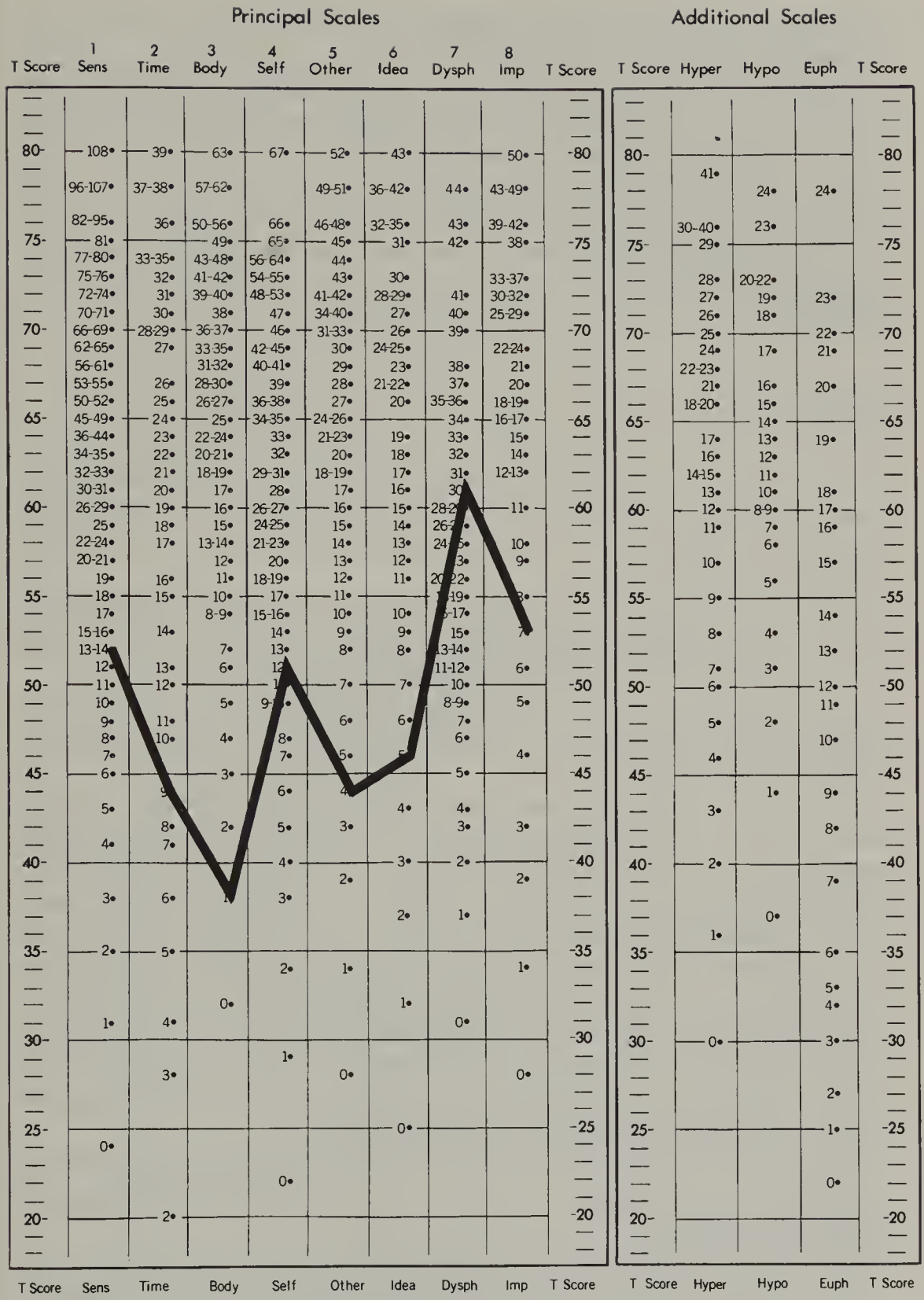


FIGURE 17-3.
EWI profile of Mrs. Roberts, a neurotic depressive.

low, much lower than would be expected from schizophrenics or psychotic depressives.

In contrast with the previous cases, this patient's profile suggests that her depressive mood occurs in the context of a relatively stable world. The ratio of self perception to perception of others is typical of depressive patients, the former being higher than the latter. This ratio is consistent with the tendency of depressive patients to be self-derogatory and intropunitive. Since the world continues to be the same as it has always appeared to these patients, their mood changes are more likely to be interpreted by them as a function of their own failure or as a matter of incomprehensible fate.

SUMMARY

This paper describes the Experiential World Inventory, a new psychodiagnostic instrument whose main objective is to measure the basic parameters of pathological experience. It brings to focus the role of disturbed perception in mental disorders, especially in schizophrenia.

The items of the Inventory are drawn from authentic experiences of actual patients, from accounts of normal subjects under the influence of hallucinogens, and from phenomenological literature dealing with psychopathology.

The emphasis in the test is on description of the patient's experience of himself in relation to the world of time, space, and people, rather than on personality dynamics or biographical material.

The test includes eight basic scales, each of which is made up of two equivalent parts. The area of perception is covered by five scales: sensory perception, time perception, body perception, self perception, and perception of others. The sixth scale, ideation, covers some aspects of thinking anomalies. The seventh scale, dysphoria, deals with depressive aspects of affectivity. The eighth scale, impulse regulation, deals with problems of emotional arousal and impulse control. Definitions of the scale and an explanation of their interpretive significance are provided.

Studies providing evidence of internal consistency and test–retest reliability in a variety of normal and clinical groups are documented. Similarly, a brief account is given of investigations dealing with various aspects of validity, demonstrating the sensitivity of the scales as measures of abnormality.

The capacity of the scales to measure changes caused by biochemical imbalance is supported by a study comparing normal premenstrual college students to a comparable control group.

Special emphasis is given to studies relating the EWI to various neurophysiological measures. These studies point to the great potential of the EWI as an instrument for the evaluation of psychological change in pharmacological studies.

Six phases of test interpretation are described: (1) description of the patient's reaction to the testing situation; (2) quantitative analysis; (3) configural analysis; (4) content analysis; (5) inferential analysis; and (6) integration of findings. These are demonstrated by three case studies.

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18

Dyschronia: Disorders of Time Perception in Schizophrenia

ALLAN COTT

"Nothing puzzles me more than time and space and yet nothing troubles me less, as I never think about them."

Charles Lamb,
in a letter to
Thomas Manning (1810)

"Time travels in divers paces with divers persons.
I'll tell you who Time ambles withal, who Time trots withal,
who Time gallops withal, and who he stands still withal."

William Shakespeare,
As You Like It,
Act III

INTRODUCTION

This paper describes the use of the metronome as a diagnostic instrument for the objective measurement of the experiences of duration and fluctuation of time flow in schizophrenia (Hoffer and Osmond, 1967; Aaronson, 1966).

The patients in this study were all treated with megavitamins. As their illness improved and the perceptual distortions receded, the distortion in their perception of time either improved or vanished.

Any discussion of the sense of time flow in man can best be introduced by reflecting upon two related matters of our own common experience. At some time during childhood each normal human being makes two discoveries of profound personal importance: birth and death. The discovery of death causes the greater impression, despite its delayed and gradual effect. Thus, the normal healthy child, learning that people die, does not brood on the fact. Nevertheless, its personal significance does not escape him. He may forget many other things learned in childhood; he will never forget this and with the passing of years its significance inevitably deepens.

The awareness of one's mortality brings with it a new element, because the knowledge that man dies causes the individual to anticipate his own death. This consciousness of one's mortal nature is a fundamental factor in any evaluation of man, for it is usually with anxiety that one foresees the termination of his own life, however far in the future he may hope it to be. The discovery of the fact of birth does not grow in terms of personal significance, but it has its function, as has that of death, in setting the terms of human life. Thus, the knowledge of birth and death invests the life of each individual with a temporal significance that is basic, and ultimately affects the evaluation of all experience (Brandon, 1966, pp. 142–143).

The enigmatic nature of time has been a subject for profound meditation by philosophers. St. Augustine in Book 11, *Confessions*, wrote:

> For what is time? It cannot be easily and briefly explained. It cannot even be comprehended in thought or the answer put into words. Yet it is true that in conversation we refer to nothing more familiarly or knowingly than time. Yet surely we understand it when we speak of it; we understand it also when we hear another speak of it. What then is time? If no one asks me, I know what it is. If I wish to explain it to him who asks me, I do not know. Yet I say with confidence that I know that if nothing passed away, there would be no past time; and if nothing were still coming, there would be no future time; and if there were nothing at all, there would be no present time. But, then, how is it that there are two times, past and future, when even the past is now no longer and the future is now not yet? But if the present were always present and did not pass into past time, it obviously would not be time but eternity.
>
> If any fraction of time can be conceived that cannot now be divided even into the most minute momentary point, this time alone is what we may call time present. But time flows so rapidly from future to past that it cannot be extended by any delay. For if it is extended, it is then divided into past and future. But the present has no extension whatever.
>
> We speak of past things as being drawn out of the memory. Yet it is not the things themselves, which have already passed, but words constructed from the images of the perceptions which were formed in the mind, like foot prints in their passage through the senses. (*In* Smart, 1964.)

G. Van Der Leeuw in his essay on "Primordial Time and Final Time" wrote,

> The riddle of time is the riddle of the beginning. We know that there can be no true beginning, for something has always gone before. In the beginning lies the whole past. The beginning is the past. Yet we say that we begin something, that we make a new beginning and we call the long list of such beginnings, time.
>
> We live in time. We live out of the fact that we always begin anew: on awaking in the morning, at the beginning of the year, with every task we undertake, with each move from one place to another.
>
> The mysterious divide between yesterday and tomorrow, the intangible now, in which and through which we have our existence, is incomprehensible to us. (*In* Campbell, 1957, p. 325.)

Bergson distinguished between spatial time and purely temporal time. Spatial time (the time of our clocks) is, according to Bergson,

> A hybrid concept, resulting from the incursion of the idea of space into the domain of pure consciousness. It is an experience of time that we have organized spatially, a sequence of segments. In reality there are no segments; nor is time homogeneous; one second passes continuously into the next and is likewise inseparable from those that preceded it. Real time is like a river or a melody. One can count seconds, because they are not time but space. In "temps-duree" there is no counting any more than one can dissect a melody into notes. The peculiarity of time is precisely that it passes through our hands like water, that it is intangible. When one announces the time, it is not time one speaks of, but only of the clock. Yet time, today's time, is our vital element. We like to imagine that we stand at a fixed point from which we look comfortably back into the past or expectantly forward into the future. But there is no fixed point, we are carried along by time, we are temporal, we are time. We can neither grasp nor hold fast a point in time, can neither grasp nor hold fast our own existence. (*In* Campbell, 1957, pp. 325–326.)

Wallis (1966) states that

> as regards time man is aware of a certain exterior duration to which he adjusts in his daily life, but he has no original consciousness of his interior time, his psychological time and does not think very much about it.

Even more than space, time has an emotional significance for human beings. Mood or affect is related to our perception of the flow of time. By using post-hypnotic suggestion to alter time perception, Fogel and Hoffer have shown that mood seems to be directly affected. An elevated mood coincided with post-hypnotic perception of the passing of time as rapid; a depressed mood coincided with the perception of the passing of time as slow.

TIME FLOW IN SCHIZOPHRENIA

Data will be presented to show that in schizophrenia the perception of duration of time, or time flow, can vary frequently each day, and that the perception of body, mind, and world time can be asynchronous. The instrument used in this study is a small portable electronic metronome with a built-in loudspeaker and a synchronized lamp. It is powered by a self-contained battery. The on-off switch and speed regulator are combined, and there is a separate switch when needed for attaining speeds from 220 beats per minute up to "white sound," when the discrete beats are lost and merge into a constant sound.

In this study, the schizophrenic patients who experienced distortions in time perception did not perceive the beat and flash of the metronome as a clock which segments time; they related to it as a measure of their perception of the flow of time. They were immediately aware of the examiner's purpose in introducing the metronome into the examination. Those patients whose time perception was not distorted did not react to the metronome, nor could they understand the purpose of its introduction into the examination proceedings. The rate of speed was immaterial to this group.

THREE MAJOR AREAS OF TIME

In the measurement of the flow of time as it is experienced it seems that we have at least three major areas of time between which we must be able to discriminate: mind time, body time, and time in the world around us. In schizophrenia any one or all of these can be asynchronous and produce many of the classical and still puzzling symptoms of the illness. Several patients in this study reacted to the highest speed on the metronome (discrete beats merging into a steady sound) with the recollection that when they were catatonic they experienced the flow of mind time at that rate. Extremely disabling is the condition in which the flow of time varies frequently or in those instances when the three levels of time are dissonant.

CASE HISTORIES

The following case histories describe the variations in the responses of ill patients to the metronome used as a diagnostic tool in the investigation of temporal distortions.

R. S.—Female—Age 20—Schizophrenia

The patient stated spontaneously that since her illness began she "hasn't had a place in time." This made her feel like she "isn't going anyplace," and her future seemed

bleak. One day blends into the other in a monotonous routine, and she can only take one day at a time without any plans for the future. When she was asked to set the metronome, she could not find any point on the scale where time felt right for her. When she was asked if she perceived time flow at different rates in her mind and her body, she realized why she could not set the metronome. She then set it at 108/minute for her body speed and at 30/minute for her mind speed. The metronome experience became upsetting to her and she began to cry because she couldn't "pin-point" time, and this made her feel her time distortion more acutely. She did not feel out of synchrony with world time. When the metronome was set and allowed to run for a while at 200/minute, she said that it was annoying her because she was trying to "keep up" with it and could not. She cried again when she said, "You're right, the world does feel like it's passing me by; I thought I didn't care, but that's a bad feeling to have because I do care. I have to care."

M. U.—Male—Age 18—Schizophrenia

States that the awareness of time bothers him because he feels that he should be doing something and he isn't doing anything—he isn't functioning. He dropped out of college after one semester, feels withdrawn from the world, and would like to "curl up in a ball and stay there." During the metronome test he cried when he realized that he was unable to set it at any speed which was comfortable for him. He finds the corollary in his life, that he has never felt comfortable anywhere at any time. He was asked to allow the metronome to run at increasingly rapid speeds for several minutes. He smiled and said, "It's strange, but as you speed it up, it speeds you up—you become used to it and it feels good. Then, when you slow it down, it feels sluggish and you feel that you have slowed down and your mind is beginning to lag."

N. W.—Female—Age 38—Schizophrenia

The metronome running at 180/minute made her very anxious and upset. Reduced to 30/minute she found it very irritating and said that she would rather have it off. When she was asked to set it at a speed comfortable for her, she tried the entire scale and cried when she realized that she could not find any point on the scale where time was comfortable for her. She stated that regardless of how she perceived the flow of time to be in her daily existence, she is "never comfortable in time." She drew a parallel between this dislocation in time and the inability to ever really feel well. When two months had elapsed on the megavitamin treatment and she had made improvement which was measured by reduction in her perceptual distortions, she was re-tested and found the slow speeds to be very annoying and 200/minute was most comfortable. With the speed gradually increased beyond 200/minute she was

surprised to find that she could endure the faster beat. She tolerated 1,000/minute for a short time and then reported that she began to experience the premonitory signs of anxiety, dizziness, and ringing of the ears which always preceded her perceptual distortions prior to treatment.

E. B.—Female—Age 21—Schizophrenia

The patient complained freely about her distortions of space, of which depth and distance were most distorted. She recalled that at the onset of her illness she felt menaced because everyone seemed to be crowding in on her, and she would frequentlypush them away. She misjudged distances and often bumped into furniture or other objects. While sitting 10 feet from me, I asked her to estimate the distance between us and she answered, "about 3 feet." She did not complain about her temporal distortions until I questioned her about it while using the metronome. When I set the speed at 200/minute, she pleaded to have it shut off because it made her very anxious. She could not find any speed which was comfortable for her, but accepted 30/minute, adding that even this was too fast. In several minutes she became upset again and said that it made her feel so speeded up inside that she could not breathe. She felt tearful and anxious for 15 to 20 minutes after the metronome was turned off, and then said that she was tolerating the feeling of faster time-flow better. On a subsequent visit she reported that time was literally standing still and she could not bear this feeling. She does not care about the other perceptual distortions; only the distortion of time bothers her and "it's driving me crazy."

V. K.—Female—Age 18—Schizophrenia

Had been hospitalized for 14 months, after making suicidal threats. During her period of hospitalization a diagnosis was not made. Brain damage was suspected and EEG studies showed normal tracings. Two 3-hour glucose tolerance tests revealed hypoglycemia. The HOD test showed perceptual distortion. "The world has become timeless for me." The EWI showed that "none of the scores reach the average of psychiatric norms—her problems are mainly problems of work adjustment. This is supported by the prominence of time disturbances. This scale is the only one that approached the psychiatric average. There is, therefore, evidence that this girl is not in tune with objective time. She experiences herself younger than her real age—does not feel the process of inner growth, nor does she seem able to deploy her energies in time." When she was questioned about work, she laughed and said that it is completely incomprehensible to her how her father can arise every workday at such an early hour, commute by train to work, then return home every evening. She

found it even more ludicrous that her father should want to do this. She would never do it.

During the metronome test she was disturbed by all speeds and complained that it made her dizzy. At high speeds she felt the impulse to cry and became agitated. Nor could she tolerate the lowest speeds. She shouted at the examiner to turn it off. The sound was turned off, but the light remained flashing, and she continued to feel great discomfort and unhappiness at 200/minute. Set at 40/minute it was not as disturbing, but it gave her a feeling "as though I am extending." She explained this as an extension through time and space. She added that the combination of the clicking sound and the flashing light makes her so upset that she feels like vomiting.

D. J.—Male—Age 30—Schizophrenia

The patient stated that he perceived the flow of time through his mind to be very rapid. He set the metronome at 400/minute for this speed and said that his body speed is slower occasionally, but usually equal to his mind speed. When reading, he becomes impatient because time is rushing through his mind and this exasperates him. Time in the world around him moves much more slowly than he does and this leaves him constantly irritable. When he enters an elevator, it must start at once or he cannot tolerate it. He frequently tries to ride a bus but must leave it and walk rapidly if the bus is in slowly moving traffic. He finds it difficult to walk on a street with people because they move so slowly and get into his way. He cannot tolerate old ladies with shopping bags because they walk slower than everyone else. People boarding or getting off subway trains make him frantic because they move so slowly. He will frequently run half a block or more in order to cross a street before the traffic signal changes, to avoid waiting on the curb for the next change. He has often narrowly avoided being struck by a car. While making the above notes, the examiner allowed the metronome to run at 40/minute with full volume. After several minutes, the patient commented, "The metronome is slowing me down inside—it makes me feel calm." Asked if this is a pleasant sensation, he stated that it was very tranquil.

R. J.—Female—Age 27—Schizophrenia

Recurring periods of depression and fatigue with many perceptual distortions and misperceptions of the intentions of other people. She stated that she had taken psychedelic substances several times and the experiences "seemed to have a very permanent effect of some kind." Asked if the effect was a disturbance or awareness of her time flow, she volunteered the information that the speed of flow through her mind is always faster than through her body. She set the metronome at 200/minute

for her mind speed and at 90/minute for her body speed. The speed of time in the world around her is always changing, and every change "puts me off balance in time." She constantly makes efforts to "pull my mind speed back, or advance my body speed" because "that would be the ultimate in comfort." She adds that she doesn't even know if that's possible. She has no hope of synchronizing all three speeds. She would be very happy to succeed in synchronizing her mind speed with her body speed or vice-versa. Whenever she has to do something that requires physical effort, like merely walking somewhere, if her mind speed is very rapid she feels that her body does not have sufficient energy to implement the effort.

D. C.—Male—Age 18—Schizophrenic Reaction Following Prolonged Daily Uses of Marijuana and Hashish

He stated that his thinking slows down greatly at times, and at other times it "races around like a windmill" and then time goes rapidly. When time slows down to normal he feels normal; but when it slows down below normal he feels bored and depressed. Asked to set the metronome for the speed of time flow through his mind, he set it at 40/minute. When the time flow feels "like a windmill" he set it at 300 to 400/minute.

R. B.—Female—Age 23—Schizophrenia

The patient had become ill while in college. She suffered from chronic depression and fatigue and had many perceptual distortions. She set the metronome at 66/minute as the speed at which she perceived time flow. In three minutes of work with the metronome she initially felt rushed, pushed, and irritable at 300/minute. She soon adjusted and reported that she was feeling better and better as I gradually increased the speed. When the speed reached 600/minute, she said, 'I could get up and dance now." Prior to this remarkable change in mood she had been profoundly depressed, fatigued, and exhausted, and in three minutes her depression had been altered. I allowed the metronome to continue for five minutes longer while she talked in a happy animated manner. Within five minutes after the metronome was stopped she slipped back into her depressed state and once again complained of great fatigue.

S. B.—Male—Age 28—Schizophrenia, Hospitalized

The metronome set at 30/minute elicited the response that it "annoys the hell out of me." It made him angry, and he felt like throwing the metronome against the wall.

He then stated that, "it seems like you're testing emotions. I know so little about my emotions." When I asked him to set the metronome at a speed most comfortable for him, he set it at 180/minute and reported that after a few minutes his body speeded up to the metronome speed and he felt very good. He smiled, then laughed and sang a few lines from "You Are My Sunshine."

B. L.—Female—Age 20—Schizophrenia

She complained of feeling emotionless, that she is not really fatigued, yet cannot do anything. She does not like being awake because "when I am awake there are more hours to live, so I would rather be asleep." She states that her perception of time is "very messed up." Sometimes time flows very quickly, sometimes it does not move at all. Her severe depressions occur when time flow is very slow or not moving. She has her greatest difficulties and suffers most when her speed of time flow changes. It can frequently change in minutes from very rapid to very slow and back again to very rapid. At times each new rhythm can last hours, days, or months and then change. Her thoughts can flow so rapidly that she cannot even contemplate them or have the time necessary to communicate them and then she sits in a state of catatonia. At other times her time flow slows almost to a standstill, her mind is blank and at these times she also sits in a state of catatonia. She usually hurries to get wherever she's going, even if she has no destination. She feels that she must hurry because she'll miss something if she doesn't get there. At other times she feels "outside of everything," that everything and everyone is moving rapidly and she's not moving at all. At these times one hour seems like a day—she will arise at 9:00 a.m. after having slept for 12 or 14 hours, and by 10:00 a.m. she would be surprised to learn that it was not already 5:00 p.m.

D. G.—Female—Age 25—Schizophrenia

The patient stated that time flows quickly through her mind, even though she is immobilized by obsessive thoughts. At times it takes her hours to move into the shower and then hours to get out. Asked to tell me how she experiences the speed of time flow during such periods of immobilization, she smiled broadly when I turned the metronome up to the highest speed and said, "Yes, that's how fast it goes."

P. H.—Female—Age 34—Schizophrenia

Was referred by her analyst for examination because of chronic fatigue. The patient complained that she is "always tired, do not have a good sense of time and am always

late for things and don't care, because I can't do anything about it." She stated that time passes slowly and she feels bored. She works as an editor and finds various ways to make time pass. She prints very carefully and painstakingly instead of crossing out and writing in. She is acutely aware of the discrepancy between her body speed and her mind speed. She said that her body usually "runs down before my mind does." When the metronome was set at 200/minute, she related it to the feeling of time flow when she is doing something she enjoys, "like shopping." 30/minute feels like the speed of time flow as it usually is for her. With the metronome set at its highest speed (the discrete beats merging into a steady hum, the light flashing with a stroboscopic-like effect) and asked if she ever experienced time flowing at that speed, she promptly answered that it was precisely like that when she was having petit mal seizures.

Between 1952 and 1959 she had about ten seizures which consisted of "having a dream while talking to someone." She added that the contents of the dreams remind her of some of the questions on the HOD test, and that the seizures were really dreams which occurred while she was awake. The metronome sound made her feel the very rapid passage of time she experienced during the seizures. She recalled that the feeling of asynchrony in time began very early in life. At age 6, while on her way to school, she would stop to pick flowers and daydream and always arrive late. When struggling to do something on time she has two speeds, either in her mind or in her body, struggling to see which will predominate. Frequently the slow speed is slower than 30/minute, the fast speed about 400/minute.

J. W.—Male—Age 17—Schizophrenia, Hospitalized

Patient stated that he had for several years been subject to seizures during which he would fall and lose consciousness or, at times, merely lose awareness. He clarified this by saying that he did not know what he was doing. Immediately preceding a seizure, time would begin to slow down very rapidly, then come to a complete halt, and he would fall to the ground. During the slowing down, he would complete whatever movement he had begun, but in slow motion. When he aroused from the seizure, he would be confused and not oriented in time. To him the elapsed time would seem like seconds, and he would learn that an hour, two hours, or half a day had elapsed. At the time of the examination he had not had a seizure for four months. Testing with the metronome did not reveal any abnormalities in perception of time flow.

D. K.—Male—Age 9—Childhood Schizophrenia

Illness began at age 6. During his third visit he spoke about his difficulties in school the year before when he could not do any homework that required writing. He hated

writing because his thinking was so much faster than he could write. This year "it's different because my thinking is slower." Examination with the use of the metronome showed his thinking last year was at the top speed, 1,000 to 2,000/minute. Present thinking speed is 200/minute, while his speed of time flow during writing is 70/minute.

T. B.—Male—Age 10—Childhood Schizophrenia

Extremely hyperactive, paced around the room during the examination. With the metronome turned up to 1,000/minute he paced rapidly and smiled; then he approached the examiner, performed his usual ritualistic hand movements, alternating with gleeful hand clapping, all performed in time with the metronome. When the metronome was slowed to 100 to 120/minute, the ritualistic hand movements ceased and he rocked his body in time with the slower rhythm. His parents commented that he has burned out several phonograph turntables because he always plays all records at the highest speeds. He lost interest in the metronome when it was slowed below 100/minute.

J. V.—Male—Age 8—Autism

He exhibited extreme hyperactivity and incessant body rocking. During the examination he sat cross-legged in a chair and rocked with such vigor that the chair moved across the floor. When the metronome was turned on at 200/minute it attracted his attention. He stopped rocking, looked in the direction of the sound, and his face lit up in a wide grin as he listened intently. When the metronome was slowed to 50/minute he promptly lost interest and resumed rocking with his former vigor.

In both cases (T. B. and J. V.) the experiment was repeated three times with identical responses. Since both children were without speech, nothing could be learned of their subjective response to the visual and auditory stimulation of the metronome.

S. B.—Male—Age 14—Childhood Schizophrenia

Patient described auditory and visual distortions, but did not speak of distortions of time until he was asked to set the metronome at the speed at which he perceives time to be flowing. He set it at 47/minute. When the speed was increased to 220/minute he said it bothered him, explaining that it made him feel like "time is going to run out." He feels that when time will stop, something disastrous will happen, "like the world is going to blow up" or he will no longer be here when time stops. He

revealed that he is constantly preoccupied with time; that it is running out and he will not have time to do things. This causes him great concern, yet he did not reveal this to anyone because he felt that it would not be understood. When the metronome was used he realized that the examiner would know exactly what he was feeling. He finished by saying that when the metronome is on he cannot wait until it stops because it accentuates his fear of time running out. This feeling is less acute when the sound is shut off and only the visual input is stimulated.

This patient had been smoking marijuana since age 13. He explained that whenever he smoked he became synchronized in time and only then did he "feel good" and lose his fear of "time running out."

N. M.—Male—Age 24—Schizophrenia, Induced by Self-Administered LSD

The patient stated that time flows either very rapidly or it slows down, but it is never really slow. The slowing down is merely a variation of the speed. When the metronome was set at 140/minute he reported that this was the speed he felt in his body. When asked about the speed of time flow in his mind he replied, "Up there I'd like it not to exist." He explained that the rapid flow of time in his mind "makes things happen very quickly and then they're gone. Nothing stays. Something happens, I'm aware of it and it's gone. Nothing stays, only my compulsive habits stay. It doesn't matter how long it takes an event to occur, when it's over it's gone, like it never happened. Like your whole childhood. It happens and it's over, it makes me feel afraid because that's my life and it's over. When I smoke grass, everything slows down. That's the comforting quality of grass." He added that time is flying by and soon he'll be dead and everybody will be dead. He revealed that he had resumed smoking marijuana because only then does time slow down and become comfortable so that he doesn't worry about dying. He said that the faster his perception of the rate of time flow is, the "crazier" he feels. On his way to the office today he came 3 or 4 miles by taxi and the ride "seemed like a flash," that he had barely settled down when he had to get out. He reiterated that he could be very happy if "everything didn't go so fast, because then I wouldn't worry so much about not having much time left to live."

R. G.—Male—Age 24—Schizophrenia

Patient is a stutterer. He reported that he feels two speeds of time flow—one in his mind, another in his body. His ideas stream rapidly in circles. He set the metronome at 180/minute and reported this as the speed of time flow in his mind. He stated that

he feels lethargic in his body and set the metronome at 30/minute for his body speed. He added that whenever the gap between the two speeds is narrowed, he feels better. The greater the gap, the more "stuck" he feels. When the gap is greatest, he experiences obsessive, ruminating thinking. Ideas race round and round, song lyrics become repetitive. Questioned about time perception preceding a suicide attempt, he said that the gap became the most exaggerated he had ever experienced and then everything became unreal and the time distortion was so great that "there was not time to go on. There was no tomorrow at all." At this point he took a massive overdose of tranquilizers and sleeping medication.

M. A. P.—Female—Age 28—Schizophrenia

The patient related that time flow in her mind and body was frequently different and both speeds often fluctuated, sometimes so frequently during each day that she felt "like it's driving me crazy; it's like you don't know what's going on." When she is occupied with work, time goes too fast and she can't keep pace with the flow of time in the world around her, with the traffic, with work or "with anything." Traffic moves so rapidly that she marvels at how people can drive, how they can find their way to where they are going, and how they can find directions. In crowds, people look like they are moving very rapidly as they did in old movies. At the time of her suicide attempt the flow of time had begun to slow down and then become "still." At this point she tried to take her life.

H. S.—Male—Age 29—Schizophrenia

The patient stated that he does not know what to do with time; does not know "how to kill it." He set the metronome at 40/minute for his mind and body speed. When questioned about his perception of time flow at the time of his suicide attempt, he recalled that time had stopped. He shrugged his shoulders and said of the episode, "Yeah, time stopped, there was nothing to do, nothing was happening, so it didn't matter, so I tried to kill myself. There was nothing to live on, there was nothing. When time stops, it's like you're dead."

P. C.—Male—Age 30—Schizophrenia

The patient stated that he always felt like he was fighting against time; that time was rushing and passing him by unless he pushed himself constantly. During a period of employment as a bus driver on an interstate route he worked "all the time" until his

superiors had to stop him and finally discharge him for fear that he would have a serious accident. He took extra shifts until he would become exhausted. He perceived the speed of time flow in his mind and body at that time to have been 1,000/minute. He was constantly irritated with everyone around him because he felt that they moved in slow motion and did not accomplish anything. For several days preceding a suicide attempt he felt that time had stopped and that he experienced "an external feeling." He told his parents that "time was running out" and shortly afterward he dug a toenail clipper into his arm and severed the blood vessels.

T. B.—Male—Age 20—Schizophrenia

The patient stated that the speed of time, as he perceived its passing, was the same in his mind and in his body. The usual speed of flow was 30/minute on the metronome. He always remained synchronized with time in the world around him. In the period preceding a suicidal attempt the flow of time began to slow down gradually. He felt that if it slowed further it would stop and he "couldn't exist peacefully." At this point he took an overdose of tranquilizers.

J. S.—Male—Age 41—Schizophrenia, Hospitalized

The patient stated that he stayed indoors all day long and paced. He set the metronome at 30/minute. When asked about his perception of the speed of time flow, he added that his life consisted now of nothing more than waiting for time to pass. All day long as he paced his small apartment he thought of the duration of time and why it "wouldn't hurry up. When will the clock show 4:00, then 4:30?" His preoccupation with time had begun with the onset of his illness five years before. It began insidiously and now occupied his awareness at all times. He understood that his distortion of time perception made everything he did seem boring because everything lasted for so long or required so much time to do. He said, "I would like to sit down and read a book and get absorbed in it as I used to instead of worrying about how long it will take to get to the end." He explained his pacing indoors instead of walking outdoors by saying, "because I have no destination." He said that it was difficult to explain why he had to pace, but he felt that only when he moved through space did he have the feeling that time was flowing. When he sat in a chair, he felt that time was standing still.

W. F.—Male—Age 13—Schizophrenia

Illness began at age 3. The patient set the metronome at 180/minute and stated that this was the speed with which his ideas rush through his head, and he finds it most

disturbing. He then set the metronome at 30/minute and said, "That's how it was many years ago and that's how I wish it was again." The patient's mother had described his behavior at home "as if he was a motor running, but he's standing still." During every visit to the office he paced rapidly and constantly around the room. During the testing, with the metronome set at 30/minute, he paced about the room in exaggerated slow motion, saying that he wished it could be like that. Eight months later, when treatment had been in progress for one and a half years and he had achieved such marked improvement that his parents had reported he was rapidly approaching a cure, he was retested. He spoke about his improvement, stated that he felt he was finally getting well and said, "I can show you on the metronome how it is." He set it at 200/minute and recalled that this was the speed with which time flowed in the past when he had to pace constantly. He then reset it at 60/minute and said, "This is how it is now and it feels fine."

J. G.—Male—Age 25—Schizophrenia

Questioning about time evoked the following: He has great difficulty in keeping appointments on time. Time generally passes very slowly for him, and he looks at his watch frequently to see "if it is already 5:00." During the metronome test he perceived time flow in his mind and in his body at a speed slower than 30/minute. He stated, "I have a very slow conception of life. I move very slowly." When the speed was increased to 200/minute he exhibited anxiety and felt "like someone is out to get me." He added that he felt annoyed and requested that the speed be decreased. He chose 80/minute as the ideal speed for him and said that he would like to have that speed in his brain because it made him feel good. When the metronome speed was accidentally increased to 85/minute, he immediately reported that he believed that the speed had increased and that he liked the previous speed better.

F. F.—Male—Age 24—Schizophrenia, Hospitalized

When the patient was tested and questioned about his perception of time flow, he was found to react normally. He recalled that when he was acutely ill, time flowed very slowly and he perceived other people's speech as being very slow. He believed that everyone was deliberately speaking slowly to him in order to annoy him, and this would infuriate him. He was most annoyed by the slowness of his grandfather's voice and of his college classmates who lived in the south. He consumed many No-Doz capsules because he felt they accelerated time. He also drank frequently during the day because alcohol would, for brief intervals, make him feel more comfortable in time.

E. T.—Female—Age 22—Schizophrenia, Hospitalized

Patient said that she perceived the flow of time in her mind to be very fast usually, yet "sometimes it goes really slow." When the metronome was set at 180/minute it seemed slow to her and she asked in amazement, "Is that fast?" When the speed was slowed to 70/minute, she complained that it felt "horrible," and asked that it be turned off. She said that it made her feel like time was stopping because the next beat would never come. Her perception of time flow changed very quickly and five minutes later 80/minute was very comfortable and 180/minute was too fast. She added that whenever she spoke, the words seemed to come out very slowly (actually, she spoke at a normal rate). When other people spoke to her, they seemed to speak so slowly that she could not listen.

J. S.—Female—Age 24—Schizophrenia

When the metronome was set at 30/minute she cried that she could not stand it, and when the speed was increased to 200/minute she smiled and said that this made her feel good. She enjoyed this speed for several minutes and then her anguish returned and she said she is tormented by the need to compartmentalize time; to know in advance exactly what she will do during each hour of this day, and the next day; how long it will take to perform each task and how long each friend will visit. She feels hurried and breathless in New York because as trucks and buses pass on the street they mark the passing of time for her. Each conclusion of a radio or TV program disturbs her because it marks the passage of another segment of time.

A VALUABLE DIAGNOSTIC TOOL

The metronome, as presently available, with a synchronized light, emerges as a valuable diagnostic tool for the quantification of aberrant time perception in schizophrenia. With some future modifications it may become a therapeutic tool of great value in adjusting abnormal time perception. In many of the cases reported in this paper depression was influenced favorably merely by increasing the patient's tolerance for a greater speed on the metronome. In several patients depression was influenced adversely by decreasing the speed below the rate which they find to be comfortable.

A number of the patients tested recalled that when they were catatonic and immobilized they did not have a poverty of ideation or a marked slowing of time flow but rather such a rapid flow of time and thought that they could neither communicate nor move at such speed.

TEMPORAL DYSPERCEPTION

The perception of time flow can be changed in many different ways, some of them still only just glimpsed. For most people spatial changes are easier to communicate than are temporal ones.[1] None of the patients tested in this investigation spoke of distortions of time perception when relating their symptoms, while most complained freely and eloquently of the distortions of space, distance, and body perception. It seems that our investigation of the time distortion in schizophrenia with the use of a metronome, which allows the measurement of time flow, reveals the emergence of a new group of psychiatric conditions. These are conditions in which time alone seems to be disturbed, with few, if any other, perceptual anomalies. Osmond has suggested that these conditions can be subsumed under the name Dyschronias.

In light of this knowledge a psychiatric examination of any patient cannot be considered thorough or complete unless the examination includes an investigation of temporal dysperceptions.

Evaluation of the perception of time flow can give lifesaving information about suicide potential in any schizophrenic patient.

Many patients suffering from temporal dysperceptions use marijuana or other drugs as means of finding temporary relief from the crippling effects of the symptoms resulting from these distortions.

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[1] On the HOD test all or most items for distortion of time perception were answered as true and the time scale on the EWI was high.

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19

Metabolic Dysperception: The Role of the Family Physician in its Diagnosis and Management

BELLA KOWALSON

Almost two millennia have passed since Juvenal, the Roman satirical poet, wrote, "We should pray for a sane mind in a sound body." The fact that in Latin *sanitas* applies either to physical or mental health indicates that even at that time the interrelationship between body and mind was recognized. There are many systemic disorders which have been proved to produce manifestations of mental dysfunction.

I proposed the term Metabolic Dysperception (Kowalson, 1967) to reaffirm the above concept, one which has progressively been gaining new adherents. It was suggested as a preferable alternative to the unscientific and emotionally charged misnomer of schizophrenia, a label which adds to the burden of shame, guilt, inadequacy, and despair of those afflicted with it.

Metabolic dysperception may be defined as a biochemical disorder which culminates in varying types and degrees of abnormal sensory perception, with corresponding changes in thought, mood, and behavior. It responds favorably to megavitamin B3 and allied therapy if treated before irreversible changes have developed. As with other serious diseases, delay of treatment until grossly obvious

manifestations have developed increases the risk of an unfavorable outcome. It follows that any method which facilitates early diagnosis of this pandemic affliction should be diligently and widely employed.

As a family physician, I have used the card-sorting HOD Test (Hoffer and Osmond, 1961) since early 1966 as a valuable aid in identifying patients who may suffer from metabolic dysperception. Children, or others faced with a language barrier, may have the questions read and explained to them by a parent or other sympathetic adult. The manual which now accompanies the test (Kelm et al., 1967) has explicit instructions for its administration and interpretation. The repeated use of this test, and the correlation of the various scores with clinical findings, are helpful in differential diagnosis, estimation of progress under therapy and, consequently, in prognosis. For practical reasons the HOD Test was not employed for general screening purposes, so the results obtained cannot be interpreted to indicate the incidence of mental disorder in the total patient population. The test was given when one or more of the following criteria were present:

1. Past or recent personal or family history of mental illness.
2. Multiple, unaccountable, and apparently unrelated symptoms.
3. Abnormal attitudes and behavior, even in the presence of definite nonpsychiatric disease.
4. Problems of adaptation during periods of increased physiological stress such as adolescence, the postpartum period, or the menopause.
5. Failure of adequate adaptation to emotionally stressful situations: social, occupational, educational.
6. Marital conflict and other intrafamilial discord.
7. Educational underachievement, including perceptual and learning disorders.
8. Frequent overindulgence, by choice or compulsion, in the consumption of alcohol.
9. Abuse of hallucinogenic, stimulant, or sedative drugs.
10. Delinquency in its various manifestations.
11. Depression, with or without contemplated, threatened, or attempted suicide.

An unexpected harvest of elevated scores was garnered. Almost one-third of the tests showed evidence suggestive or diagnostic of metabolic dysperception.

One feels justified in endorsing the widespread use of this easily administered test as a public health measure in schools, colleges, and correctional institutions. Many cases of undiagnosed incipient or established mental disease would be discovered.

Mental and physical illness do not offer reciprocal immunity. Further

investigation revealed a preponderance among metabolic dysperceptives of the following manifestations:

1. Signs of moderate to severe deficiency of water-soluble vitamins, especially ascorbic acid, which plays a vital role in adrenal metabolism and the reaction of the body to stress. This was indicated by the prevalence of unaccountable bruising, swollen, bleeding, and infected gums, and loose and prematurely carious teeth. A lingual vitamin C test (Cheraskin et al., 1964) has been used routinely as a diagnostic aid and to follow progress with replacement therapy. Other signs of stomatitis, magenta tongue, and cheilosis pointed to other deficiencies, including that of riboflavin.
2. Evidence of autonomic imbalance with signs of sympathetic overactivity: facial pallor, peripheral vasoconstriction, hyperhidrosis, and dilated pupils leading to photosensitivity. Wearing of sun glasses was found to be beneficial. These people also exhibited oversensitivity to sympathomimetic drugs.
3. Endocrine disturbances such as secondary amenorrhea, severe premenstrual tension, hirsutism in young as well as in older women, and hypothyroidism. Depression was particularly intractable in women who were taking contraceptive medication.
4. Severe acne, resistant to treatment, in both sexes.
5. Secondary anemia and other signs of malnutrition.
6. Relative or reactive hypoglycemia, in some instances so severe as to prompt investigation for insuloma. Clinically, a craving for sweets was elicited, as well as aggravation of symptoms such as nervousness, headache, trembling, sweating, and faintness during periods of hunger. Care must be taken not to dismiss these as due to psychoneurosis. Five-hour or six-hour glucose-tolerance tests usually confirmed the diagnosis.

   These patients were instructed to take frequent feedings of a diet high in protein, low in carbohydrate, and moderate in fat. The quantity and type of the latter was adjusted in cases of obesity or hypercholesterolemia.

   Drinks or drugs containing caffeine were prohibited. Wheat germ was included as a good natural source of vitamin B complex, and for its rich content of phosphorus, which is vital in the intermediate metabolism of carbohydrate, fat, and amino acids. No cases of diabetes were found, although prediabetic tolerance curves were not uncommonly demonstrated. The use of artificial sweeteners was discouraged, in the hope of breaking the acquired preference for sweets. It has been shown that palatability does not necessarily insure nutritive efficacy (Pangborn, 1967).
7. Aggravation of symptoms during and following periods of supervening infection. The increase of vitamin dosage was therefore advised at such times. The

general rule of using antibiotics for specific indications only should be closely observed, particularly since many of them are known to inhibit the B-producing intestinal flora.

Apparently favorable results were reported with the use of an oral cold vaccine by a few people who had previously been subject to repeated attacks of upper respiratory infection. Tuberculin testing is advisable as an added precaution.

8. A history of having taken amphetamine derivatives for varying periods before onset of illness was not infrequently elicited. Several of those who did not recover from the drug effects after withdrawal had a family history of mental illness. Usually, but not invariably, amphetamines were taken for weight control. One mother of a retarded child reported that she had taken "diet pills" for one year previous to and during her early pregnancy. Although this does not furnish conclusive evidence, certainly amphetamines belong among the mounting number of drugs which should be restricted generally, and definitely prohibited in pregnancy.
9. Abuse of other drugs, mainly marijuana and LSD, was admitted by several young people. Most claimed to have given up the habit, but that the symptoms which it had precipitated had persisted. A few insisted that they had been "disturbed" or "unstable" previously, and had unsuccessfully sought relief in the use of these substances. These claims were not always substantiated by the few parents who were aware of the problem. They insisted that the psychedelic drugs had been the cause of abnormal behavior in their children, and a few feared that they were still being used.
10. An alcoholic current seems to course through the family histories of many cases. A large proportion have a problem themselves. Some are overt alcoholics. One wonders whether this is more than a coincidence of two common conditions. If so, is there a reciprocal relationship, or do they have a related etiology? In any event, the people who had high scores during periods of abstinence, and who benefited by megavitamin therapy, by definition, fell into the classification of being metabolic dysperceptives. Thiamine, the anti-neuritic vitamin, was added to their treatment, as was the anti-hypoglycemia diet which was usually indicated. Neglect of treatment seemed to induce resumption of drinking. Conversely, even moderate drinking led to an aggravation of symptoms, despite therapy.

Ambulatory patients whose scores warranted the diagnosis of metabolic dysperception were advised to undergo megavitamin therapy. A condensed and updated treatment program (Hoffer) is now available to physicians. A modified form of this treatment was used for children (Cott, 1969).

More serious cases, those for whom additional treatment such as ECT or other specialized care was indicated, required psychiatric consultation or referral.

The concept of a biochemical disorder was more readily accepted than the frightening and often derogatory implications of schizophrenia. An attempt was made to explain the nature of the illness, and the hypoglycemia which often accompanied it. Cooperation of the patient and of his immediate family was further ensured by suggesting reading material related to the subject, available from or recommended by the American and Canadian Schizophrenia Associations.

Several people refused treatment, or failed to continue it for adequate periods. They are probably obtaining help elsewhere. Some left this area, often asking to be referred to physicians who would supervise their program. A few stopped their medication prematurely, feeling that they had recovered, only to return when their symptoms recurred.

Of the patients who persisted with the recommended therapy, the rate and degree of progress was roughly, but not invariably, inversely related to the severity and duration of their illness. Improvement was shown by a fall in the HOD scores, clinical evidence, and the patients' subjective account.

Nicotinamide was generally used at first. If niacin was deemed preferable in older or unresponsive patients, it was added very gradually, so that a combination of both was given, at times to be supplanted by niacin alone. Cyproheptadine is usually effective in controlling the flushing (Robie, 1967), which may occur with the latter, especially early in its use.

Ascorbic acid was given concomitantly.

As often happens, substances which coexist in nature usually have a synergistic biochemical action. One or more of the following B vitamins were added when indicated or when progress was slow: thiamine and pyridoxine often, riboflavin and calcium pantothenate occasionally.

Patients were encouraged to take their medication consistently over long periods. They were told to expect a slow but gradual improvement and not to discontinue medication without advice. For irresponsible or depressed patients, supervision of medication by a relative was urged, especially when antidepressants or tranquilizers were prescribed. As the effects of the latter are usually potentiated by niacin, frequent adjustment of their dosage was necessary.

Eating and sleeping habits required correction. In most cases the antihypoglycemia diet was found beneficial. A snack at bedtime as well as during wakeful periods at night ameliorated the prevalent insomnia. If necessary, nonbarbiturate sedatives, hypnotics, or minor tranquilizers, preferably those that do not interfere with REM sleep, were given. Their use was gradually reduced with a warning to expect a few restless nights during the withdrawal period.

Appropriate advice was given in an attempt to remove or alleviate all extraneous

forms of stress—physical, emotional, or physiological. Concomitant medical disorders were treated. Participation in exercise and recreation was encouraged.

As improvement progressed an attempt was made to break the protracted pattern of invalidism. Methods for the development of self-confidence and independence were suggested. Those who did not return to work or resume their education were urged to become useful members of their household and their community. Reassurance often had to be given that the natural manifestations of human imperfection and individual idiosyncracy did not indicate a relapse.

A few young people, whose scores had been but slightly elevated and in whom treatment had been instituted as a therapeutic test, recovered so promptly and completely as to suggest that they had been suffering from subclinical pellagra (Green, 1970; see Chapter 20). A history of grossly inappropriate diet substantiated this conclusion. They were instructed to follow a diet rich in animal protein to provide the essential amino acid tryptophan, and were maintained on a high potency vitamin B and C compound.

Increasingly frequent reports of success in the treatment of metabolic dysperception with massive doses of niacin support the hypothesis that this disease is due, at least in part, to the diminished utilization, through faulty body chemistry, of this essential nutrient. This disorder, or a predisposition to it, is believed to be genetically determined (Huxley et al., 1964).

On a more optimistic note, I would like to introduce the concept of secondary metabolic dysperception by suggesting that similar syndromes may be produced through other mechanisms.

Without concrete genetic evidence, it is often difficult to differentiate between hereditary traits as opposed to the results of familial and cultural habits and customs. Neither can one ignore the possibility of various deleterious prenatal influences which can harm a potentially normal child, or even identical twins. Hyperinsulinism in infants of diabetic mothers is an obvious example.

I was once privileged to hear the late Dr. Bernhard Zondek, the eminent endocrinologist, dispute the widely held theory that diabetes is a hereditary disease. He attributed most manifestations of this metabolic disorder, which has a high familial and even racial incidence, to ill-advised types of diet over many years.

Hypoglycemia has been acknowledged to be a pre-diabetic condition. The significance of the hypoglycemia so commonly associated with metabolic dysperception, and its reciprocal relationship with adrenal dysfunction, merit further clarification. The nutritionally indiscreet habit, initiated in infancy, of consuming an overabundance of refined and concentrated sugars may well augment the prevalence of this condition. The contributing potential of endocrine disease, drug abuse, alcoholism, pellagra, and scurvy has already been intimated. Other nutritional disorders such as arise from anorexia nervosa and certain malabsorption syndromes may be implicated as well.

As yet, little is known about the prevention of this syndrome, and the prevalence of incipient cases is impossible to estimate. Most patients, by the time the diagnosis is first suspected, have been complaining of obscure symptoms for a long time. It is the responsibility of the family physician who sees them to make the diagnosis early in the course of their disease. Treatment at that stage is relatively simple and effective.

Investigation of other family members is at least as mandatory as follow-up of tuberculosis contacts. Conjugal pairs of dysperceptives do occur, and the potentially increased hazard to their children must be anticipated.

Let those whose pessimism is based on the hereditary implications of metabolic dysperception recall that there are other genetic defects for which we have learned to compensate. For that matter we are all predisposed by our inherent biological characteristics to drown if we fall into the water. We can learn to swim if we do not throw up our hands.

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20

Subclinical Pellagra

R. GLEN GREEN

Subclinical pellagra is a deficiency syndrome characterized by the presence of perceptual changes, affecting any or all of the special and proprioceptive senses, which results in neurasthenia. It is caused by a deficiency of or an increased demand for niacin, the administration of which leads to prompt disappearance of the syndrome complex (Green, 1970).

Because a disease is out of fashion is no reason to believe that it has disappeared. Since the addition of niacin to white flour in 1941, pellagra as a disease has gradually been dropped from the thoughts of clinicians when they consider differential diagnosis for various symptom complexes. Those of us who graduated from medical school after 1945 met with pellagra only in passing. It was mentioned in a historical fashion, as though the cause had been found, the vitamin given, and the disease cured. This is indeed a strange way to deal with a disease whose very existence depends on poverty, ignorance, and the avarice of man. It would seem to me that as long as people are poor they buy very little red meat and other expensive high-protein items. As long as people are ignorant they eat what pleases the taste

buds and satisfies the appetite. As long as there are people to whom profit means more than the health of the nation, the poor and the ignorant will be exploited by hucksters peddling puffed wheat, cornflakes, and "Instant This and That," nearly all at the expense of the protein and vitamin values of food.

HISTORY

Pellagra is described as the disease of the four D's—dermatitis, diarrhea, dementia, and death.

Casal in 1735 first recognized the disease and Frapolli of Italy in 1771 named it *pelle agra.* The cause remained obscure until Joseph Goldberger of the U.S. Public Health Service proved beyond doubt that faulty dietary habits were to blame. Funk in 1912 expressed the opinion that pellagra might be a vitamin deficiency disease similar to beri beri.

The first mention that I could find of subclinical pellagra was made by Spies (1938) in his paper "The Mental Symptoms of Pellagra":

> Subclinical pellagrins are noted for the multiplicity of their complaints, among which are many that are usually classed as neurasthenic. The most common of these symptoms are fatigue, insomnia, anorexia, vertigo, burning sensations in various parts of the body, numbness, palpitations, nervousness, a feeling of unrest and anxiety, headache, forgetfulness, apprehension, and distractibility. The conduct of a pellagrin may be normal, but he feels incapable of mental or physical effort, even though he may be ambulatory.

In a controlled experiment, Spies used as his subclinical pellagrins 199 patients who had a recurrence of pellagra each spring over a period of several years. Giving niacin in doses up to 600 mg a day, he found that there was prompt relief of the majority of neurotic symptoms, often within one to twelve days. The symptoms returned when a placebo was substituted. Vitamin B1 was one of the placebo tablets, and he found that the manifestations of peripheral neuritis associated with pellagra could be cleared with B1 but not the alimentary or central nervous system disturbances of pellagra. He also states the frequent repeated large doses of niacin prevented the development of mental symptoms associated with subclinical pellagra in mild pellagrins. There is no mention of illusions or hallucinations in these patients except for the advanced pellagrins. When these "psychoses" occur, the patients were always in desperate straits and required large doses of nicotinic acid. Death was not uncommon, because they were so sick that they could not eat and so psychotic that they would not eat.

During the past two years I have been investigating the occurrence of perceptual dysfunction in children and adults, as described by Spies. I have also studied the

illusions of these patients, and their response to large doses of niacin or its amide. Since the patient gets better with the addition of vitamin B3 and does not get better without it, it seems reasonable to assume that subclinical pellagra exists and that it can be cured by this vitamin. It has been my practice to use much larger doses than Spies used. Hoffer and Osmond (1960) and Hoffer (1962) suggested doses of niacin of 3 grams or more a day to treat hallucinations of schizophrenia.

Niacin or one of its derivatives is required by all living cells. It is an essential component of two coenzymes which function in glucolysis and tissue respiration. Niacin becomes a component of nicotinamide adenine dinucleotide (NAD), in which form the vitamin is used by the body. If there is deficiency of niacin or its precursor tryptophan, full-blown pellagra will eventually develop. It is reasonable to assume that lack of niacin would lead to some changes in the functioning of the cerebral cortex, resulting in changes of perception; that is, perceptual dysfunction.

DISTRIBUTION OF SUBCLINICAL PELLAGRA

Like pellagra, subclinical pellagra must occur worldwide. It is found where people are poor and cannot buy foods which contain niacin or its precursor tryptophan. Tryptophan is an amino acid found in meats and other protein foods and its conversion ratio to niacin is 60 to 1. Pellagra occurs where people are ignorant of proper dietary habits. While it is usually the poor who are also ignorant, it is not necessarily so. In these days of so-called instant breakfasts and dehydrated foods, the pop and potato chip meal is increasingly common. How often do you see high school students, and college graduates too, eating improperly? Poverty and ignorance are not restricted to any climate or geographic area. From the Arctic to the Antarctic, at any latitude or longitude, one can find unmistakable evidence of subclinical pellagra. It is more likely to occur in areas where there is a low living standard, as in South America, China, and India. Subclinical pellagra is also common in Canada, where the average income is twenty to forty times that of South American countries.

INCIDENCE

Prince Albert, Saskatchewan, is in the center of an area with a quite large Indian population (eight reserves in the immediate vicinity). I get referrals from the north up to 400 air miles away. By accident and design my office practice is about 85 percent Treaty Indians, the balance are Caucasian and some Metis (part Indian). I have been diagnosing subclinical pellagra for two years, and most of my current

patients have been observed during that time. My records from November 1, 1968 to March 1, 1971, show the following:

Diagnosed as definite subclinical pellagra	147
Diagnosed as suspect subclinical pellagra	36
Diagnosed as subclinical pellagra but did not return to my office	17
Diagnosed as likely schizophrenia	9
Total	209

I believe that about 10 percent of my patients have subclinical pellagra. The average income of the Indian population is about $1,200 per annum, including Family Allowance checks. The purchased food is often supplemented by moose, deer, rabbits, small game, and fish. I surmise that if this supplement were not available the incidence of the disease would be much higher. Among my Caucasian patients I estimate incidence to be about 3 to 5 percent, and among the Metis about 10 percent. If one could visit the pediatric out-patient department of a busy general hospital, I estimate that one case in ten would be found to have the common symptoms of subclinical pellagra, and most of these patients would respond to the administration of vitamin B3.

Incidence in Relation to Age

The condition exists in all age groups, from the very young to the very old. Diagnosis in a 2-year-old is uncertain, but one must suspect the condition when the patient responds to nicotinamide. There is no upper age limit. Indeed we must suspect subclinical pellagra in any old person who rather suddenly changes in character and habits from his norm. If the patient is not senile, one can get positive signs of the disease by asking him about perceptual changes, and when they developed. The results of vitamin B3 therapy in these people are very gratifying to the patient and his family.

Incidence in Relation to Sex

In the 209 cases the distribution between male and female patients was approximately equal.

Incidence in Relation to Economics

The condition is definitely related to the economic background of the family. A poor person does not come to see the doctor unless he thinks he is sick. If one finds no well-defined disease one must consider the possibility of subclinical pellagra. Of those who walk into my office, 10 percent have the signs and symptoms of subclinical pellagra. These people are either not eating properly or there is an increased demand for B3 which cannot be met without extra vitamins.

Seasonal Incidence

Contrary to the increased incidence of pellagra in late spring and early summer, there is no real relationship to sunshine and heat, at least not in central Saskatchewan.

PATHOLOGY

The condition is not fatal and none of the patients in whom the diagnosis has been made have died; therefore necropsy results are not available. The pathologic findings associated with death from pellagra show very little that is truly diagnostic, and probably the findings in subclinical pellagra would be even less informative.

SIGNS, SYMPTOMS, AND COMPLAINTS

The signs of subclinical pellagra are subtle, but the symptoms are often dramatic. The surest signs are the general attitude and actions of the patient. One must remember that the patient comes to us with complaints which are not imaginary to him, and it behooves us to search for the somatic or psychic basis, arrive at a diagnosis, and begin treatment. A typical patient is a frightened, quiet-spoken child. He comes in behind his mother, eyes down and sad of countenance, and will not volunteer anything. He will stand or sit as he is directed, usually very quietly, but at times he jumps and moves about continually. The mother will tell his complaints, but the child will say nothing unless the mother is quiet and I wait until he sees that I really do want to talk to him. The child feels that there is something amiss, but does not know what. He is having so many new experiences every day that perceptual changes and even physical changes are accepted as a matter of course and are never, or rarely, questioned. It is imperative to establish rapport by asking about things that he understands and by investigating his physical complaints while I

question his ability to see, to hear, to touch, and to feel. I can often gain his confidence and respect very quickly and I am then able to ask more definitive questions which will not upset the mother at the crucial stages of the examination. It is just as important to have her cooperation as that of the child. A mother can accept perceptual changes in her child if she hears the child admit it calmly and coolly in the course of his physical examination.

Presenting Complaints

HEADACHE

The pain may be facial, frontal, temporal, occipital, or nuchal in location. It may be throbbing, light, continual, or intermittent in character.

EARACHE

This is a common complaint in children. It is usually a vague pain, and patients point in the general direction of the ear or neck or postauricular area.

THROAT

The site of the sore throat is indefinite, from the teeth to the clavicle. Time and date seem to be important; for example, it is sore at night but not in the morning; it is not sore on weekends. The physical complaints are usually poorly defined.

CHEST

Here the complaint varies from difficulty in breathing at times, to deep-seated pains which may or may not be constant. There is sometimes a history of trauma or pneumonia. There is rarely, if ever, any limitation of movement, any abnormal breath sounds, or pain on pressure. Patients often complain of pain in the chest, and yet they point to the epigastric area, the back, or the shoulder.

HEART

Many patients complain of missed beats, pain of a fleeting nature, and difficulty in swallowing or breathing when the pain is present. The doctor can rarely find much of note to explain the pains. The electrocardiogram, blood pressure, and general

circulation are usually fine. If the patient is older arteriosclerosis or emphysema may be found.

GASTROINTESTINAL TRACT

This system is the source of most of the patient's complaints, those of the greatest intensity. Some patients complain of taste changes, some of lump in the throat, difficulty in swallowing, heartburn, eructations, gas, bloating, dyspepsia, water brash, cramps, colic, nausea, vomiting, constipation, diarrhea, pain in the side, or anorexia. The time relationship and the type of food seem to have little bearing on the problem, which helps to distinguish the pellagrin from the patient with gallbladder dyspepsia or ulcers. It is not uncommon to find perceptual changes of a marked degree in children who have duodenal ulcers proved by x-rays. No one is prepared to say which is the cause, and which is the effect, but by use of a high-protein, low-carbohydrate diet and vitamin supplement, the symptoms and the ulcers are made to disappear, and also the dysperceptions.

GENITOURINARY TRACT

In children the presenting complaint is frequency, dysuria, and sometimes enuresis. In older people the symptoms involve the reproductive tract in the usual way: dysmenorrhea, backache, heaviness in the pelvis, "kidney pain," low back pain, pain in the groin, constipation, decreased libido.

Most patients have minimal pathologic findings to account for their complaints. In women with gynecologic symptoms surgical procedures fail to relieve the complaints. It is often in these cases that the gynecologist is forced to perform procedures which do little to effect a cure. Much depends on how bitterly the patient complains and how convinced the physician is about the nature of the problem.

LOCOMOTOR SYSTEM AND SPINE

Backache is a common complaint, but the site varies from vertebra T_1 to S_5, from the midline to the flanks. The treatment of backache is difficult because the patient has to work at it. Finding perceptual changes is a great help to the doctor to explain the problem to the patient. Often one hears complaints of sore knees, ankles, calves, tired feet, ache in the arms, numbness, and tingling. Experience has taught me that any complaint that brings the patient to my office can be due either to familiar demonstrable disease, for example, epiphysitis, or to the dysperceptions of subclinical pellagra.

Other Somatic Complaints

As a rule the patient presents himself with a single problem, such as sore throat or chest pain. It is not difficult to elicit many of the generalized complaints which are present in most cases of subclinical pellagra.

FATIGUE

The patient states that he is more tired than he should be. The fatigue is sometimes so severe as to keep him in bed for hours or days. The school child will lie down after school instead of playing outside. He goes to bed early and sleeps late, yet often feels the need of even more sleep. The mother seldom complains of this problem unless she is particularly observant, because a sleeping child is one less problem in her day. Adults, when asked, may readily admit fatigue. It is worthwhile to find out when the symptoms started; the shorter the time, the faster the cure.

SLEEP

The patient may have difficulty in going to sleep or he may wake often. Sleep is easily disturbed and not as restful as the patient feels it should be.

TEMPER

The patient is usually more cranky than usual. He is easily upset and fights with his siblings. The adult becomes obstructive, the teenager obstreperous. Laughter is rare and short-lived, while depression is common and prolonged. The normal interests in school or work are diminished and the delights of accomplishment are not particularly appreciated by the patient. Progress at school or work is lackadaisical because of dysperception and depression. Since he is irritable and fatigued he tends to stay by himself more and more and may eventually be called antisocial. The patient may appear happy, but he readily admits to depression and fatigue, fear, and anxiety. Being frightened is a common symptom. He is frightened of things that previously did not bother him. Anxiety and depression coexist in many cases.

THOUGHT PROCESS AND FORGETFULNESS

Forgetfulness is often present. The patient forgets what he reads, what he was talking about. There may seem to be a momentary "blacking out" of the thought process, lasting a second or much longer. The patient may say that he has trouble thinking and that it takes a long time to get an idea in his mind. The student who previously could learn things easily now must spend hours trying to get the same

amount learned. He finds his grades may stay the same but only with greatly increased effort, or they may fall. If the vitamin deficiency continues over the course of years the patient's thinking becomes confused. He feels he is right and society is wrong, and this leads to much trouble for him and for authority.

PERCEPTUAL COMPLAINTS

Complaints of a perceptual nature are rarely voiced. The physician must ask, and be very specific. I have had only one patient volunteer information about visual changes, and he was not complaining—he merely thought it was interesting. Perceptual disorders in the young are not complaints; they are accepted as normal because the child does not know differently. Children are fatalists and can accept incredible handicaps with equanimity. As the age group advances and experience broadens, the patient still will not discuss his dysperceptions. I have patients who have not read for ten years because the words moved, and they never mentioned it to anyone, not knowing that it was abnormal. The same holds true for watching television—they watch for only a few minutes and then sit and do nothing.

Perceptual Changes

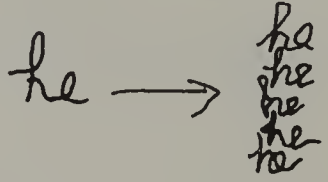
All five senses are involved. They will be discussed in order of importance and incidence.

VISION

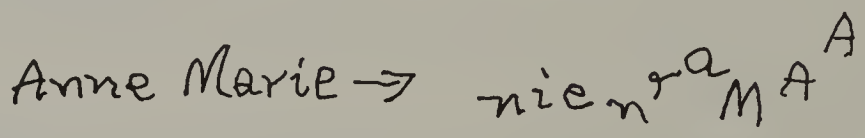
A child may complain of faulty vision. An observant teacher may move him about the classroom in an effort to help him see better. In many cases the parents have had an optometrist or ophthalmologist examine him. Often a pair of glasses is prescribed, usually with less than one diopter correction. If the child has a correctable defect, such as myopia, the glasses are of some benefit, but they do nothing to correct the dysperceptions. When asked, "Do you have any trouble when you read?" the patient will say "No". He might admit that his eyes hurt, the letters blur, or his head hurts. Often an adult patient has stopped reading altogether. When they say their eyes get sore then you must start being more specific in the search for dysperception:

"Do words move?" Answer—"No."
"Do words move a little bit?" Answer—"No."
"Do words move a little bit sometimes?" Answer—"Yes."

This is the most common symptom in subclinical pellagra, and if it is missing one should be very careful about making a diagnosis. Occasionally a patient categorically denies that words move, but if you ask him to think back a few months or years, he will recall that they did at one time. The way words move is fairly well delineated and is surprisingly constant in these patients. The words may move up and down or laterally in short jumpy motions, or move to the left or to the right without coming back. Some children say the words seem to move right off the blackboard or off the page, and they cannot learn how to catch them. There is also what I call the "zoom effect"; words move away from the reader and then come close. Some patients say the words get smaller and bigger, but others deny this. Very often the words have a shadow or become double; for example, the word is seen superimposed on itself. One child saw the same word five times and demonstrated it in this way:



In more severe cases the letters of a word get out of alignment and may even be reversed; for example:



Other children have trouble recognizing letters or numbers at all. The children have difficulty with arithmetic when the numbers change shape or orientation or both:



Since these children have such dysperceptions, it is little wonder that their teachers have a difficult time and that the child does too.

As the dysperceptions wax and wane, the attitude of the patient and his success in school change. Often a child will claim he cannot see but the ophthalmologist can find nothing wrong. The problem is sometimes the presence of a fog between the child and what he is looking at. The fog is usually white but may be gray, black, or another color. Sometimes he says that the light shines on the board the wrong way; yet no matter where he sits in the room the problem is rarely corrected for long, or another problem replaces it. Sometimes the feeling is described as seeing through a sheet of plastic. Corroborative evidence to words moving, but less common, is the statement that pictures move. Sometimes pictures move and words do not. The movements are usually similar to those of words, that is, up and down or back and

forth. It is the whole object that moves, as a rule. Sometimes they say that the picture is walking, sometimes that the animal is breathing, or is looking at them.

An important clue to diagnosis is given when the patient looks into a hand mirror. I observe what happens, and also question the patient carefully. The most common symptom is that the face gets small; it also may appear to move away, or get small and then big. It may appear wavy in the horizontal or vertical direction, or rippled. In more severe cases the patient cannot see parts of his face; he doesn't worry much about it—that part is a void to him, and he cannot explain it. The void may be either dark or light. One child could see nothing but her eyes. Many complain that their hair looks odd. One prisoner had to have someone shave him because his face changed so much that he would cut himself severely. Another penitentiary inmate claimed he had no trouble with shaving and that his face did not change when he looked in the mirror. He had many other positive symptoms of subclinical pellagra, and I eventually discovered that he used two mirrors—when the image in one mirror went blurred or distorted he would look in the other mirror, back and forth until he had finished shaving.

If a child is frightened and refuses to look in the mirror, he is possibly schizophrenic. If the mirror shows that the face changes in shape he should then be asked about other things—if other people change shape too as he looks at them.

The difference between the illusions of subclinical pellagra and the hallucinations of schizophrenia is a matter of degree. The pellagrin knows that what he sees is not so, while the schizophrenic is not at all sure. Many subclinical pellagrins refuse to watch television because of their visual dysperceptions. The picture becomes distorted, there may be a light around the set or around the people in the picture. Some see lines or bugs, or a fog in front of the set. If the patient does not watch television, this may be the reason.

Other visual phenomena reported by patients are that they see animals or people when none are present, that buildings and trees seem to lean over, that people and objects change shape and become distorted, that some objects change color, and that people look like animals, most usually the face looks like that of a dog or rat.

AUDITORY DYSPERCEPTIONS

Hearing things is the next most common problem. It is upsetting to some patients but of little consequence to others. If you ask, "Do you sometimes hear someone calling your name when there is no one there?", the patient usually answers in the affirmative. Many hear themselves thinking, either inside or outside their head; that is, they hear their own voices saying what they are thinking. Some hear another voice, usually a familiar one, telling them to go out and play or fight someone, but this is rather uncommon. Some hear noises, such as bells, doors slamming, or dogs barking. For many of these patients the auditory illusions are very disturbing. If

they happen at night, the patient may wake up and be unable to get back to sleep. Subclinical pellagrins are, however, not much bothered with auditory dysperception as a rule.

DYSPERCEPTIONS OF TOUCH

The tactile sense is the next most disturbed. In some cases it causes more distress than the auditory problems, yet it seems to occur less frequently. In investigating this system the questions are difficult to phrase and are easily misinterpreted, so that one has to do more explaining to let the patient know what is meant.

A good question is "Does your pencil seem to feel different now?" Quite often the answer will be that it feels fat or slippery or big or is changed in some way. Many patients feel numb in places, usually the hands and feet or arms. Some even have to pinch themselves while looking at the arm to know that it is really there. The sensation does not last long, but it is distressing. Another interesting phenomenon is that the patient often does not know where his arms or feet are without looking. Occasionally he will say his clothes feel hot or cold, or that his arms feel like fur or plastic when he rubs them. Often when he sits down he feels his bottom getting bigger and bigger, as though it may not fit the chair.

Included in the tactile sense is the problem many patients have with walking. Strange things happen and may even be noticed by others. Some feel that their feet get bigger when they walk, or that they are walking on balloons or cotton batting. To some the ground is spongy, like a muskeg, and moves up and down as they walk. Occasionally the person will try to walk over the waves of moving ground in a stepping motion almost like a general paretic. This may bring comments from his friends. The ground sometimes moves in a forward direction, sometimes to the side. He may feel he is walking uphill or down while he is actually on flat ground. Many of these people have visual dysperceptions at the same time: the trees and the buildings lean, and the patient has trouble walking because what he feels and sees is not really there. Many of them, when they climb stairs, feel that the stairs are getting longer or shorter or are moving. The patient may get dizzy, fall down, feel ill, or vomit. One child felt that she was going faster and faster; she then walked into a tree and hurt herself.

OLFACTORY AND GUSTATORY DYSPERCEPTIONS

Since taste and smell are closely related they will be discussed together. Patients claim that food has no taste or smell, or that various foods smell bad or rotten. One clue is not eating a former favorite dish because the taste has changed. The food may taste too sweet or salty, or tastes may be confused; for example, sweet things are bad, bland things are sweet. Spies (1939) mentioned these changes as

being quite distressing sensory disturbances. These problems are especially distressing to the pregnant woman. I suspect that many cases of hyperemesis gravidarum have their roots in subclinical pellagra. Many pregnant women that I see have perceptual disorders.

DIAGNOSIS OF SUBCLINICAL PELLAGRA

The physician must have an open mind. If he lacks interest in the disease he will never diagnose it. If, for instance, he discounts visual symptoms because the ophthalmologist says there is nothing wrong with the patient's eyes, he may fail to make a correct diagnosis. One must search for the symptoms that the patient does not volunteer by taking a good history. (I may mention that I convinced myself for years that American Indians rarely had diabetes mellitus, whereas in fact I had not looked for it.)

Somatic Complaints

The patient may have a headache, sore throat, chest pain, bladder trouble, backache, or joint pains. The complaint might be quite definite as to its origin, site, or duration, or it may be quite indefinite. After more than twenty years in practice I have learned that people do not come to a doctor's office for frivolous reasons—they are suffering in one way or another and it is up to the physician to discover what brought them. If the patient complains of a sore throat and on examination one finds no cause for it, this does not mean that the patient is not suffering from a sore throat. He may be suffering from dysperception, and it behooves us to broaden our history-taking to include perceptual dysfunction. Many of these patients will complain of abdominal pain that has not responded to ordinary treatment. It is possible that dysperception is the source of their problem.

If a doctor asks questions such as "Do words move when you read?", the skeptics may say that he is putting thoughts into the patient's head. But these skeptics do not feel that questioning about dyspnea or dyspareunia is also putting thoughts into their heads. I have found that it is not possible to produce dysperceptions merely by questioning. The patient will not accept the thought. If the patient does have perceptual disorder, however, he is relieved when the doctor asks about it. While examining the patient one should ask the questions most pertinent in establishing the diagnosis. I have found that the best questions are the following:

1. Do words move when you read? Do you find that words seem to move up and down a little bit sometimes when you look at them?

2. Does the ground seem to move when you walk?
3. Do you sometimes hear your name called when there is no one around?
4. When you look in a mirror does your face seem to change?
5. Do pictures sometimes seem to move a little bit when you look at them?

While asking these questions, the physician should be in the examining room doing the physical examination and establishing rapport. This takes only a few minutes. If the doctor is assured the patient does not have perceptual disorders, he can continue his routine. However, if perceptual disorders are indicated, many more questions may be asked.

In general practice one looks for shortcuts. The Hoffer-Osmond Diagnostic test had been my shortcut until I developed my own set of questions, which I call the Perceptual Dysfunction test. With little effort these tests give a rough estimate of the physical and psychic problems which the patient may have. I have been developing the test over the past two years, and it seems to give a good picture of the physical complaints that brought the patient to the office, and the psychic problems about which he has not complained. The questions are grouped rather loosely into several parts, dealing with sensory dysperception and the somatic complaints that are also changed by his perception problems.

The questions are arranged in such order that the patient will not see a pattern in them.

While the idea for the test evolved directly from the HOD, the questions are more dissimilar. The Perceptual Dysfunction Test (PDT) is for determining perceptual changes and somatic complaints in the main, with very little emphasis on depression, paranoia, and thought content. The HOD test on the other hand is concerned with the broader parameters of disturbed psychic function and very little with somatic complaints. The HOD has been seldom used for patients under 13 and is not recommended for use with children. The patients in whom subclinical pellagra is common fall into the younger age group and as a rule are difficult to question. If one can establish during the course of the examination that the child has perceptual dysfunction, then the mother or the child can easily be persuaded to answer a set of questions which will elucidate the problem. Quite often I give the patient the PDT and the HOD; the first for perceptual and somatic complaints and the second to check on depression and paranoia. If he scores high on the PDT and low on the HOD, one must re-check with the patient, to see if he understands the test. It does not take an expert to realize whether or not the patient misunderstands the test. Our experience has been that patients do not try to fool the examiner or lie to him in the answers, but misunderstandings do occur and must be watched for and corrected. For example, the patient may readily say that words move when he reads, the ground moves, objects change shape, but he may not readily admit that his face

changes when he looks in the mirror. If one feels he is most likely having trouble when he looks in the mirror, review the questions with him and ask them in different ways. For visual dysperception, typical questions are:

When you read do the words blur or go fuzzy?
Do your eyes seem to get blurred?
Do your eyes get sore and tired quickly?
Do you get a headache when you read?
Do the words go double when you read?
Do the words seem to get bigger and smaller?
Do letters get mixed up when you read?
Do words seem backwards when you read? for example, saw—was.
Do numbers move?
Do you forget what you read?
Do you sometimes think you see animals when there are none there?
Do you see people?
Does the television picture look different now?
Do you see things on television your friends don't see on the same program?
Is there a fog between you and the television set?
Do people seem to have a light around them at times?
Does it seem sometimes that your face gets bigger or smaller when you look in a mirror?
Does there seem to be a fog in front of the mirror so it is blurred or hard to see yourself?
Does your face seem to get wavy when you look in the mirror?
Do pictures seem to move a little bit, at times, when you look at them?
Does a chair seem to move at times or change shape?
Do people in pictures seem to breathe or to watch you?
Do people seem strange or different when you look at them?
Do objects seem to move, or get big or small, when you look at them?
Do letters seem to change shape? for example $\varepsilon \rightarrow$ s
Do numbers seem to change shape? for example 9 $\rightarrow$ q
Do numbers seem to change direction? for example 3 $\rightarrow$ ε
Do numbers seem to change around? for example 41 $\rightarrow$ 14
Do pictures or objects seem to change color at times?

Questions on the Auditory Sense

Do you think you hear someone calling your name when there is no one there?
Do you think you hear voices when there is no one there?
Do you think you hear animals or noises when there are none there?
Do you hear voices talking or yelling when there is no one there?
Do you hear your own voice inside your head when you are thinking?
Do you hear your own voice outside your head when you are thinking?

Questions on the Tactile Sense

Do some things seem to feel different now, than before, when you touch them?
When you pet a dog does he feel as a dog should feel?
When you write does the pencil feel different from what it should?
Do you think you feel someone touching you when there is no one there?
Do you seem to feel that you get bigger when you walk?
Do you seem to feel that you get smaller when you walk?
Do you feel that your feet seem to get big when you walk?
Does it seem that you are walking off the ground sometimes?
When you are walking on level ground, do you feel as though you are going up hill or down at times?
When you walk, does the ground seem to go up and down?
Do you feel the stairs seem to get higher or lower when you climb them?
Do trees and buildings seem as though they move or lean over?
Do your bones feel soft and rubbery at times?

Smell and Taste

Do you feel that your sense of taste has changed lately?
Have you noticed that your food has no taste?
Have you noticed that your food seems to taste rotten or have you noticed that you can't smell your food?
Do some foods smell rotten?
Do some foods smell different from usual?

Physical Complaints

Do you often get a sore throat?
Do you often have painful joints?
Do you often get pains in your stomach or your chest?
Do you often suffer from cramps?
Do you often get an earache?
Do you sometimes wet the bed?
Do you bite your fingernails?
Does your school work seem to tire you more than it used to?
Does your school work seem harder than it used to be?
Do you feel like throwing up?
Do you get scared or feel nervous most of the time?
Do you often wake up at night for no good reason?
Do you find it difficult to go to sleep?
Do you feel sad most of the time?

Diet

Questions regarding diet and eating habits are of interest for obvious reasons. They are important also in the differential diagnosis. Here a word of caution. All doctors know patients often do not tell the truth about what they eat and drink. An example is the obese patient on a diet who gains weight yet swears that he is following the instructions faithfully. Subclinical pellagra is a deficiency disease, and accordingly questions on the dietary habits are necessary and important for diagnosis, treatment, and continuing care. The doctor must make the patient diet-conscious, and the way to do it is to talk about diet.

The diagnosis of subclinical pellagra is made by a combination of several factors:

1. Diet. The history usually shows a low protein intake and a high carbohydrate intake.

2. Physical complaints. All parts of the body may be loci of aches and pains, numbness, loss of movement, or weakness. A common finding is being very tired in spite of adequate sleep. These patients need x-rays and laboratory investigations and a physical examination. Finding a duodenal ulcer does not exclude subclinical pellagra. The ulcer may be a result of it.

3. Perceptual changes. There are many perceptual changes, involving all five senses. Some changes are more important than others. There are five important changes about which you ask to determine if there is need to question further: (1) When you look at a book, do the words seem to move a little bit sometimes? (2) Do pictures seem to move a little bit at times when you look at them? (3) When you look in a mirror does your face seem to get bigger or smaller? (4) Do you sometimes hear your name called when no one is present? (5) Does the ground seem to move up and down as you walk?

   If all five questions are answered in the affirmative, the diagnosis of subclinical pellagra is very likely. The other questions one asks are to establish the degree and severity. The length of time the symptoms are present is a matter of some concern. The school child can pin down the time quite well by correlating it to his grade in school and to school holidays; for example, before or after Christmas. In adults, unless it is of recent origin, there will be difficulty in pin-pointing the time of onset. As a general rule, the more recent the onset, the more quickly a cure can be achieved. If the child has symptoms only for a month or two, the treatment can stop the perceptual changes within days.

It is the combination of symptoms and treatment which makes the diagnosis secure:

1. There must be complaints of a physical nature: pain, fatigue, neurasthenia, and the like.
2. There must be evidence of perceptual difficulties, the perceptual distortions mentioned above.
3. There should be a positive history of a low protein intake.
4. The patient should respond to the administration of niacin or niacinamide.

A therapeutic test which results in the disappearance of the perceptual changes and of the physical complaints is proof of the diagnosis of subclinical pellagra.

LABORATORY INVESTIGATIONS IN SUBCLINICAL PELLAGRA

There is no decisive chemical test for the detection of subclinical pellagra. Until a method is devised that can measure blood or cellular levels of niacin or its products, there is little hope for positive laboratory findings. Goldsmith (1964) states that the excretion of less than 3 mg of N-methylnicotinamide and its pyridone, which is N-methyl-6-pyridone-3-carboxylamide, in 24 hours is characteristic of pellagra. A similar test for subclinical pellagra might be developed.

DIFFERENTIAL DIAGNOSIS

Chronic Malnutrition

The signs of malnutrition can vary from emaciation to obesity. To diagnose a specific deficiency is next to impossible in the early stages. The symptoms are fatigue, anxiety, lassitude, aches, and pains. A therapeutic trial is a help to establish the diagnosis. To eliminate the perceptual changes of subclinical pellagra the patient is given 1.5 to 6 grams of niacin or niacinamide each day.

Schizophrenia

The diagnosis of schizophrenia is based on (1) disturbance in affect, (2) disturbance in thought process, and (3) disturbance in attention.

AFFECT

The outward expression of emotion is bland, inadequate. In subclinical pellagra there is no such change. The child may be frightened but this is easily overcome and cooperation is the rule, not the exception.

THOUGHT PROCESS

The schizophrenic thinking is illogical, irrelevant, and peripheral. In subclinical pellagra the patient, even while admitting to marked perceptual changes, knows that such things are not real. The pellagrin seeks medical attention, the schizophrenic often does not.

ATTENTION

The schizophrenic has lapses in attention. He is preoccupied with his own thoughts. Later in the disease it is very difficult to attract or hold his attention. In subclinical pellagra the patient is very interested in his complaints as being explored by the physician and answers readily. Hyperactivity is a sign which is more common in schizophrenia than in subclinical pellagra. Hyperactive children admit to few perceptual changes, which points to schizophrenia rather than subclinical pellagra. Hyperactive children take longer to respond to megavitamin therapy.

Hoffer states that pellagra and schizophrenia are similar orthomolecular diseases. In pellagra the diet is deficient in niacin. In schizophrenia there is a block between the substrate vitamin B3 and its synthesis into NAD (nicotinamide adenine dinucleotide). He calls pellagra a B3-deficiency disease and schizophrenia a B3-dependency condition (Hoffer, 1970).

Other Psychiatric Conditions

Perceptual changes are brought about by hallucinogenic drugs, alcohol, bromides, and so on. A careful history and physical examination with the specific laboratory tests will establish the proper diagnosis.

Relative or Absolute Hypoglycemia

This disease is discussed in other chapters. People with this problem show the symptoms of subclinical pellagra with the exception of perceptual changes.

TREATMENT

Once the diagnosis has been established, the patient is put on 2 grams of niacin or niacinamide three times a day. I use these large doses to get a rapid response; the cost is very slightly greater. It is possible that 0.5 g or 1 g per day would be enough.

Measure of Treatment

The patient is given the HOD test and the Perceptual Dysfunction Test to diagnose the condition. In the HOD test, the total score is usually high. After a month the test is repeated; the total score has usually come down, as well as the perceptual score. The depression recovers at about the same rate.

CASE REPORT I

H. K., who was born in July 1957 was a sad-looking, quiet boy who came to see me on November 25, 1968, complaining of a sore throat. He had a dejected appearance and a very soft voice, and would say little. Examination of the ears, nose, and throat showed no abnormality. He admitted that words moved when he tried to do his schoolwork. On his return visit, November 27, 1968, the HOD test showed:

Total score 143
Perceptual score (PerS) 33
Paranoid score (PS) 10
Depression score (DS) 13
Ratio score (RS) 11
Short form (SF) 11

He was in Grade V and said the trouble started in Grade IV. He was finding school very difficult. Words moved and went crooked, there was number reversal (69–96), his face changed, cars seemed too close, people got bigger and smaller and had a bright light around them. His mind would go blank several times a day. He heard his mother's voice and his own. His hands would get big, he felt tired all the time yet could not sleep well. Some of the letters in a word would disappear, pond became pon, d and p looked the same, Henry looked like Henre. The patient was put on 1 gram of B3 and 1 gram of vitamin C three times a day, and told to eat more meat.

Six weeks later he returned to tell me that his face did not change any more, he sleeps better, hears voices less frequently, and words have stopped moving. His

food tasted better and he felt better all over. A repeat HOD test at this time showed:

TS 29, PerS 4, PS 3, DS 4, RS 7.5, SF 3.

He was seen again in April 1969, and was told to continue his vitamins. A HOD test done in December 1969 showed:

TS 11, PerS 0, PS 2, DS 0, RS 11, SF 1.

He had been off the vitamins since the summer holidays of 1969, his marks had improved and he wrote the following letter:

> I don't see and feel these things, that used to bother me. Now things are coming up and more than they used to, like I use to be very forgetful and always drowsy. I think and I am feeling a lot better than I used to be. I have more friends which I joke and play with. I find life more easy than to be sick. I thank you Doc. Green for helping me out with this problem. And I think it did help me.
>
> Henry
>
> P.S. My marks used to be very low as in the 20's or in the 40's. Now they are 50's and up. My highest mark was 75% and I think I still can go up higher.

In September 1970, he was the captain of the school soccer team and was a normal boy.

CASE REPORT II

A. H., born June, 1941. This man illustrates a typical story of subclinical pellagra in an adult male and the social and economic consequence it causes. A. H. is a heavily built Indian male with a brush cut and a wall eye. He is 5 feet 6 inches tall, and weighs 190 pounds. He is a happy fellow usually. He has a very obese diabetic wife and five young children. He took his family responsibilities seriously and was rarely in a doctor's office. On August 28, 1968, this man was hospitalized with a stab wound to the abdomen which required a laparotomy. Following this, he saw doctors frequently because of abdominal pains, headaches, inability to work, and general unhappiness with life.

I saw him first in my office on March 24, 1969, when he complained of severe left upper abdominal pains in the area of the stabbing. I reviewed his hospital chart, and could see no reason for the pains from a surgical point of view. He also complained of nightmares, and that he was not able to enjoy himself. He was tired all the time, he had headaches, and the muscles on his right side would twitch.

Perceptual changes: meat tasted funny since his stabbing.

Smell: some foods had no smell.

Sight: television blurred, people did not look right, the television story would not make sense, faces would blur when he was worried, words moved and pictures moved.

Hearing: he heard people talking at night and he heard his name called.

He was given a prescription for niacin, 1 gram three times a day, Tofranil 25 mg morning and night.

He returned April 8, 1969—his HOD test scored as follows:

TS 70, PerS 12, PS 7, DS 7, SF 10, RS 5.

I did not see him again until June 20, 1969. He had run out of niacin. He stated he was free of headaches and abdominal pains, he was working as a fire warden, and he thought he should continue his vitamins. He was given more.

In November 12, 1969, he returned for more niacin. He had no complaints, but was worried about gaining weight.

On January 5, 1970, he sprained his ankle and was put in a nursing home, where he repeated the HOD test, with the following results:

TS 10, PerS 0, PS 3, DS 2, RS 5, SF 0.

The man was feeling well in spite of being unemployed, and he had hopes for the future. He has been to the office since then, and is doing very well.

This story is that of a hard working and responsible head of a family who started to drink. He had not been much of a drinker, but when he started having nightmares and seeing strange things he took to drink. He became involved in a drinking brawl and was stabbed. Usually a happy fellow, he became surly. When his perceptual changes were discovered and megavitamin therapy was instituted he quickly reverted to his good-natured, provident self.

SUMMARY

Subclinical pellagra is a deficiency syndrome characterized by physical complaints and perceptual dysfunction. There is always a somatic complaint in patients who come to the office. If examination reveals little or no physical problem, subclinical pellagra should be suspected. The patient is asked the following questions:

"Do words move?"
"Do pictures move?"
"Does the ground move when you walk?"
"Does your face change when you look in the mirror?"

If some or all of the answers are "yes," you must suspect subclinical pellagra and explore it more fully by using the HOD test and, if possible the Perceptual Dysfunction Test in younger people.

The clinical proof of the condition is the prompt disappearance of the symptom

complex after the administration of large doses of niacin or niacinamide. I have been using 1.5 to 6 grams a day with excellent results. Control studies are now in progress. Preliminary results indicate that placebos have no effect. Utilization of the suggested questions may reveal subclinical pellagra in 5 percent of a general practice. If the physician does not ask the questions, he will never diagnose subclinical pellagra.

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21

Preliminary Observations of Altered Carbohydrate Metabolism in Psychiatric Patients

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OTTO W. WENDEL

After more than twenty years experience, in private psychiatric practice and in a state mental institution, the inherent deficiencies of the strictly analytical approach to the treatment of mental illness became increasingly apparent to us. The use of psychotropic drugs, electroconvulsive therapy, and other current forms of treatment has failed to produce the effective, long-term remissions and cures that had been expected. This is not to imply that psychoanalytic therapy should be abandoned, but rather that all potentially effective forms of therapy, including biochemical, should be utilized to the greatest advantage of the patient.

Several years ago Hoffer, Osmond, and their associates (1957, 1960, 1961, 1962, 1965, 1966) introduced a rational, psychochemical approach to the diagnosis and treatment of schizophrenia, supported by a practical diagnostic test and biochemical evaluation procedure. For the past few years the Hoffer-Osmond Diagnostic test (HOD) has been routinely employed along with the paper chromatographic assay for mauve factor. In addition, several thousand patients have been treated with niacin and ascorbic acid.

Considerable interest was aroused by the reports of Fawcett and Bunney (1967), Sachar et al. (1963), Salzer (1966), and Tintera (1955, 1966, 1967) that presented evidence implicating the adrenal cortex and abnormal carbohydrate metabolism in psychoneurotic and psychopathological disorders. It would appear that the internist and psychiatrist have consistently overlooked or ignored the possibility that neuroendocrine and metabolic disorders may either give rise to psychiatric manifestations, or complicate a latent predisposition to certain forms of mental illness. No particular contraindication exists between the reports of Hoffer and Osmond (1957, 1961), which demonstrate the effectiveness of niacin and ascorbic acid, and the altered adrenal cortical function and functional hypoglycemia in schizophrenia reported by others (Salzer, 1966; Fawcett and Bunney, 1967; Tintura, 1967). There is, in fact, a growing literature which indicates that niacin and ascorbic acid are directly involved in adrenal cortical steroidogenesis.

CONSTRAINTS OVER CLINICAL RESEARCH IN PRIVATE PRACTICE

Private practitioners will readily appreciate and identify with the problems we encountered when attempting to engage in clinical research studies with private patients. It is the primary responsibility of the private practitioner to employ any and all of the therapeutic armamentaria at his disposal. Double-blind studies cannot be justified in this context. Therefore, in addition to using niacin and ascorbic acid, it has been necessary and advisable to employ electroconvulsive therapy, phenothiazine derivatives, metabolic regulators, and other recognized forms of therapy. Every attempt, however, has been made to obtain baseline biochemical values for all patients prior to the institution of any therapy; this has not always been accomplished and will be noted where applicable.

Another problem over which the private practitioner has limited control is the patient who does not stay in therapy. The patient may demonstrate an extremely rapid and favorable response to therapy and erroneously conclude that additional treatment is no longer required. Or he may experience an adverse initial response to therapy, become disenchanted, and then cease to keep appointments or follow the prescribed treatment.

The clinical laboratory data and psychiatric evaluation collected from 130 psychiatric patients are presented, together with an indication of the psychometabolic approach carried out in our clinic. These include:

1. Glucose tolerance test (GTT) results.
2. The GTT response in relation to age and sex.

3. Statistical evaluation of the clinical psychiatric impression and HOD test results, in relation to GTT response.
4. A discussion of the potential implications of niacin and ascorbic acid as it may influence adrenocortical steroidogenic activity.

PSYCHIATRIC EVALUATION AND THE PSYCHOMETABOLIC CLINIC APPROACH

A routine decision process has been followed with all patients referred to the clinic for psychiatric evaluation and treatment. The steps in this process are outlined in Figure 21-1. All patients receive a clinical evaluation, which consists of a psychiatric

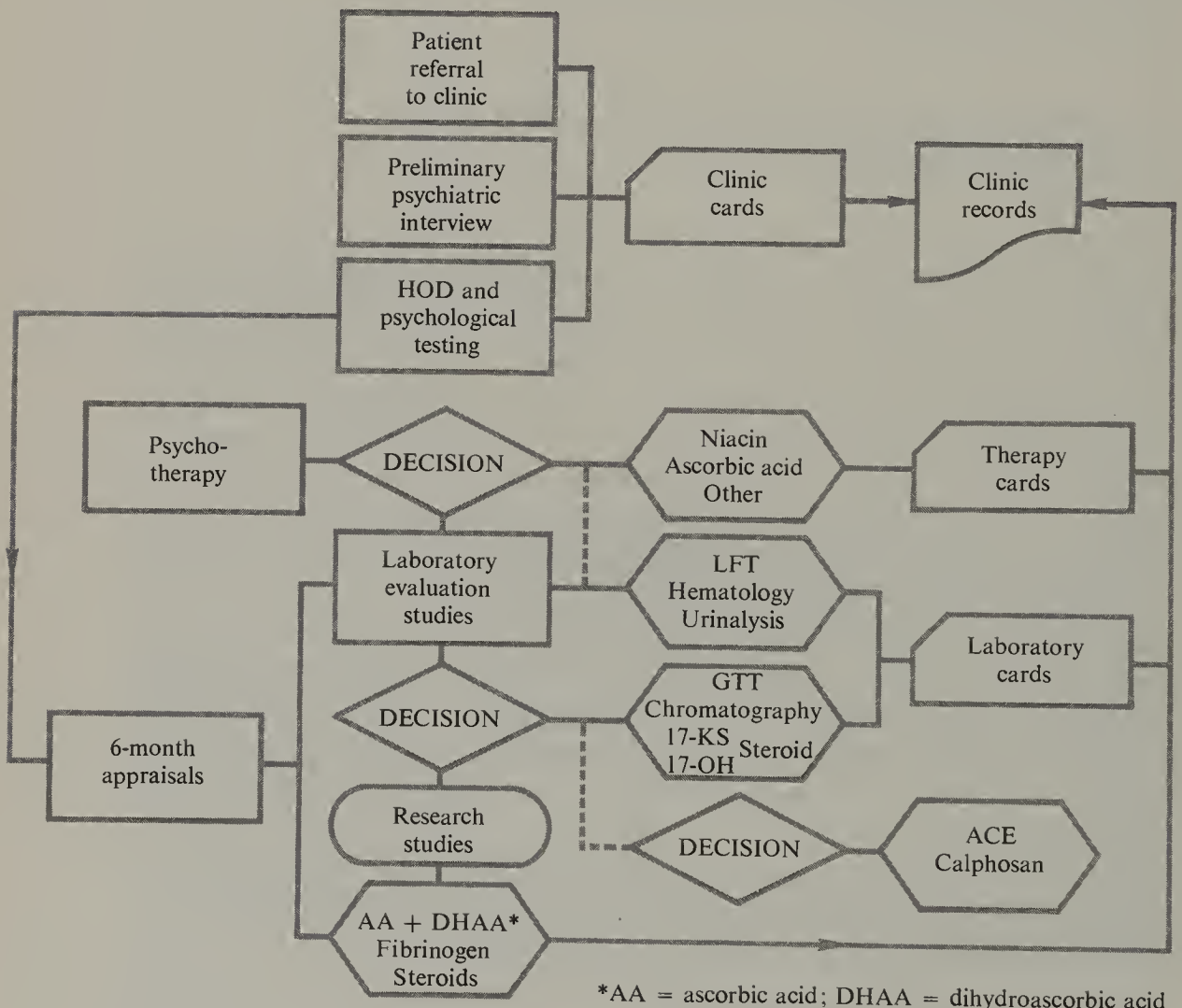


FIGURE 21-1.
Routinized decision process for psychiatric and clinical laboratory evaluation, diagnosis, and therapy.

interview, and a psychological test battery. The tests include the HOD, Zung's Self-Rating Depression Scale, Ammons' Full-Range Picture Vocabulary Test for I.Q., and Graham and Kendall's Memory for Design Test, for organic brain syndrome or psychosis. An initial clinical impression is made at this time, based upon the findings of the tests and procedures.

Laboratory Evaluation

A clinical laboratory evaluation, made up of the following tests, is provided before therapy is initiated.

1. Liver function tests. This series of tests includes serum glutamic-oxalacetic transaminase, serum glutamic-pyruvic transaminase, total serum protein and electrophoretic fractionation, total bilirubin, and cholesterol. It is important to exclude liver disease before using phenothiazine derivatives and other hepatotoxic drugs. In one series of patients, three exhibited diabetic GTT responses, and each later demonstrated chronic, severe hepatic disease.
2. Routine hematology. This consisted of a complete blood count. A marked incidence of eosinophilia and lymphocytosis was revealed from an examination of the differential blood smear. This finding is consistent with the observations of others (Thorn, 1951; Tintera, 1967) who have studied hypoadrenocorticalism.
3. Routine urinalysis.
4. Mauve-factor assay. A modification of the published procedure of Hoffer and Mahon (1961).

Based upon the psychiatric evaluation, psychometric tests, and the clinical laboratory findings, a decision is made whether the patient should undergo a GTT and a urinary assay of 17-ketosteroids and 17-hydroxycorticosteroids.

5. Glucose-tolerance-test procedure. The patient is instructed to fast after the evening meal the day before the test is to be given. The next morning fasting blood and urine specimens are obtained, and the patient is administered a cola-flavored 100-gram glucose drink. Subsequently, at intervals of 0.5, 1, 2, 3, 4, and 5 hours, additional blood and urine specimens are taken.

   The Somogyi-Nelson procedure for analysis of "true" glucose was used throughout most of this study, but some blood specimens were analyzed by an ultramicro glucose procedure employing glucose oxidase. Parallel studies indicate that the glucose values obtained by the two methods are identical.

With each group of specimens assayed, serum quality controls and primary chemical standards were routinely included. Values exceeding two standard deviations of the means were rejected; for example, 2 S.D. = ±8 mg/100 ml.

6. 17-Ketosteroids and 17-hydroxycorticosteroids. These steroids were determined in urine by the Hycel methodology, making use of the Zimmerman and Porter-Silber colorimetric complexes. A superior technique developed by Chen (1953) for the assay of 17-hydroxycorticosteroids was also used.

THERAPEUTIC REGIMEN

The specific therapy employed must be designed to meet the needs of a particular patient. The types of chromotherapeutic agents frequently employed, however, together with an indication of the customary dosage are listed below:

1. Niacin (or niacinamide): 3 grams per day.
2. Ascorbic acid: 3 grams per day.
3. Eschatin (Parke, Davis & Co.), a form of adrenal cortical extract: 10 ml, intravenously, weekly for five weeks; 2 ml, intravenously, weekly for four or more weeks.
4. Calphosan (Carlton Corp.), is calcium glycerophosphate and calcium lactate, with 300 μg vitamin B12 per 10 cc.: 10 ml, intramuscularly, weekly for nine weeks.
5. Seale Harris diet (Abrahamson and Pezet, 1951).

RESULTS

The results presented are limited to an evaluation of the GTT response, with respect to patient age and sex, and a comparison with the clinical psychiatric evaluation and the HOD test diagnosis.

An outline of the GTT response criteria is shown in Table 21-1. These criteria were applied to categorize the glucose data derived from 133 patients. Nine types of response curves have been developed. These were derived empirically, except that the hypoglycemia categories follow those recommended by Harris (1936), Tintera (1966), and Salzer (1966). When constructing graphical displays it has been found convenient to lump the "normal" and "flat, no hypoglycemia" categories into a single group; the "pre-diabetic" and "diabetic" into a second group; and the remaining miscellaneous types of hypoglycemic responses into a third group.

TABLE 21-1.
Glucose Tolerance Test Response Criteria

Normal	No elevation greater than 160 mg %; below 150 mg % at end of first hour; below 120 mg % at end of second hour.
Flat; no hypoglycemia	No variation more than ±20 mg. % from fasting value.
Pre-diabetic	Over 120 mg % at end of second hour.
Diabetic	Over 180 mg % during the first hour; 200 mg % or higher at the end of first hour; and 150 mg % or higher at the end of second hour.
Relative hypoglycemia	A normal 2 or 3 hour response curve, showing a decrease of 20 mg % from fasting level during the final two hours.
Probable relative hypoglycemia	Same as relative hypoglycemia, except there is a decrease of from 10 to 20 mg % below fasting level.
Flat; hypoglycemia	An elevation of 20 mg % or less, followed by a decrease of 20 mg % or more below the fasting level.
Pre-diabetic hypoglycemia	A 2-hour response identical to the pre-diabetic, but showing a hypoglycemic response during the final 3 hours.
Hyperinsulinism	A marked hypoglycemic response, with a value of less than 50 mg % during the third, fourth, or fifth hour.

The next nine illustrations (Figures 21-2 through 21-10) illustrate the typical types of responses observed from among the patients examined.

Figure 21-2 depicts a normal response. The normal fasting range for the blood glucose method employed is 65 to 110 mg per 100 ml. The narrow black lines delineate the accepted range of variation considered normal limits for the GTT response. The broad red-lined curve was constructed from the timed-interval mean values for the number of specimens noted. The broad black-lined curve illustrates a typical patient response pattern, in this case, patient no. 424.

Figure 21-3 shows a flat curve but without hypoglycemia. This type of curve is probably representative of altered gastrointestinal absorption of the glucose challenge, and may be attributed to one or more pathophysiological conditions—hypoadrenocorticism, hypothyroidism, hypopituitarism, or celiac disease.

Figures 21-4 and 21-5 show GTT response curves which are typical for the pre-diabetic and diabetic, respectively. Three of the five patients categorized as diabetic are chronic schizophrenics; two of the three have chronic, severe liver disease. Another patient in this diabetic group also has liver disease of lesser severity.

Figure 21-6 illustrates a typical relative hypoglycemia response. Without exception, there is a greater than 20 mg per 100 ml decrease in blood glucose from fasting levels.

Figure 21-7 illustrates what Salzer (1966) terms "potential relative hypoglycemia." In this study it is termed "probable relative hypoglycemia," because it is altogether probable that these patients are truly hypoglycemic. The shape of the curve mimics relative hypoglycemia, except that the decrease in glucose concentration below the fasting level is somewhat less, between 10 and 20 mg per 100 ml.

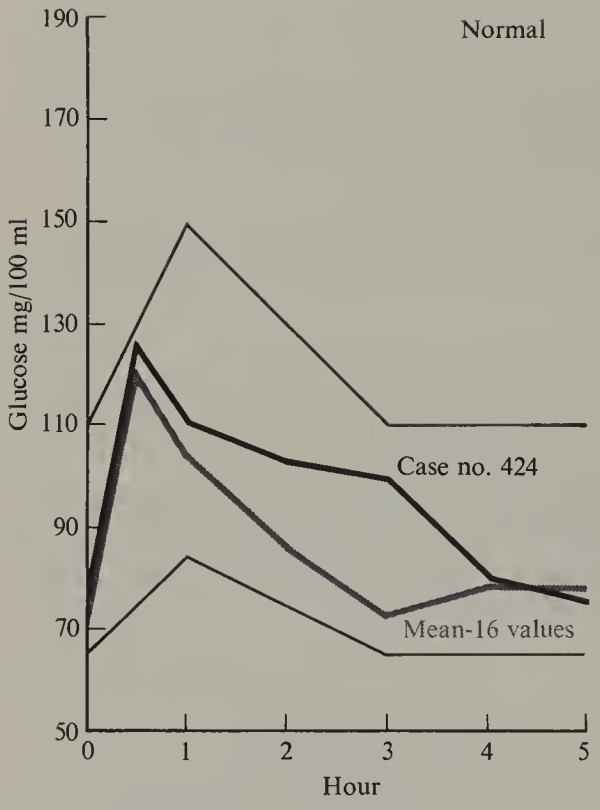


FIGURE 21-2.
Normal glucose tolerance response curve. (The narrow black lines delineate the accepted range of variation.) The gray curve was constructed from the timed-interval mean values for the number (N = 16) of specimens included. The heavy black-lined curve illustrates a typical patient response (no. 424).

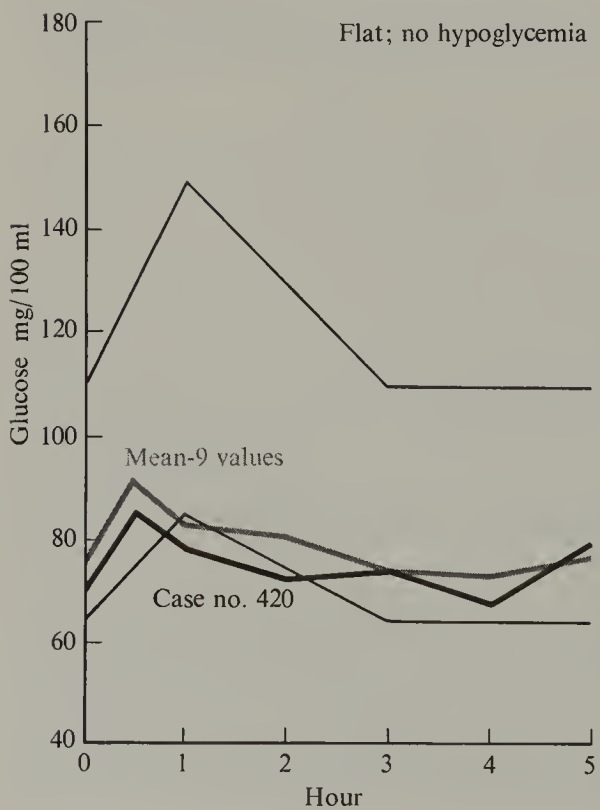


FIGURE 21-3.
Flat glucose tolerance response, without hypoglycemia.

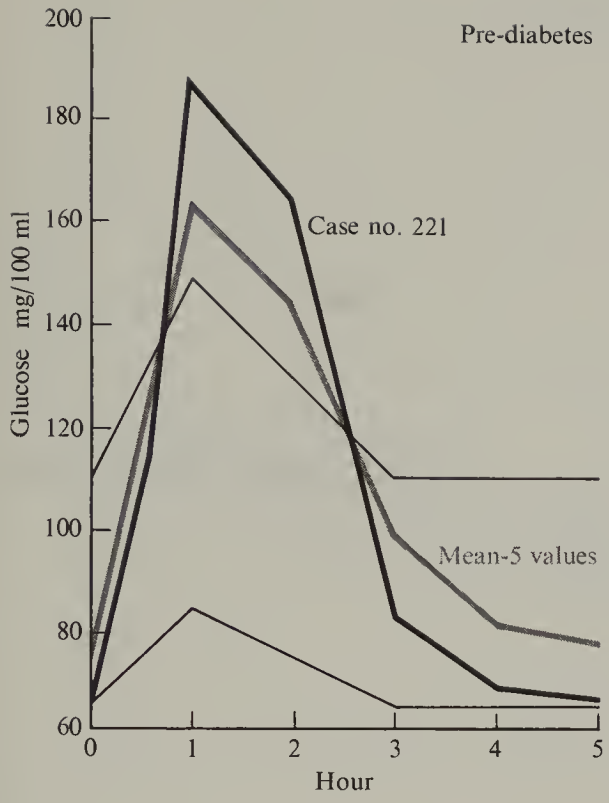


FIGURE 21-4.
Pre-diabetic glucose tolerance response.

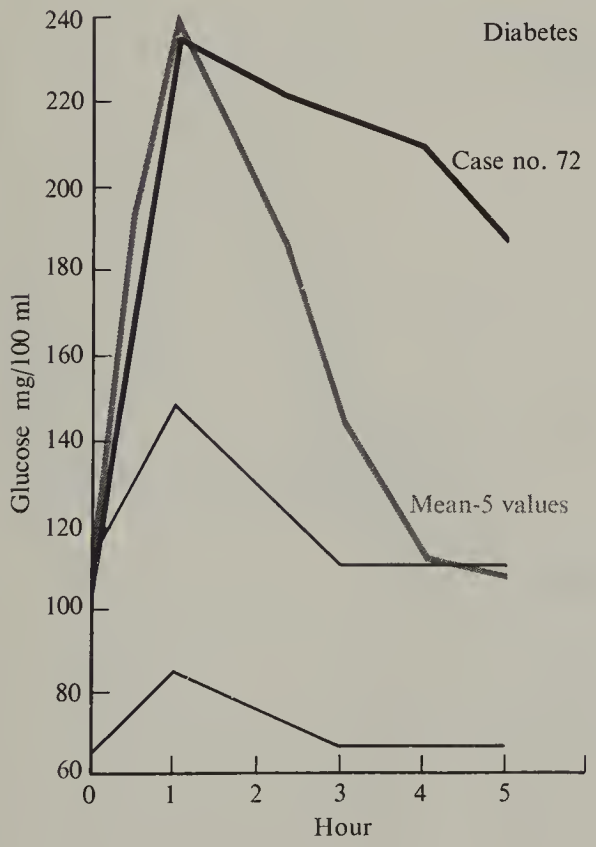


FIGURE 21-5.
Diabetic glucose tolerance response.

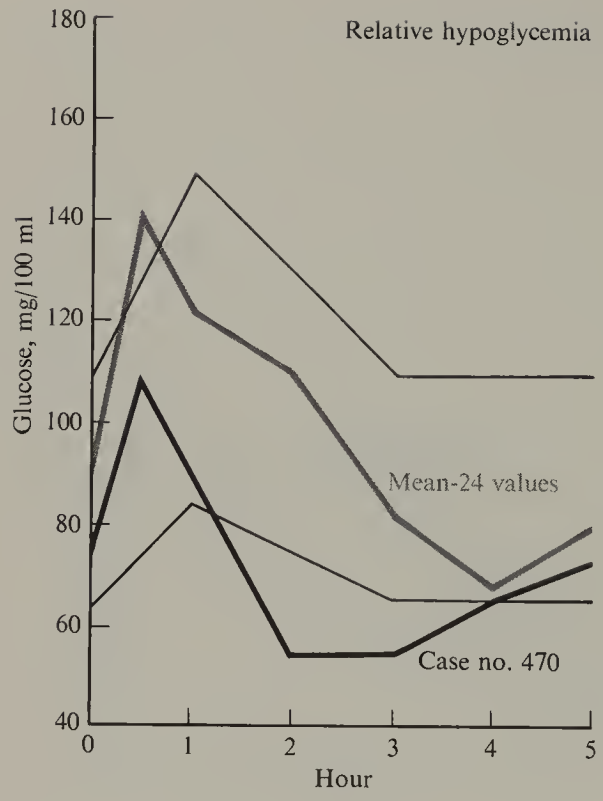


FIGURE 21-6.
Relative hypoglycemic glucose tolerance response.

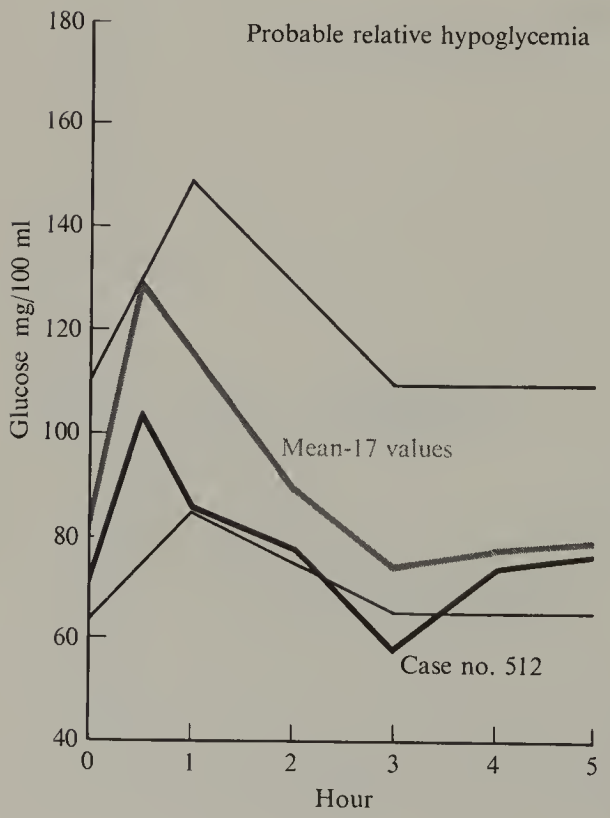


FIGURE 21-7.
Probable relative hypoglycemic glucose tolerance response.

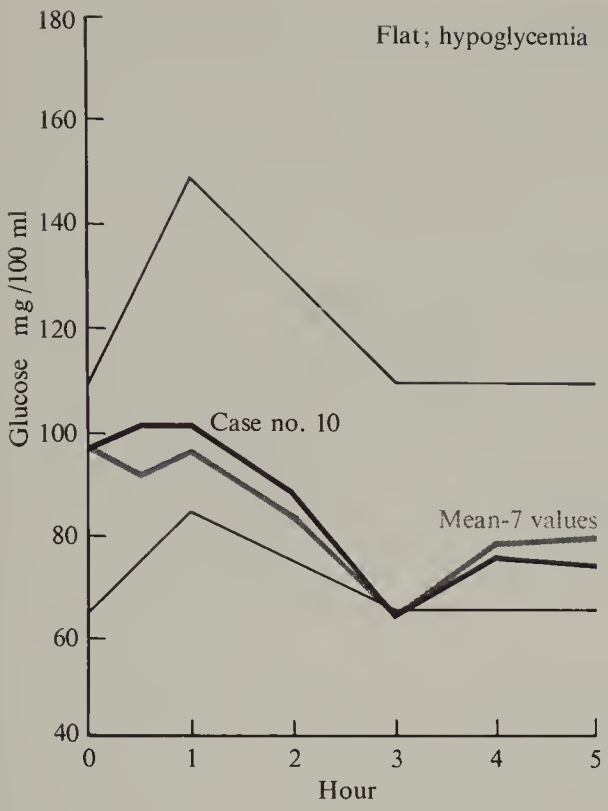


FIGURE 21-8.
Flat hypoglycemic glucose tolerance response.

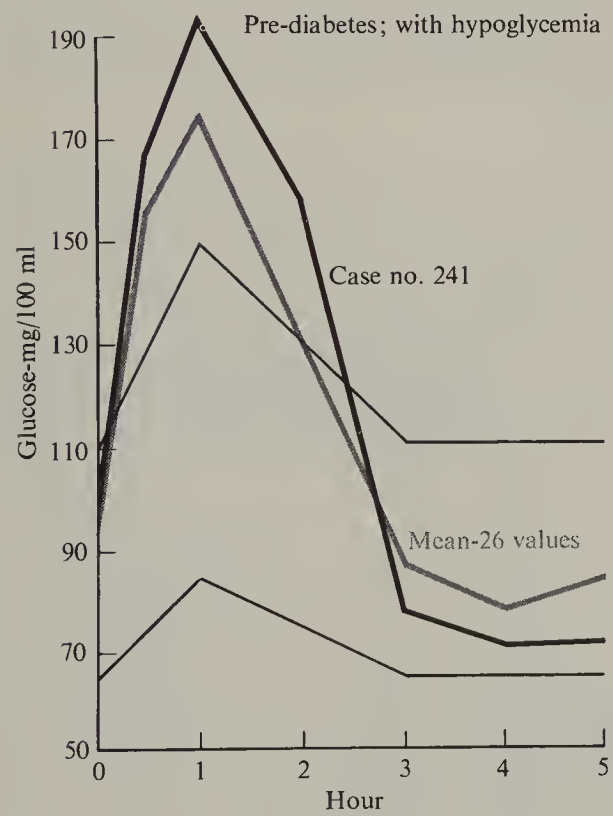


FIGURE 21-9.
Pre-diabetic glucose tolerance response, with hypoglycemia.

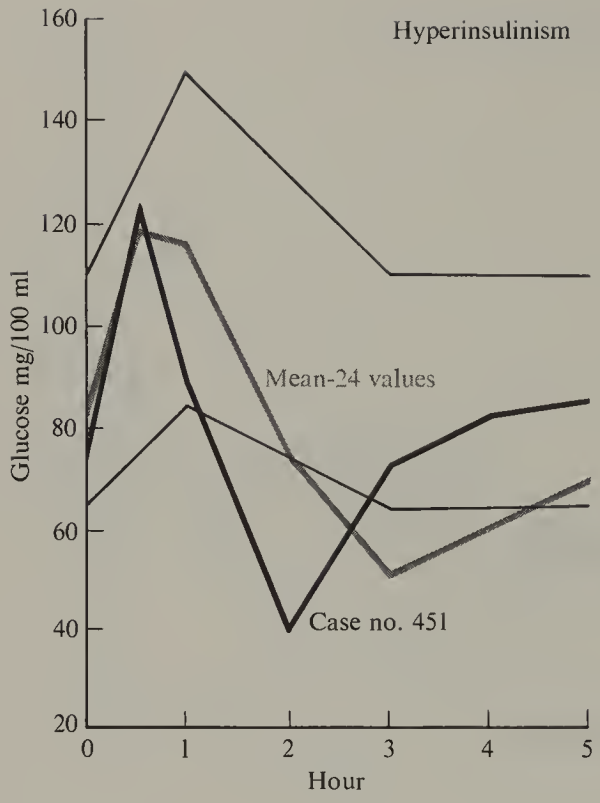


FIGURE 21-10.
Hyperinsulinism glucose tolerance response.

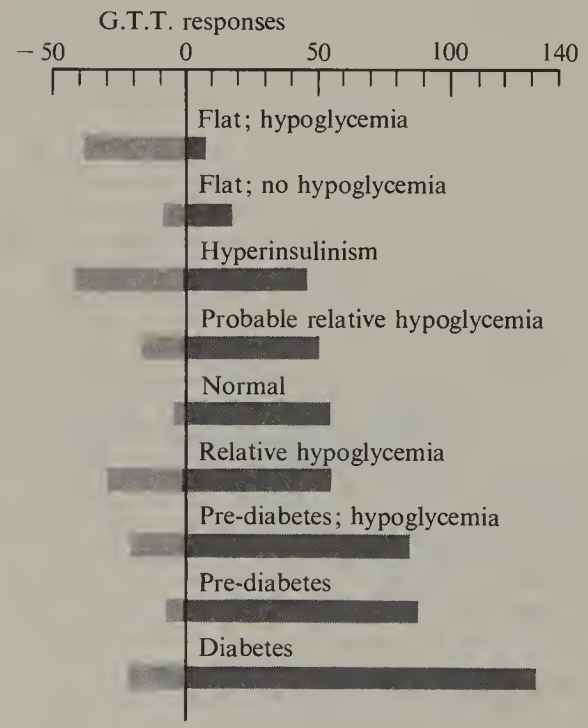


FIGURE 21-11.
Mean positive and negative fluctuation in glucose concentration from the fasting level for the nine categories of patients described.

A series of patients was found who demonstrated a relatively high-normal fasting blood glucose level which, after the glucose challenge, showed little or no elevation in blood glucose but exhibited a decrease of more than 20 mg per 100 ml. This flat response, depicted in Figure 21-8, may also be due to malabsorption, caused by any one of the pathophysiological disturbances noted earlier.

The eighth category of response is shown in Figure 21-9. The largest number of patients are found in this category, characterized as pre-diabetic with hypoglycemia. Although this designation is contradictory, the psychophysiological manifestations are equally confusing.

The data depicted in Figure 21-10 conform to Harris' (1936) definition of hyperinsulinism, where the blood glucose drops below 50 mg per 100 ml. A surprisingly large number of patients comprise this category, and even more surprising is the number of patients who showed blood glucose concentrations between 20 and 40 mg per 100 ml during the five-hour test interval. Again, there is insufficient laboratory data available to define this as a problem of the pancreas, adrenal cortex, or the anterior pituitary.

The histogram in Figure 21-11 illustrates the mean minimal and maximal fluctuations of glucose concentration from the fasting level for the nine categories of patients described. Of the 133 patients evaluated for GTT response, 95 (71 percent) demonstrated a hypoglycemic response of one type.

The data were then examined to determine whether there was either an age- or sex-dependent relationship associated with the GTT response. From the data shown in Table 21-2 it is seen that the sex of a patient shows no statistically significant

TABLE 21-2.
Sex Distribution in Relation to Glucose-Tolerance Response

GTT Response	Males	% all Males	Females	% all Females	Total	% of Total
Normal	4	7.8	12	14.6	16	12.0
Flat, without hypoglycemia	4	7.8	5	6.1	9	6.8
Pre-diabetic	2	3.9	3	3.7	5	3.7
Diabetic	2	3.9	3	3.7	5	3.7
Relative hypoglycemia	13	25.6	11	13.4	24	18.0
Probable relative hypoglycemia	4	7.8	13	15.8	17	12.8
Flat, with hypoglycemia	2	3.9	5	6.1	7	5.4
Pre-diabetic, hypoglycemia	9	17.6	17	20.8	26	19.6
Hyperinsulinism	9	17.6	15	18.3	24	18.0
Total	51	38.4	82	61.5	133	100.0

relationship to the GTT response. Similarly, from Table 21-3 it is apparent that there is no relationship between age and response, other than the majority of patients being between the ages of 20 and 49.

Finally, the GTT responses were compared with the initial psychiatric impression, and also with the HOD-test diagnoses. As will be noted from the data presented in Table 21-4, there is a large incidence of relative hypoglycemic responses

TABLE 21-3.
Patient Age in Relation to Glucose-Tolerance Response

GTT Response	20	20–29	30–39	40–49	50–59	60–69	Unknown	Subtotal
Normal	2	5	4	2	1	0	2	16
Flat, without hypoglycemia	0	4	3	0	0	0	2	9
Pre-diabetic	1	1	0	2	0	0	1	5
Diabetic	0	4	0	0	1	0	0	5
Relative hypoglycemia	1	4	8	5	0	0	6	24
Probable relative hypoglycemia	1	6	4	2	1	0	3	17
Flat, with hypoglycemia	0	2	3	1	0	0	1	7
Pre-diabetic, hypoglycemia	2	8	6	3	1	1	5	26
Hyperinsulinism	0	4	6	4	3	1	6	24
Total	7	38	34	19	7	2	26	133

and pre-diabetic–hypoglycemic responses in chronic schizophrenics, and a similar relationship between hyperinsulinism and psychoneurosis. Of those patients categorized as chronic schizophrenics, 70 percent exhibited some form of hypoglycemia. Although the initial clinical impression cannot be directly compared with the HOD-test diagnosis, the incidence of various hypoglycemic responses was essentially the same, as was the relationship between hyperinsulinism and psychoneurosis. Of the patients yielding positive HOD-test results, 69 percent are included in the general category of hypoglycemia. These findings are tabulated in Table 21-5.

DISCUSSION

The responses of randomly selected psychiatric patients to a five-hour GTT in this study amplifies the observations of Tintura (1966, 1967) and Salzer (1966). Of 300 patients evaluated by Salzer (1966), 39 percent were classified as hypoglycemic. In Tintura's (1967) study of 200 patients, 26 percent were hypoglycemic. On the basis

TABLE 21-4.

Comparison of Glucose-Tolerance Response with Psychiatric Evaluation

GTT Response	Chronic schizophrenics		Acute schizophrenics		Borderline		Psychotic		Nonpsychotic		Neurotic		Other	
	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
Normal	7		0		6		0		0		2		1	
Flat, without hypoglycemia	4		0		3		0		0		2		0	
Total	11	22	0	0	9	39	0	0	0	0	4	14	1	13
Pre-diabetic	1		0		0		0		2		2		0	
Diabetic	3		0		1		0		1		0		0	
Total	4	8	0	0	1	4	0	0	3	30	2	7	0	0
Relative hypoglycemia	13		0		4		2		2		2		1	
Probable relative hypoglycemia	6		4		2		0		1		3		1	
Flat, with hypoglycemia	1		0		2		1		1		1		1	
Pre-diabetic, with hypoglycemia	10		3		3		0		3		4		3	
Hyperinsulinism	5		1		2		2		0		13		1	
Total	35	70	8	100	13	57	5	100	7	70	23	79	7	87
Grand Total	50		8		23		5		10		29		8	

TABLE 21-5.

Comparison of Glucose Tolerance Response and HOD Diagnosis in 113 Psychiatric Patients

GTT Response	Positive		Positive reversal		Positive paranoid		Borderline		Neurotic		Other	
	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
Normal	11		3		1		1		2		1	
Flat, without hypoglycemia	2		2		1		2		1		0	
Total	13	27	5	36	2	50	3	27	3	12	1	10
Pre-diabetic	0		1		0		2		1		1	
Diabetic	2		2		0		0		2		0	
Total	2	4	3	21	0	0	2	18	3	12	1	10
Relative hypoglycemia	8		0		0		0		4		2	
Probable relative hypoglycemia	8		0		0		0		4		1	
Flat, with hypoglycemia	2		1		0		1		0		1	
Pre-diabetic, with hypoglycemia	11		2		2		3		1		3	
Hyperinsulinism	5		3		0		2		10		1	
Total	34	69	6	43	2	50	6	55	19	76	8	80

of an initial clinical psychiatric impression and clinical laboratory findings, 74 percent of our 133 patients were classified as hypoglycemic. Utilizing the HOD-test diagnosis for 113 patients, 66 percent were classified as hypoglycemic. The larger percentage of patients classified as hypoglycemic in this study can be attributed to the nature of the patient population entering the study.

There are insufficient clinical laboratory data available to state categorically that hypoglycemia is a consequence of hypoadrenocorticism, although the general symptoms observed by Tintura (1955, 1966, 1967), together with the psychoendocrine studies of Portis and Zitman (1943), Conn and Seltzer (1955), Sachar et al. (1963), Bunney and coworkers (1965), and Fawcett and Bunney (1967) would appear to implicate adrenal cortical function in certain types of mental illness. In the light of what is known about the "general adaptation syndrome" of Selye (1946), the use of adrenal cortical extract as proposed by Tintura (1966, 1967) would appear to be advisable. Crude adrenal cortical extract provides a balanced hormone preparation which appears to uniformly promote realignment of carbohydrate metabolism and readjustment of salt-water balance, without overwhelming an already exhausted adrenal cortex, as is believed to be the case in hypoglycemia.

If the adrenal cortex is involved in psychiatric disturbances, particularly schizophrenia, then why have Hoffer et al. (1957), Hoffer and Osmond (1960), Ward (1967), Tobin (1967), and Herjanic et al. (1967) been able to report consistently favorable results using niacin and ascorbic acid in the treatment of schizophrenia, and in the absence of supplemental steroid therapy?

The increased production of steroid hormones from the adrenal cortex, stimulated by corticotropin, is believed to result from increased supplies of reduced nicotinamide-adenine dinucleotide phosphate ($NADPH_2$). An attractive theory has been proposed which ascribes the initiation of this process to the production of adenosine triphosphate (ATP) from adenosine-3′,5′-diphosphate, which, in turn, activates phosphorylase. Glycogen is then converted into glucose-1-phosphate at an increased rate, and this to glucose-6-phosphate, which is metabolized by a process of dehydrogenation. Consequently, increased amounts of $NADPH_2$ are synthesized, and these serve as a source of energy for a number of steps in steroidogenesis (Haynes et al., 1960).

In addition, steroid dehydrogenases use both nicotinamide-adenine dinucleotide (NAD) and nicotinamide-adenine dinucleotide phosphate (NADP) as coenzymes, and steroid hormones exert their action by catalyzed transhydrogenation of reduced nicotinamide-adenine dinucleotide ($NADH_2$) to NADP. The general requirement for $NADPH_2$ and oxygen in the utilization of steroidal 11β-, 17- and 21-hydroxylases is well established (Pincus, 1959). These steroid enzymic catalysts exhibit a high degree of specificity with respect to the position and steric configuration of the hydroxyl group undergoing oxidation. Catalytic quantities of some steroids mediate transfer of hydrogen between NAD and NADP in the presence of certain

hydroxy-steroid dehydrogenases. An 11β-hydroxysteroid dehydrogenase from liver is effective with both NAD and NADP, converting cortisol to cortisone.

Ascorbic acid, also in catalytic quantities, has been shown to exhibit an inhibitory effect on steroid 11β-hydroxylase in the adrenal cortex (Hayano, 1966), and Cooper and Rosenthal (1962) demonstrated a similar effect with steroid C-21 hydroxylase. Kitabachi (1967) has theorized that the high concentration of ascorbic acid found in the adrenal cortex regulates steroidogenesis, and that during stress or stimulation by corticotropin the bulk of ascorbate is released before steroidogenesis can proceed. If the cortex is deficient in ascorbic acid, continual stress will result in a depletion of nonregenerative catalytic products, with a continuous outpouring of cortical steroids until the gland is exhausted. It would appear, therefore, that ascorbate restrains steroidogenesis, and niacin (as NAD or NADP) promotes it.

CONCLUSIONS

In a group of 133 psychiatric patients a marked incidence of hypoglycemic responses was determined during a 5-hour glucose-tolerance test.

Based upon an initial clinical psychiatric impression there appeared to be a significant incidence of relative hypoglycemia in chronic schizophrenic patients, and an equally large incidence of hyperinsulinism in psychoneurotics. When tested in relation to the HOD-test diagnosis, the comparison holds for hyperinsulinism in psychoneurosis.

Neither age nor sex are apparently related to either the GTT response or the psychiatric classification employed.

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22

Relative Hypoglycemia in Schizophrenia

ROBERT L. MEIERS

"Relative Hypoglycemia is a clinical syndrome in which patients develop symptoms referable to any system of the body as the result of a relative drop in the blood sugar level in response to a high carbohydrate intake and/or stimulants such as caffeine" (Salzer, 1966). This condition, which was first described by Harris (1924), has been referred to as functional hyperinsulinism, functional hypoglycemia, neurogenic hypoglycemia, idiopathic hypoglycemia, benign hypoglycemia, functional hypoadrenal corticism (Tintera, 1955), and reactive hypoglycemia (Buehler, 1962). The terms reactive and relative are more consistent with the method of diagnosis and our current understanding of the condition than are the other terms, which imply an underlying cause or process that may be correct, but at the present time cannot be easily identified in clinical practice. The diagnosis is often suspected from the history, including eating habits and presenting symptoms, but generally can be confirmed by a six-hour glucose-tolerance test. The patient's own fasting level is the base or standard from which the other readings are judged. If any subsequent glucose concentration drops 20 mg percent (that is, per 100 ml of blood) or

more below the fasting level, the diagnosis is definite (Gyland, 1957; see graphs A, B, C, E, Figure 22-1). Often there is an increase or recurrence of symptoms coincident with the drop, often occurring if the rate of drop is 1 mg percent per minute or more (Striker, 1952; Hoffer, 1970; graph A). A drop of 10 to 20 mg percent below the fasting level is considered to be within the borderline area (Buehler, 1962). A flat curve in which the glucose concentration does not rise more than 20 mg percent above the fasting level is also considered positive (Salzer, 1966; Abelson, 1966; Tintera, 1966; graph F). The normal boundaries of the six-hour glucose-tolerance test have been determined by Buehler (1962) and Phillips (1959).

In some instances it is difficult or impossible to do a six-hour glucose-tolerance test because the patient has very difficult veins to find, or is afraid of needles. In such cases the number of blood withdrawals can be reduced to the fasting, the third hour, and the fourth hour (graph H). Another procedure is to give the glucose as if the test were going to be performed; instead no blood is withdrawn, but the patient keeps a record of how he feels during the following six hours. If there is an aggravation or recurrence of symptoms that cannot be otherwise explained, this constitutes presumptive evidence of the diagnosis. Of 180 consecutive patients who had the six-hour glucose-tolerance test, I was able to make an accurate diagnosis in 80 percent from the history and the description of their reaction during the test before I saw the results of the test. Another short test that has been used by Fredericks and Goodman (1969) for screening is to take a fasting level, after which the patient eats his normal breakfast and the test is repeated 45 to 60 minutes later. If the blood sugar at that time has not risen 50 percent or more above the fasting level, the patient is presumed to have relative hypoglycemia. Finally, if the symptoms and the laboratory tests are still doubtful or conflicting, a therapeutic trial sometimes will resolve the problem. Gastrectomized patients will almost always show a marked abrupt rise with a marked abrupt fall within two hours. Occasionally a severe "dumping" syndrome will be precipitated, which raises doubts as to the advisability of doing the test on these patients (Nawman, 1966; Alpert, 1967; graph I).

The six-hour glucose-tolerance test monitors the glucose regulating mechanism following a challenge. Many factors have been identified that influence the blood glucose level, including diet, alcohol consumption, stimulants, the gastric secretion of insulin-stimulating hormones (Unger, 1967), glucose absorption rate from the intestinal tract, the liver's ability to store and convert glucose as well as release it, the pancreas' rate of producing insulin and glucogon, the adrenal's capacity to produce adrenalin and glucosteroids, the thyroid, human growth hormone (Luftet al., 1966), central glucose regulating centers in the hypothalamus, plus the autonomic regulating centers and the emotions acting through the higher cerebral structures on the regulating centers (Buckley, 1966). This is not a complete list of the factors involved, but it is enough to help recognize that at any given time the blood glucose level is the result of many complex forces. In spite of this, most patients

respond favorably to a relatively simple treatment; that is, a diet low in carbohydrates, especially sugar, high in proteins, moderate fat with frequent feedings, and the avoidance of caffeine, alcohol, and smoking, if possible (see Table 22-1).

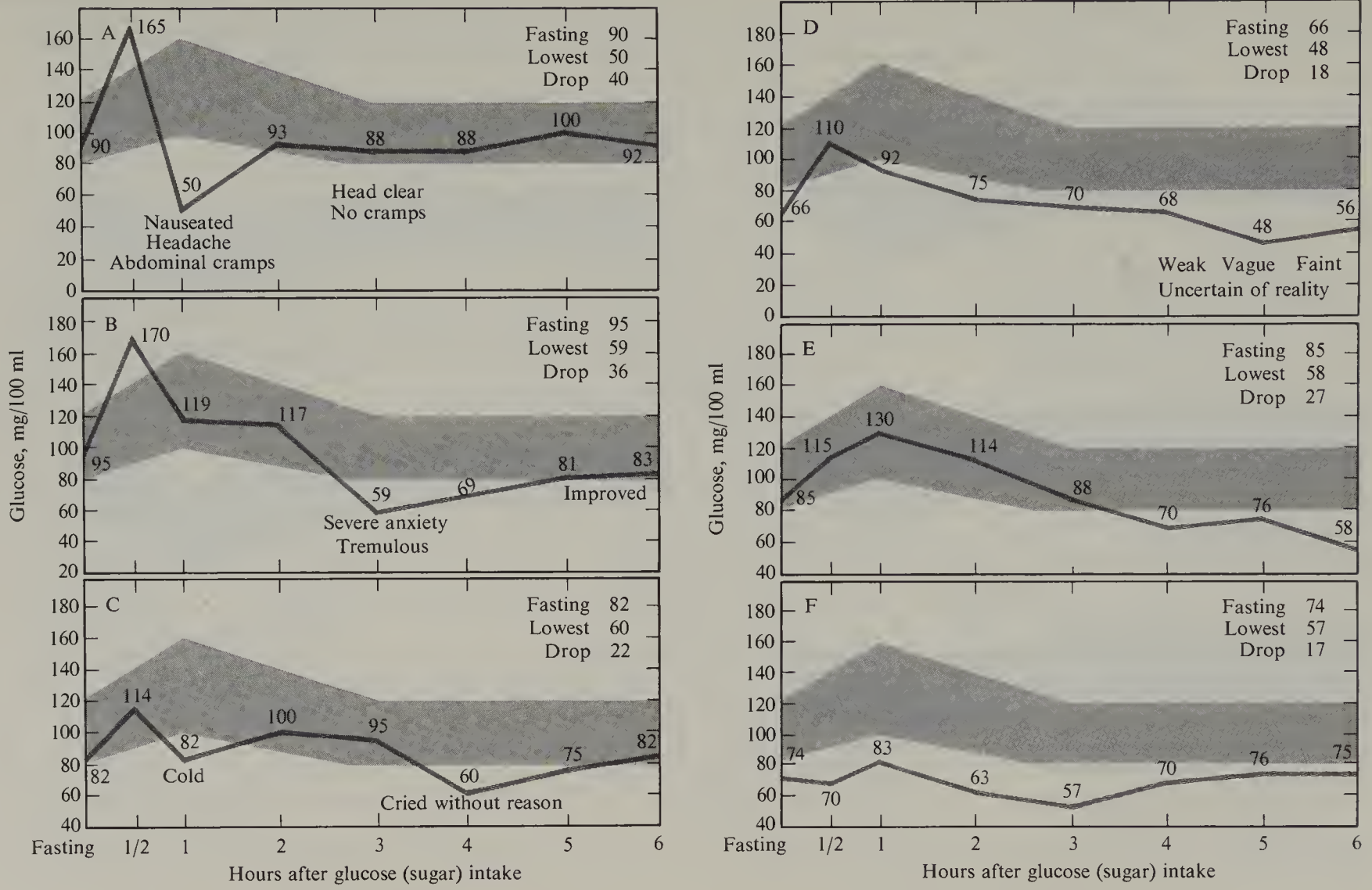
It should be pointed out that relative hypoglycemia does not have a special relationship to schizophrenia, as compared to other psychoses and neuroses. Of the few psychiatrists who have incorporated the treatment of this condition into their practice, none have reported it to be more prevalent in any particular diagnostic category (Salzer, 1966; Fabrykant, 1955; Cott, 1967; Meiers, 1967; Ward, personal commun.). They find it to occur in from 30 to 70 percent of all their psychiatric patients. The difference in the percentage reported can be explained partly by the fact that before the physician becomes known for his awareness of relative hypoglycemia, he is seeing an average distribution of patients. Later, his referrals become increasingly selected by ex-patients, who are amazingly accurate at predicting the diagnosis. However, the symptoms of fatigue, depression, confusion, and anxiety that frequently occur with relative hypoglycemia are also seen as the first early symptoms in many schizophrenics (Cott, 1967). In my own practice, I am finding it in approximately 70 percent of those tested. Some patients are not testable, either because they are too disturbed or because it would be unwise to discontinue their medication for the few days required before the test. There are some conditions that are not purely psychiatric in which there is an extremely high incidence of relative hypoglycemia. A few of these are alcoholism, peptic ulcer, and asthma. In my own experience, it occurs in 95 percent of alcoholics.

Even though relative hypoglycemia is not specific to schizophrenia, it is important to anyone working with schizophrenia to recognize that relative hypoglycemia can be an aggravating or precipitating factor in anyone predisposed to schizophrenia. Treating the relative hypoglycemia can be a valuable adjunct in the total treatment program, both in helping to reduce relapses and in attaining a higher level

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FIGURE 22-1.
(*See following two pages.*) Examples of results of 6-hour glucose-tolerance test. Left margin shows the blood sugar in milligrams per 100 ml of blood (mg percent). The shaded area shows the normal range. Normally, sugar will be lost through the kidneys when the level reaches 160 to 200 mg percent. At one-half hour the blood sugar level should not exceed the fasting level by more than 75 mg; the one-hour level should not be over 160 mg. A drop of 10 points below the fasting level is considered suspicious of hyperinsulinism and a drop of 20 or more points is definite. A flat response is also considered to show hyperinsulinism.

Discussion of examples: A. A first-hour drop, which would have been missed on the modified test. B. A third-hour drop (third- and fourth-hour drops are the most common). C. A fourth-hour drop. D. A fifth-hour drop. E. A sixth-hour drop, showing value of the 6-hour test. F. A flat curve. G. This chart demonstrates that even when diabetes is suspected it is valuable to do the 6-hour test instead of a 2-hour test to check for a reactive hypoglycemia. H. Example of a modified test, with only fasting—third-hour and fourth-hour samples. I. A typical test (post-partial gasterectomy). J. A significant drop with no symptoms—patient was much improved after one month of treatment. K. Less than 20 mg percent drop, yet produced symptoms—patient improved on diet.


A
Fasting 90
Lowest 50
Drop 40
165
90
50
93
88
88
100
92
Nauseated
Headache
Abdominal cramps
Head clear
No cramps
B
Fasting 95
Lowest 59
Drop 36
170
95
119
117
59
69
81
83
Severe anxiety
Tremulous
Improved
C
Fasting 82
Lowest 60
Drop 22
114
82
82
100
95
60
75
82
Cold
Cried without reason
D
Fasting 66
Lowest 48
Drop 18
110
66
92
75
70
68
48
56
Weak Vague Faint
Uncertain of reality
E
Fasting 85
Lowest 58
Drop 27
115
85
130
114
88
70
76
58
F
Fasting 74
Lowest 57
Drop 17
74
70
83
63
57
70
76
75
Glucose, mg/100 ml
Fasting 1/2 1 2 3 4 5 6
Hours after glucose (sugar) intake

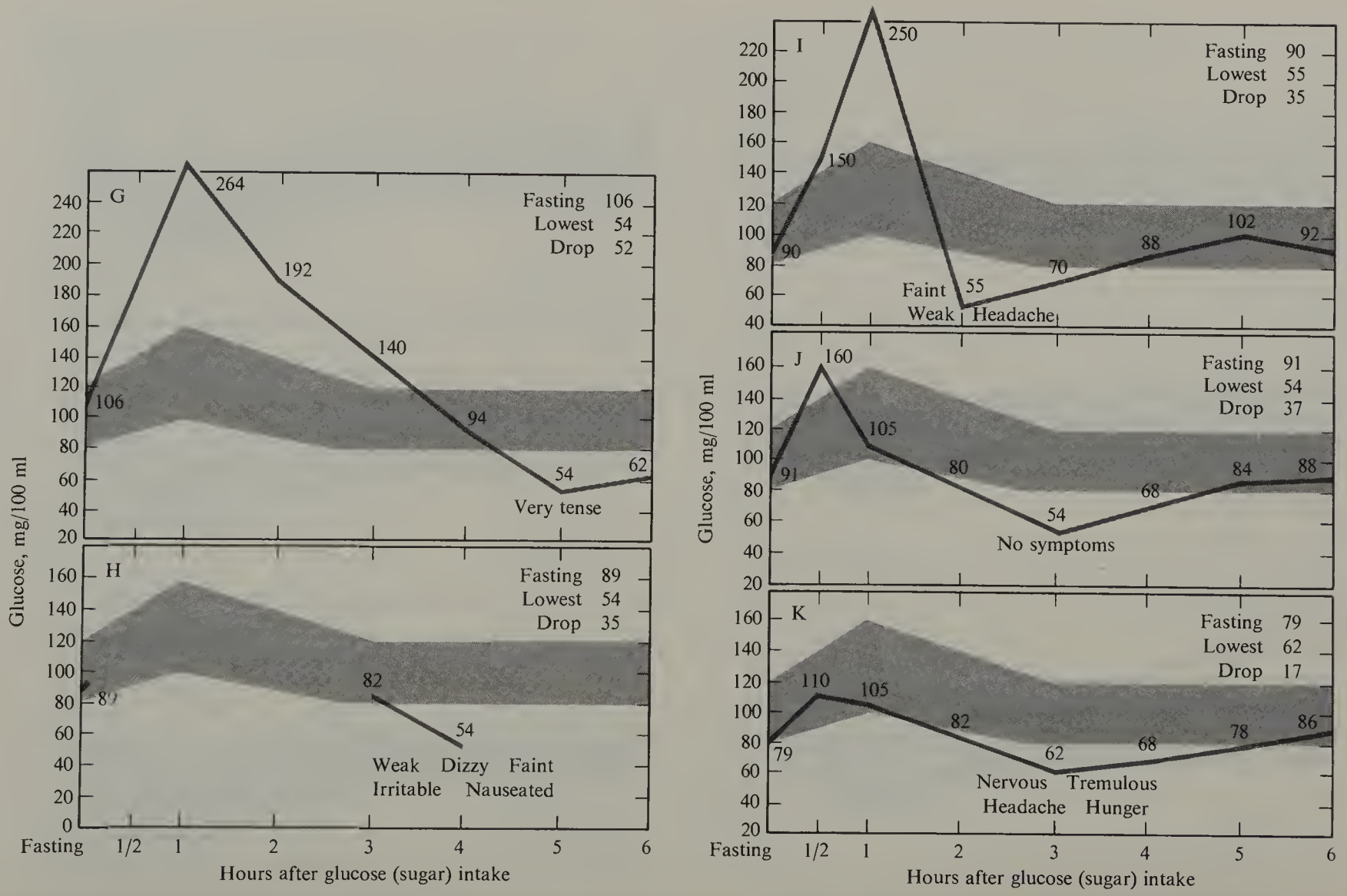

G
Fasting 106
Lowest 54
Drop 52
264
192
140
106
94
54
62
Very tense
H
Fasting 89
Lowest 54
Drop 35
89
82
54
Weak Dizzy Faint
Irritable Nauseated
I
Fasting 90
Lowest 55
Drop 35
250
150
90
70
88
102
92
55
Faint
Weak Headache
J
Fasting 91
Lowest 54
Drop 37
160
105
91
80
68
84
88
54
No symptoms
K
Fasting 79
Lowest 62
Drop 17
110
105
82
79
62
68
78
86
Nervous Tremulous
Headache Hunger
Glucose, mg/100 ml
Fasting 1/2 1 2 3 4 5 6
Hours after glucose (sugar) intake

TABLE 22-1.

Diet for Relative Hypoglycemia

Immediately on Arising: one medium orange or 4 to 6 oz. fresh or frozen orange juice
Breakfast: fruit or 4 oz. juice; 2 eggs with meat or cheese; one slice of whole grain bread, or toast with butter or oleomargarine; milk
fresh milk fortified with non-fat milk powder, eggs, soyflour, protein powder, but preferably with yeast, may be substituted for breakfast
Two Hours after Breakfast: 8 oz. of juice or milk, buttermilk, yogurt, peanut butter, cheese, protein tablets, or small handful of nuts, sunflower or pumpkin seeds
Lunch: meat, fish, cheese, or eggs; vegetable or leafy salad with dressing; if desired, one slice of whole grain bread with butter or oleomargarine; fruit, milk, buttermilk, or yogurt
2 or 3 Hours after Lunch: same as mid-morning snack
One Hour before Dinner: 4 oz. juice or milk
Dinner: soup if desired (not thickened with flour), and/or salad; meat, fish, cheese, eggs or poultry; vegetables; one slice of whole grain bread if desired, with butter or oleomargarine; fruit; milk, buttermilk, or yogurt
Before Retiring: same as earlier between meal snack
If symptoms are severe, a high protein snack may be temporarily taken hourly throughout the day.

Foods and Drinks Allowed

Vegetables: fresh, frozen, or canned artichoke, asparagus, avocado, beets, beet and turnip greens, broccoli, Brussels sprouts, cabbage, cauliflower, carrots, celery, cucumbers, eggplant, garlic kale, chard, lettuce, mustard greens, mushrooms, okra, onions, peppers, pumpkin, radishes, sauerkraut, soy beans, spinach, squash, string beans, sunflower seeds, tomatoes, turnips, water cress (corn, limabeans, lentils, peas, brown rice, and potatoes in very small amounts)
Fruits: fresh or unsweetened cooked, frozen, or canned apples, apricots, berries, cherries, coconut, grapefruit, kumquats, lemons, limes, mango, melons, papayas, peaches, pears, pineapple and tangerines—with or without cream but without sugar (plums, grapes, and bananas only as dessert)
Juices: the following if unsweetened: apple, grapefruit juice, pineapple, tomato, vegetable (orange juice or whole orange only on arising or as a dessert)
Beverages: milk, buttermilk, juices, caffeine-free tea, or decaffeinized coffee
Oils: one or two tablespoons of salad oils daily used in cooking, salad dressings, and as seasoning for vegetables
Desserts: unsweetened fruits

Strictly Avoid the Following

sugar, honey, candy, cake, chewing gum, sweetened gelatins, pastries, pie, puddings, sweet custards, jam, jelly, marmalade, ice cream and sherbet

coffee, tea, cola drinks; any sweetened carbonated drinks; fruit juices not listed above such as grape or prune; beer, cocktails, cordials, wine

dates, dried fruits, figs, prunes, raisins

macaroni, navy and kidney beans, noodles, white rice, spaghetti, ravioli, pizza

medications containing caffeine such as Anacin, A.P.C., Trigesic, A.S.A. Compound, B.C., Caffergot, Coricidin, Empirin Compound, Florinal, Four Way Cold Tablets, Salfayne, Stanback (plain aspirin and Bufferin are permitted)

Read the label on every can of juice, fruit, vegetable, meat and other products. Select only those containing no syrup, honey, or sugar. These can be found on the dietetic counters in all large markets.

To understand the diet for relative hypoglycemia, read *Let's Eat Right to Keep Fit*, and *Let's Get Well* by Adelle Davis; *Low Blood Sugar and You* by Carlton Fredericks, Ph.D., and Herman Goodman, M.D. Then, using a table of food analysis, count grams of protein. Obtain 80 to 100 grams a day, divided into six meals, preferably three main meals of a minimum of 20 grams each and between meal snacks of 10 grams each.

of functioning (Cott, 1967; Meiers, 1967; Ward, personal commun.). The physician's awareness of relative hypoglycemia and its treatment leads him into the area of nutrition and a recognition that he was never really exposed to the field of nutrition. As a result, he never felt the need to consider it important enough to include in his histories or treatments. Once he is aware, he becomes concerned about the diet of the general population, including his own, and appalled at the diet of most of his patients. The diet he is prescribing for his patients with relative hypoglycemia is not special in the sense that the diets for peptic ulcer or gout are, but is a good natural diet for everyone. In fact, there is reason to believe that persons who have developed relative hypoglycemia and possibly many other illnesses are those whose systems have not been able to tolerate our cultural diet with its heavy emphasis on sugar, coffee, cola, caffeine-containing analgesics, and alcohol (Salzer, 1966; Tintera, 1967; Yudkin, 1963). If these actually are sources of stress to the body, and the removal of stress is one of the goals of treatment, then this diet for relative hypoglycemia is potentially of value in the treatment of all patients with schizophrenia and most other illnesses. This line of thinking applied in practice has produced many surprisingly pleasant results. As a standard procedure, after diagnostic evaluation and recommending appropriate treatment for schizophrenia, I add, "I am also placing you on a more natural diet." This applies to all patients, whether they have relative hypoglycemia or not. The point is that the improved nutrition itself might be the most beneficial factor (Meiers, 1967). Fortunately for patients who are interested in learning more about their condition and its treatment, the following books are available, written for the layman but also of value to the physician: *Body, Mind and Sugar* by Abrahamson and Pezet (1951); *How to Live With Hypoglycemia*, by Weller (1968); *Exhaustion, Causes and Treatment* by Roberts (1967); *Nutrition and Mental Health* by Blaine (1969); and *Low Blood Sugar and You* by Fredericks and Goodman (1969). An increasing number of articles on this subject are appearing in popular lay magazines, including the A.M.A.'s "Today's Health" (Cole, 1968). There is also a Hypoglycemia Foundation (149 Wilmot Road, Scarsdale, New York) which disseminates information to laymen and physicians. In reviewing the medical literature since 1924, it is amazing to find how many papers have been published on this subject in most of the medical journals in the United States. This being the case, it is puzzling, indeed, why such a common disorder has remained almost unknown in the medical profession. It is analogous to the physician who said that after graduating from one of the finest medical schools he thought the most common cause of a cough was cystic fibrosis of the pancreas. Some of the physicians who have tried very hard to correct this oversight have been Harris (1935, 1936), Portis and Zitman (1943), Portis (1950), Abrahamson, Gyland, Fabrykant, Tintera, Buehler, and Salzer. The above-mentioned books contain almost all of the relevant information about relative hypoglycemia since it was first described.

Salzer (1966) has tabulated the incidence of presenting symptoms which can be helpful in increasing one's suspicion. However, since the incidence of relative hypoglycemia is so high in psychiatric patients, I have made the six-hour glucose-tolerance test a routine part of the initial evaluation, when possible. Without the test, how can one differentiate the cause of the following symptoms attributable to relative hypoglycemia: depression, insomnia, irritability, anxiety, lack of concentration, crying spells, phobias, forgetfulness, confusion, unsocial and antisocial behavior, and suicidal thoughts? In addition, the patient might complain of headache, dizziness, internal and external tremulousness, numbness, blurred vision, staggering, faintness, and twitching. Very often, exhaustion, chronic or episodic fatigue, and lack of drive are presenting symptoms. It has been surprising how readily patients accept this test, which reveals the problem to be the physician's reluctance and not the patient's. Often, when I am explaining a positive curve to a patient, he will volunteer additional symptoms that now make sense to him. If he is asked why he had not mentioned them before, he will say that he had tried to discuss them with other doctors and had been told repeatedly that they either were of no significance or were part of his emotional reaction, since all physical and laboratory examinations were normal.

It is important to chart the six-hour glucose-tolerance test on a graph. The patient can understand and appreciate the mechanism involved much better when viewing a graph, which motivates him toward following the treatment. In the explanation of the curve, the use of the mechanism of the thermostat is often helpful. The patient can understand that normally the glucose regulating mechanism keeps the blood glucose level within certain limits. When it is not operating properly, it allows the blood sugar level to fluctuate too much; in their case too low, in diabetics too high. Those physicians who view the disorder as primarily functional hyperinsulinism will explain to their patients that an abrupt rise in the blood sugar level normally stimulates the pancreas to produce insulin to utilize and store the glucose and bring the level back to the fasting level. But, they will continue, their patient's problem is that his pancreas has become hypersensitive and produces too much insulin when stimulated and causes the blood sugar to drop too low.

Those physicians who view the disorder primarily as functional hypoadrenalcorticism explain to their patients that the response to glucose stimulation is normal during the initial rise, with an appropriate insulin response, but that the adrenals are unable to respond adequately as the blood sugar level is dropping, thus allowing it to drop too low.

Many of the symptoms can be explained in terms of the reaction to (1) a rapidly decreasing blood sugar concentration, (2) the final lowered level, when the body, including the brain, has less fuel to function optimally, and (3) the compensating reaction to the hypoglycemia, especially the secretion of the adrenals. Fabrykant

(1955), Altschule (1966), and Buckley (1966, 1969a, 1969b) have described the mechanisms involved in considerable detail.

Another important factor is the patient's sensitivity to a change in glucose concentration. There is a wide variation. Some people can have rather marked fluctuations in their curve and experience few, if any, symptoms (graph J); others will have fairly severe symptoms with less than a 20 mg percent drop (Ashe et al., 1927; graph K). The first group will generally have less incentive to follow the treatment but if they do, they often report feeling better in general or being relieved of symptoms they had failed to mention earlier. It is important to remember that the treatment is aimed not only at relieving stress from excessive sugar, stimulants, and alcohol but also at improving nutrition. Because of this, it is difficult to assess which produces the desired effect and to what extent. This raises a very interesting point. If everyone were receiving optimum nutrition, what effect would this have on the incidence and severity of all illnesses, as well as the general level of functioning? Optimum is the key word, since there is increasing evidence that members of the same species have a considerable variation in their nutritional requirements (Williams, 1951, 1962, 1967). If our cultural diet continues to deteriorate and many illnesses increase in frequency, I can foresee a time when physicians will require many of their patients to correct their diet before proceeding with the evaluation or treatment. There is a possibility that the gradual change in dietary habits away from those of primitive man, especially the increased use of refined sugar, caffeine, alcohol, and nicotine, might be contributing to the development of relative hypoglycemia (Powell, 1934). Yudkin (1963) has explored this possibility in relation to obesity and myocardial infarction.

The diet originally prescribed for relative hypoglycemia by Harris was later modified by Gyland. His diet has been modified and brought up-to-date with the help of the nutritionist Adelle Davis. The patient is given a copy of the diet (Table 22-1) which includes some suggested reading. A multivitamin-mineral supplement is recommended. In addition, various adjuncts have been and are being used. Abrahamson and Hoffman (1949) and Salzer (1966) advise using injections of 10 ml of Calphosan (a calcium glycerophosphate preparation), especially during the first two to four weeks. Buehler (1962) has found injections of vitamin B complex, vitamin B12, and nicotinic acid to be helpful, especially in those who do not respond satisfactorily to diet alone. Tintera's treatment (1955, 1966, 1967) routinely includes injections of whole adrenal cortical extract plus other hormones. Fabrykant and Pacella (1947) reported finding hypocalcemia and electrocerebral dysfunction in a high percentage of patients with relative hypoglycemia. When they added calcium and Dilantin® to the treatment, their results improved. For outpatients, I usually prescribe only the diet plus oral vitamin supplements for a month. If there is little or no improvement, I begin adding the above adjuncts. They do help some patients but I have not found any way to predict which adjunct will help which patient. This

fact reveals the complexity of the condition and our lack of understanding. I have found it helpful to have patients analyze their daily activities and learn to identify those that are stressful for them and avoid them if possible. If not, an attempt is made to modify their attitudes about the activity or situation which will decrease their experiencing it as stressful. Also, in the beginning of treatment, it is helpful to have the patient simplify his life as much as possible and develop a routine which allows an appropriate amount of rest and exercise. The most common time of the day for fatigue or tension to occur is middle to late morning or middle to late afternoon, which are appropriate times to schedule rest periods.

I have purposely excluded the usual physical causes for hypoglycemia, such as insulinoma, because they are included in textbooks and therefore are well known even though they are quite rare. Conn and Selzter (1955) have reported comprehensively on this aspect of hypoglycemia. As a generalization, it can be stated that if the blood sugar does not drop below 50 mg percent during the first two hours, it is not likely to be due to an insulinoma (Abelson, 1966).

SUMMARY

Relative hypoglycemia is present in up to 70 percent of patients with schizophrenia; inadequate diet exists in almost 100 percent. Since the diet used in the treatment for relative hypoglycemia also improves nutrition in general, it is a valuable adjunct in the treatment of all patients with schizophrenia.

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23

Blood Histamine, Basophil Counts, and Trace Elements in the Schizophrenias

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VENELIN ILIEV
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FOREWORD

The clinical investigator may have several cogent biochemical theories backed by his clinical observations. These are far from proved facts, but then the whole of neurobiology is only a continuous "progress report" on how best to cope with schizophrenic patients who do not get well with the medications presently available. With our biochemical approach to therapy many suggestions (entirely of a research nature) will be made in this chapter. This seems justified since each patient with the symptoms of schizophrenia is a research problem requiring extensive biochemical studies and careful physiological judgment. It is to be hoped that research studies involving trace metals will attract the attention of research workers in all countries to the many problems found in the gigantic biochemical hodge-podge now classified under the heading of "schizophrenia."

One of the most likely biochemical defects in the schizophrenias is an overactive methylation process (Smythies, 1963). Methylation of any biogenic amine results in a

compound with greater lipid solubility and greater brain stimulant effect. The amines presently under study are (1) dimethoxyphenethyl amine (DMPEA) and its acetyl derivative, (2) bufotenine and other tryptamine derivatives, (3) 6-hydroxydopamine, (4) adrenochrome and adrenolutin, and (5) methylated homo-anserine derivatives. We postulate that all these compounds are brain stimulants, which may produce a schizophrenic-like syndrome which is biochemically unique but neuropharmacologically similar, in that the net result is an individual who is over-aroused or overstimulated.

EVIDENCE FOR THE THEORY OF OVERSTIMULATION IN THE SCHIZOPHRENIAS

Goldstein et al. (1965) have shown by statistical analysis that the brain waves of chronic male schizophrenics are relatively nonvariant, or hyperregulated. This and other abnormalities are characteristic of a continued overalertness or state of overstimulation, and distinguish the schizophrenic from the normal subject, who has hyperregulated brain waves only under the influence of LSD-25 or other profound stimulants. Pfeiffer et al. (1965) have shown that treatment of schizophrenic patients with Thorazine® or Trilafon® is accompanied by a return of the brain waves to the normal range of variation and that the degree of schizophrenic behavior and overstimulation is decreased.

Goldstein and Beck (1965) have also shown that doses of 1 μg/kg of LSD-25 given to normal volunteers causes hyperregulation of the brain waves, which then simulate the brain waves of the schizophrenic. This is because LSD-25 is a profound, and probably specific, brain cortical stimulant. All the hallucinogens have been shown to be brain stimulants in rabbits. The use of antidepressants has given rise to a new side action as a result of the brain stimulation which accompanies overdosage. A schizophrenic psychosis may develop upon treatment of a depressed patient who previously had frequent episodes of depression, but no episodes of schizophrenia. Similarly, a recent study of such stimulants in schizophrenics under blind test conditions has shown that these medications will make schizophrenics significantly worse. A study of an antidepressant in the New Jersey Neuro-Psychiatric Institute showed that as the quantitative brain waves became more hyperregulated, the behavior of the schizophrenic patients worsened. The use of iproniazid as a stimulant was in part the direct outgrowth of the euphoria and stimulation seen in tuberculous patients. Iproniazid in overdosage produced a psychotic state.

We have shown by both behavioral and objective EEG (electroencephalogram) data that schizophrenics can tolerate a cerebral depressant, such as an oral dose of 200 mg of pentobarbital, better than the normal volunteer can. In contrast, as

judged by emotional outbursts, the schizophrenic's tolerance of 1 μg/kg of LSD-25 was less than a normal subject's.

In February 1968, at a meeting on the "neurobiology of psychopathology" three groups of investigators essentially agreed with Goldstein that overstimulation is inherent in the schizophrenic. Venables (1966) presented his evidence for overstimulation, which was confirmed by the findings of Kornetsky and Mirsky (1966). Marjerrison et al. (1967) also found the brain waves of the schizophrenic to be hyperregulated, and that the degree of arousal anxiety increased when the patient had hallucinations. Calloway (1969) states that the quantitative brain wave is a useful index of arousal anxiety in the schizophrenic, and that the so-called withdrawn, unresponsive, chronic schizophrenic is extremely aroused, even though he may be just sitting with his eyes open. He is unresponsive only because he is pushed to his limit.

The schizophrenic patient has long been known to be an isomniac. This insomnia may precede the psychosis, extend through catatonic states, and be evident in the hospital wards at night if the patients are not treated with tranquilizers. Preliminary brilliance or prepsychotic stimulation may be one of the first signs of a psychotic break. The psychosis of prolonged wakefulness may also provide an example of the psychogenic effect of forced overstimulation that is physically induced. While no quantitative data are available, the brain waves of prolonged wakefulness are, by inspection, similar to those of the schizophrenic. Thus, these various observations would indicate that the schizophrenic is, indeed, in a chronic overstimulated or overaroused state.

This overstimulation does not respond to the usual doses of barbiturates, alcohol, or other anti-anxiety drugs. The patient can be sedated only by adequate doses of the truly antischizophrenic drugs.

HISTAPENIA (H−), HISTADELIA (H+), AND THE BASOPHIL COUNT

We first tested our new method for the determination of blood histamine on August 10, 1966, on a group of hospitalized male chronic schizophrenics. Their mean blood level was lower than that of our male and female laboratory personnel: 27.2 $\pm$ 23 ng/ml for patients versus 44.6 for normal males and 46.6 for normal females. This same low level was again found one month later. After three months of treatment with antipsychotic medication, the histamine level in these schizophrenic patients rose to a normal level of 47.9 $\pm$ 22. Since many more patients were needed to determine the significance of this initial finding on the small group of 20 males, we turned to outpatient schizophrenics to test the theory that some of them have low blood histamine, and that this abnormality may reflect their degree of schizophrenia.

Histamine, a decarboxylation product of the amino acid histidine, is found in nearly all body tissues, usually in the mast cells. It is present in sufficient quantities so that the total amount of bound histamine in the body could be lethal if suddenly released, as in anaphylaxis. Histamine is found in all nerve cells, with the highest concentration in the postganglionic sympathetic nerves. The brain tissue as a unit, however, has the lowest level of histamine of any soft tissue. The distribution in the discrete parts of the brain follows that of serotonin and norepinephrin. In addition to the mast cell histamine, which is bound with heparin and zinc, histamine occurs in the CNS and other organs in a form free of mast cells which occur only rarely in the CNS. When tested in the trained rabbit, histamine is a CNS cortical stimulant, and this property is enhanced by methylation of the aliphatic amino group. Most of the blood histamine (95 percent) is contained in cellular elements such as the basophils and platelets. The total blood histamine is constant in males, but in females varies with the menstrual cycle, with the lowest level at one week after cessation of the menses and the highest level at or before menstruation. A head cold may be accompanied by an abnormally high blood histamine level.

Histamine was considered around 1930 to be a possible factor in schizophrenia, when one theory held that intoxication by amines absorbed from the large intestine could cause schizophrenia. However, the most pertinent observations that might link histamine to the schizophrenias are as follows (see Green, 1970, for review):

1. Infrequent allergic reactions in hospitalized schizophrenics.
2. High tolerance to injected histamine, shown by minimal skin response, no headaches, and minimal biological effects of large doses.
3. Blood serum from some schizophrenics decreases the histamine contraction of the guinea pig ileum in vitro.
4. Leblanc and Lemieux (1961) found fewer mast cells in the tissues of schizophrenics. After therapy an increase occurred in the number of mast cells, with the increases proportional to the therapeutic response to chlorpromazine.

Most of these studies considered the schizophrenic population as homogeneous or afflicted with a single disorder, so the previous work on histamine might have been more understandable if various possible biochemical types of schizophrenia had been taken into consideration. This is important, since seven or more disease entities (and hence biochemical types) have been separated from the schizophrenias since the turn of the century (Pfeiffer et al., 1970a).

Historically, the research scene shifted to serotonin when the specific biological relationships to LSD-25 and reserpine were discovered. The present intense biochemical effort concerns the catecholamines mainly because the methods for study have been evolved to a high degree of sophistication. The therapeutic use of L-dopa in Parkinsonism has also focused research on catecholamines.

Histamine and the polyamines spermidine and spermine have attracted less attention than these other biogenic amines in efforts to disclose new etiologies for the schizophrenias. Until now a specific and sensitive chemical method for the determination of blood and tissue histamine was lacking. The discovery of spermidine as the interfering substance in the chemical determination of blood histamine casts doubt on previous histamine studies (Kremzner and Pfeiffer, 1965). Furthermore, no longitudinal studies to determine the change in histamine levels with change in mental state have been reported. A better understanding of the role of histamine and histidine in the biochemical processes of the human body is needed, now that Heath and Krupp (1967) have presented the hypothesis that brain auto-immune mechanisms are involved in schizophrenia.

The accurate method for the determination of blood histamine, the quantitative EEG method for precise assay of the degree of brain arousal, and the Experiential World Inventory (EWI) to determine the degree of disperception and thought disorder now make possible the correlation of biochemical findings with the neurophysiological status and psychiatric state of the schizophrenic patient. With sufficient samples and patients the correlations can be made by the application of statistical methods to the large number of simultaneously collected numerical observations. The simultaneous measurements have been 20 or more, as follows: mean energy content (MEC) of the occipital leads of the EEG, coefficient of variation (CV) of the EEG, EWI total score, the eight subheadings of the EWI, blood histamine, spermidine, spermine, serum uric acid (SUA) level, age of the patient, serum iron, serum copper, and serum zinc. Serum creatine phosphokinase was also determined. Our previous studies have dealt with the computer output on histamine levels and the types of schizophrenia. This report will deal with several individual patients of the histapenic (H−) and the histadelic (H+) types. The patients are chosen because of the severity and chronicity of their schizophrenic symptoms and the contrasting nature of the findings in regard to blood histamine levels. The studies on 102 patients (Pfeiffer et al., 1970a) with their correlations have already been reported, so graphs and a few individual case studies will suffice to illustrate the role of histamine levels in directing therapy.

Clinical Symptoms of the Histapenic (H−) and Histadelic (H+) States

On visual inspection of the charts of individual patients it is found that 50 percent have a low blood histamine with a rise in blood histamine as they improve, while 20 percent have a high blood histamine with a decrease as they improve. This may indicate that most patients have an optimal level near the mean where their symptoms are lessened.

A few patients may have normal blood histamine (50 ng/ml), which then rises to 70 or 80 as their psychiatric status improves.

The H− patients are characterized by a lower intercorrelation of the subparts of their EWI tests (a mean of r of +0.48 compared with +0.84 for the H+ group). At present this can only be explained as a greater variety of disperceptions and basic symptoms which peak more randomly. This is borne out by the clinical histories: the H+ patients have depression, obsession with suicide, disperception, and thought disorder, and the H− patients have all the classic symptoms of schizophrenia, including paranoia and hallucinations (Table 23-1). Some of these differences

TABLE 23-1.

Differences in the Clinical Symptoms and Responses of Low and High Blood Histamine Patients

	(H−) Histapenia (50%)	(H+) Histadelia (20%)
Psychiatric symptoms		
Suicidal depression	1+	4+
"Blank mind"	1+	4+
Thought disorder	4+	2+
Paranoia	3+	1+
Hallucinations	4+	1+
Metabolic differences		
Blood basophil count	>0.4%	<0.6%
Headaches	1+	4+
Fat distribution	Stalagmitic	Normal
Speed of ejaculation	Slow	Fast
Reaction to pain	1+	4+
Dental caries	4+	1+
Salivary flow	1+	4+
Head colds (symptoms)	None	Normal
Skin pigmentation	Fair	Normal
Allergies	Rare	Common
EEG overarousal	4+	4+
Familial disorder	1+	3+
Age at onset	Any	Adult
Responses to Therapy		
Antipsychotic drug treatment	3+	1+
Niacin/vitamin C	3+	?
Folic acid 2.5 mg/day—B-12, 1 mg	3+ Sometimes dramatic!	Worsens
High protein diet	Yes	No
ECT/Insulin	3+	1+
Methadone and antihistamines	0	3+
Zinc and manganese therapy	2+	3+
Diphenylhydantoin therapy (Dilantin)	Worsens	Benefits

are useful in the classification of the patients. The lack of head colds or allergies, and failure of the male to accomplish ejaculation indicate H−, probably because these phenomena depend on a normal supply of tissue histamine. Presence of allergies, headaches, premature ejaculation, and a familial history of schizophrenia with suicide probably indicates H+. The reaction to pain may depend on tissue histamine levels. Fat distribution and skin pigmentation are more difficult to understand at present.

A composite case history of a histapenic (H−) patient can be given as follows. The patient is a hyperactive male child who is unnaturally healthy. For example, the rest of the family may get head colds but the H− patient either misses the cold, or the virus infection fails to produce a rhinitis. He is hypoallergic and sneezes only as a reflex, for instance, when he moves from shadows into bright sunlight. He may show no signs of pain even when seriously bruised or when a venous blood sample is obtained. Corporal punishment is relatively useless because a slap causes little pain. The child is constantly active and sleeps poorly, with the hyperactivity he may show compulsive stereotyped movements. Ideation, thought processes, and verbalization may be delayed in development, or may be bizarre. His attention span is short and learning is poor. Although his ability in some areas may be high when tested, a high degree of disperception may be present in many spheres, such as sensory, time, body, self, and perception of others. The teenage patient will be depressed and/or confused by the disperceptions, which will contribute to a very high HOD or EWI score. These teenage patients may develop paranoia or hallucinations. With paranoia alone the HOD or EWI score may be low.

The quantitative EEG will show a high degree of brain-wave overregulation, so that the standard deviation of the EEG will be very low—perhaps less than half that of the normal.

Finally, the blood histamine will be below the normal level of 50 ng/ml (5.0 mcg percent) and the basophil count may be well below 0.5 percent (Figure 23-1).

A composite case history of a histadelic (H+) can be given as follows. The patient presents herself as one who is unhappy and has a blank mind. An intense preoccupation with suicide occurs frequently, and the family will have a history of depression or suicide: a single, ineffective method of suicide is usually considered. The patient is referred to as being schizophrenic although the interview may give the initial impression that he has a neurotic or psychotic depression. However, the EWI test (Experiential World Inventory) discloses schizophrenia with psychotic depression and suicidal tendencies. The MMPI test gives a high rating (90) in schizophrenia and a high rating (80) on depression.

The past history shows that ECT and/or insulin therapy has not provided lasting benefit. The usual procedures, such as megavitamin therapy plus antipsychotic medication, may improve the patient to a definite plateau but no further. This may be inadequate since unreality, blank mind, and depression persist although the patient

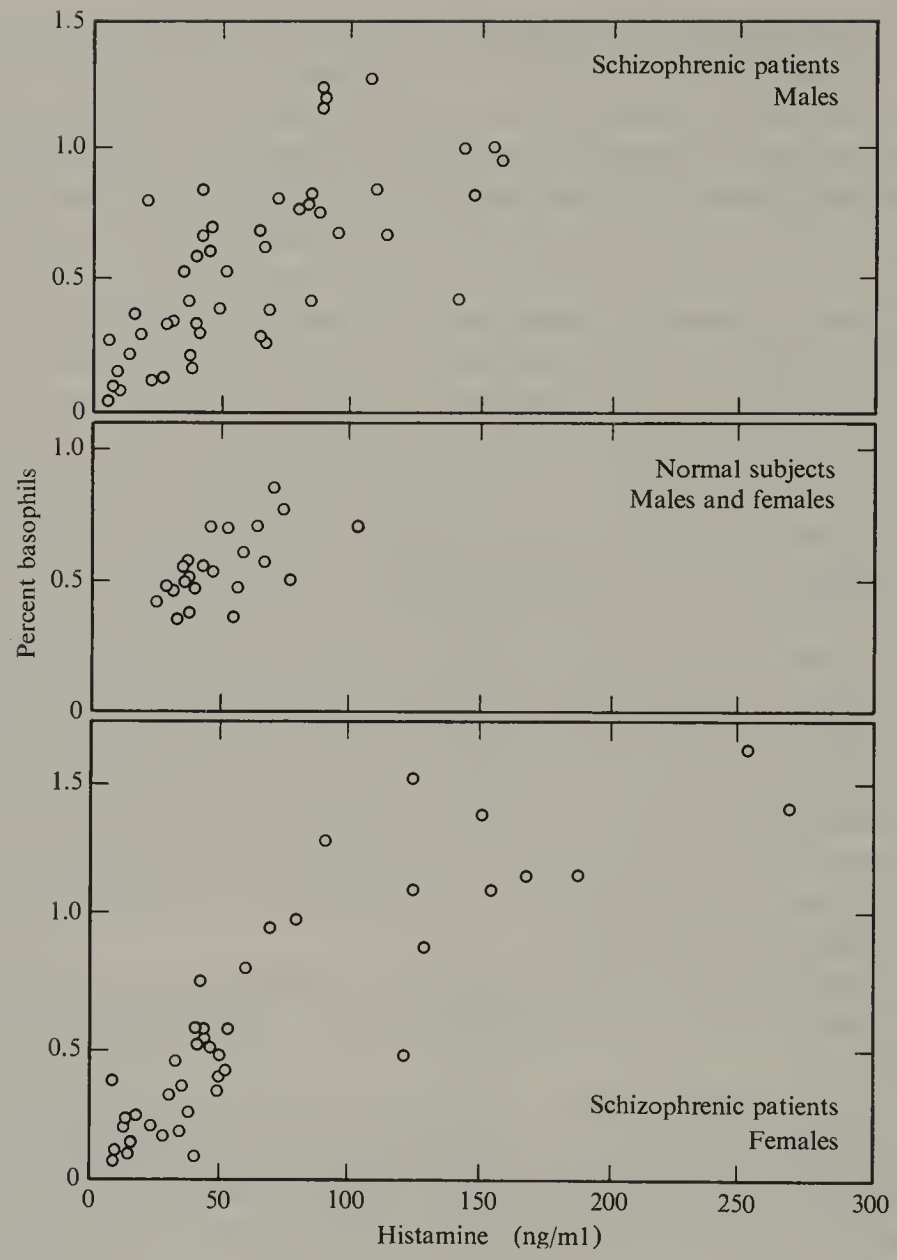


FIGURE 23-1.
Comparison of basophil count versus blood histamine plots in normal subjects and schizophrenic outpatients. Normal basophil count is 0.5% and blood histamine is 50 ng/ml. The normals cluster around these two values. Schizophrenics are frequently either low or high in their basophil count and blood histamine. For male schizophrenics the value of r was 0.75, $P < 0.0001$; for normals 0.60, $P < 0.001$; and for females 0.87, $P < 0.0001$. This knowledge is helpful since few hospital laboratories can do histamine levels, but all can learn to do accurate basophil counts (Shelley, 1963). Statistical analysis of these data was done using Box's (1949) criterion for comparison of covariance matrices. In this case the estimated Chi-square value was 33.28. With 3 degrees of freedom, this value corresponds to a probability $P < 0.0001$ that the patients (both males and females) and the normals belong to the same statistical population.

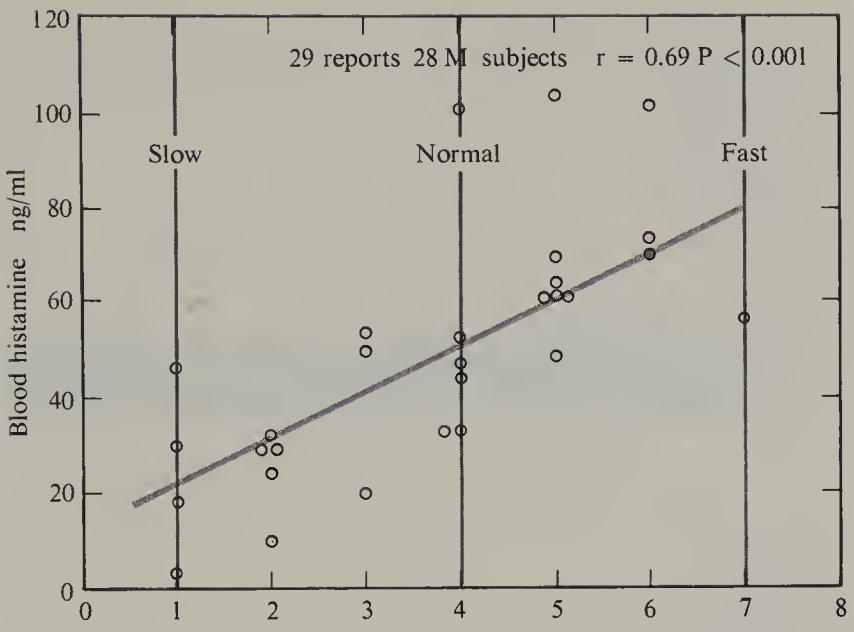


FIGURE 23-2.
Relative speed of ejaculation in male schizophrenic patients when not on Mellaril. Category 1: inability to achieve ejaculation. Category 7: ejaculation on reading a pornographic story. Most of the high-histamine males have premature ejaculation. The very low-histamine patients cannot achieve ejaculation, but this ability returns to normal when therapy raises the blood histamine.

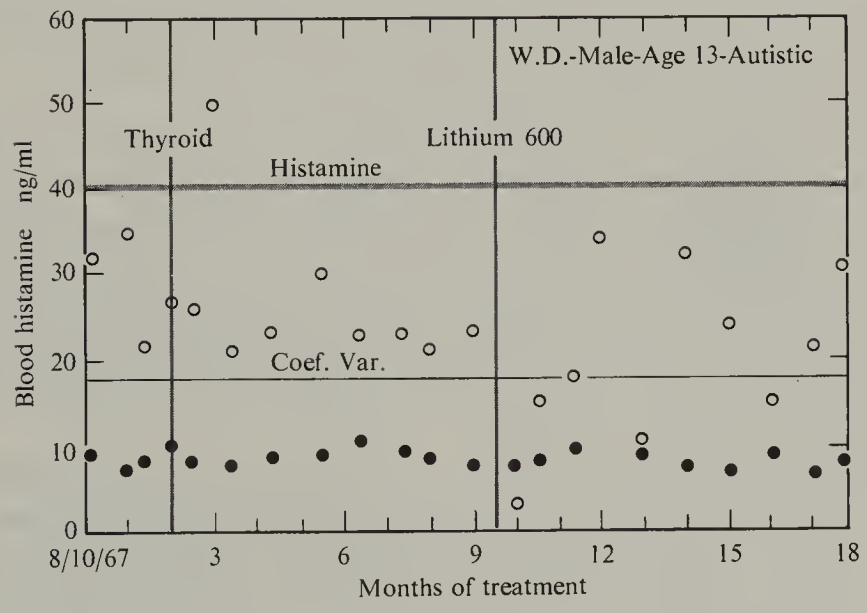


FIGURE 23-3.
Quantitative EEG and blood histamine, autistic male, tested from age 11½ to 13 years. The brain waves remained overregulated for the 18-month study period. Only one histamine (after thyroid) was in the normal range. Patient improved with puberty, and at age 14 his histamine was 39.5 ng/ml and EEG 8.4, which is low compared to 18 for normals.

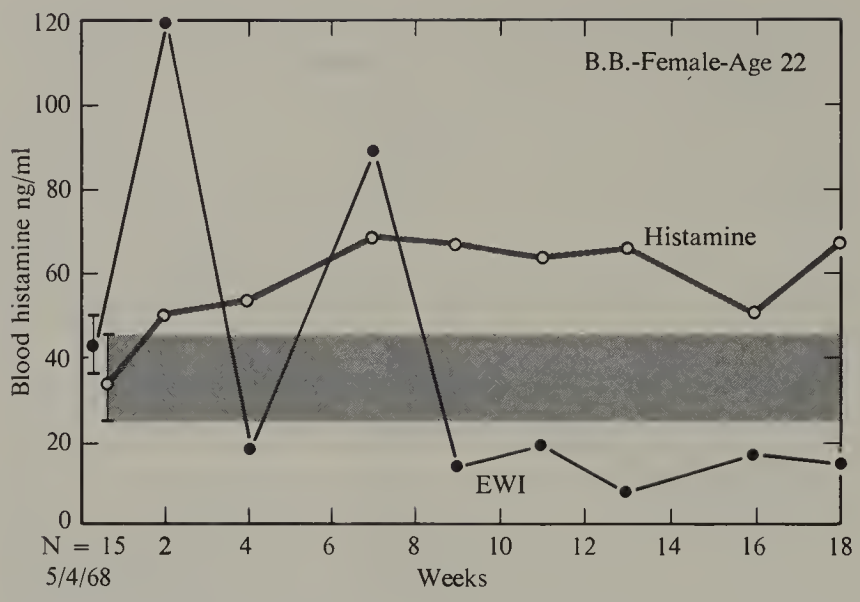


FIGURE 23-4.
Change in Experiential World Inventory after starting lithium therapy in a 21-year-old female schizophrenic patient (B. B.) who had not responded to megavitamin therapy in 15 months of treatment. The histamine (which averaged 33 ng/ml (lines represent mean ± S.D.) rose to about 60, and the EWI came down to normal. Remission of schizophrenia occurred when histamine rose. In spring of 1970 patient used contraceptive pill and symptoms of schizophrenia recurred with rise in copper level. (See Table 23-8.)

does not have hallucinations or paranoia. In our experience the majority of these patients are female although this preponderance may merely indicate the greater efficiency of the adult male in his suicide attempts.

A degree of H+ also characterizes the addict, but he usually has in addition a character disorder which makes him unreliable in treatment. We do know that when all else (ECT, insulin and antipsychotic drugs) fails, the patient may respond slowly to small doses of methadone given at bedtime, and when we consider the alternatives, methadone becomes a life-saving drug. Before starting therapy, methadone treatment should be discussed fully with the patient and responsible relatives. The main side effect is nausea and occasionally vomiting when the patient is given methadone while taking other major CNS drugs.

The histadelic patient shows a blood histamine level greater than 60 ng/ml (normal blood histamine level is 40 to 60 ng/ml and a basophil count above 0.6 percent of the WBCs.) Approximately 20 percent of the so-called schizophrenics fall into this class.

Since the main differences in the H− and H+ patients is in degree of depression and the degree of paranoia, we have compared the available age-matched Minnesota Multi-phasic Personality Inventories of male and female patients. In each instance an H− patient was matched against an H+ patient of the same age. Five pairs of males and seven pairs of females were compared (Table 23-2; note that each group

TABLE 23-2.

Schizophrenic Patients Age-Paired for MMPI Comparison

Patients	L	F	K	HS	D	Hy	PD	MF	PA	Pt	Sc	MA	SI
Females: 7 pairs													
High histamine mean*	43	81	47	60+10	87+8	72+10	84+8	47+10	83+10	87+9	94+12	64+11	67+10
S.D.	+2	+15	+7										
Low histamine mean	44	74	50	65+10	81+12	75+6	84+10	41+5	76+12	75+16	85+13	63+13	65+10
S.D.	+12	+10	+7										
t-test P										<0.05	<0.1		
Males: 5 pairs													
High histamine mean	51	73	53	72+13	102+17	78+12	71+9	77+10	67+6	92+10	85+19	46+12	74+8
S.D.	5	12	11										
Low histamine mean	45	69	51	68+4	79+9	73+6	74+12	74+6	70+11	83+6	83+9	65+15	58+18
S.D.	7	6	10										
t-test P					<0.05					<0.1		<0.05	<0.1

* All blood histamine values are ng/ml.

Scales

L Overly defensive
F Exaggerating
K Overly defensive
HS Hypochondriasis
D Depression
Hg Hysteria
PD Psychopathic deviant
M-F Male-Femaleness
PA Paranoia
Pt Phobias, obsessions
Sc Schizophrenia
Ma Hypomania
Si Social interaction

TABLE 23-3.

Distribution of Two Psychiatric Symptoms among Schizophrenic Patients Divided According to Their Blood Histamine Levels. All numbers are percentage of patients showing either paranoia or suicidal depression. Paranoia is more frequent in a low-histamine patient, while suicidal depression is much more frequent in the high-histamine patient. This skewed distribution would occur by chance only once in 200 times.

Sex	Paranoid			Suicidal depressed		
	Low	Medium	High	Low	Medium	High
Male	36.7	16.7	27.3	0	19.4	50.0
Female	33.3	26.3	6.7	2.1	21.0	60.0
Total	35.0	20.0	18.9	1.0	20.0	54.0

$\chi^2 = 98.2$ $P = 0.005$

is very high in the "schizophrenia" and "psychasthenia" categories). Both male and female H+ groups are higher in depression, and with the male group this change attains statistical significance. In addition, the male H+ group is lower in the MA scale of the MMPI, "hypomania."

Yet another objective approach which relates the level of blood histamine to paranoia at the low end, and suicidal depression at the high, is the incidence of these two symptoms when the patients are divided into *Low*, *Median*, and *High* level blood histamine (Table 23-3).

Any generalization at this time on the role of histamine in schizophrenia is obviously premature. One is tempted to suggest, however, that histamine may be important in neurohumoral transmission and that stores of histidine (as in proteins or in the dipeptides homocarnosine and homoanserine) may be depleted during stress in one of the large subtypes of schizophrenias. Conversely, a smaller percentage and different subtype (perhaps one-fifth of the patients) may have an elevated blood histamine with schizophrenic symptoms. The schizophrenics would appear to have several biochemical changes which may correlate with psychiatric improvement.

Low-Histamine Patient (R. B.)

Female patient, age 21, onset of illness at age 12. Disorder started with two nights of crying and insomnia following marked fear of school plus other fears, such as of death and darkness. Returned to sleeping with mother in lighted room. Thorazine in large doses helped, barbiturates did not. Completed 8th grade but tolerated poorly

TABLE 23-4.

204 Total Group Significant Correlations. Computer readout of significant correlations of findings on 204 schizophrenic outpatients. The first two are well known to electroencephalographers and internists; namely, that brain waves get smaller with age and that older people get gout. The decrease in paranoia and increase in depression with age are well known trends.

Age of patient	vs.	Mean integrated amplitude	−0.282 (e)
Age of patient	vs.	Serum urate	+0.181 (c)
Age of patient	vs.	Paranoia	−0.138 (a)
Age of patient	vs.	Dysphoria	+0.151 (a)

P = 0.1 for a, 0.05 for b, 0.01 for c, 0.001 for d, etc.

the change to high school. Moderately controlled by large doses of Mellaril® for a 2-year period. Niamid® produced a complete breakdown with hallucinations, paranoia, ideas of reference, and inappropriate laughter and confusion.

After the sophomore year she stayed home, and on large doses of Stelazine® the disorder was sufficiently controlled so that she became a self-taught artist, but was too fearful to look for a job. Her only friends were in a nearby half-way house. She had stalagmitic obesity and shuffling gait during her teenage period.

Placed on megavitamin therapy at age 21 (3/25/67). Her blood histamine was found to be low. This therapy helped but her blood histamine stayed low until lithium therapy was added (5/4/68). Folic acid helped further (11/23/68). Zinc and

TABLE 23-5.

Group of Low-histamine Schizophrenic Outpatients. A 54 percent incidence of histapenia for schizophrenics is given by 111/204 patients. Abnormal ideation and impulsivity are significant only for males, while histamine versus disperception of self and time is significant only for females. The original negative correlation of histamine versus the total EWI score holds for males only. The menstrual cycle of the female causes the blood histamine to fluctuate.

Group	58 males	53 females
Age vs. mean int. amp.	−0.438 (d)	−0.308 (b)
Age vs. serum urate	+0.306 (b)	+0.289 (b)
Age vs. abnormal ideation	−0.273 (b)	—
Age vs. abnormal impulsivity	−0.232 (b)	—
Histamine vs. total EWI	−0.258 (b)	—
Histamine vs. disperception (self)	−0.256 (b)	−0.288 (b)
Histamine vs. disperception (time)	—	−0.279 (b)

P = 0.1 for a, 0.05 for b, 0.01 for c, 0.001 for d.

TABLE 23-6.

The D Family, a Typical Low-histamine Family (4 Daughters). The incidence of miscarriages of boy babies and presence of all girl families is high.

Family	Age	H	SPD	SP	SUA	Date
Normal values*		40–60	0.90	1.2	4–5	
Mr. D	59	15.2	0.60	1.27	7.09	07/26/69
Mrs. D	54	24.9	0.76	1.56	4.57	07/26/69
2 miscarriages						
4 daughters						
Pa	31	22.0	0.48	1.54	6.05	07/26/69
Na	21	30.1	0.68	1.40	3.43	06/12/69
Sa	19	24.5	1.34	1.83	7.68	02/03/69
		20.4	0.95	2.56	6.78	04/11/69
		16.4	0.82	1.99	5.07	06/11/69
		19.7	0.89	3.06	6.37	06/28/69
Ba	19	17.4	0.57	1.06	3.67	01/17/69
		31.8	0.52	1.56	3.91	01/31/69
		17.1	0.94	2.50	4.65	03/12/69
		23.5	0.75	1.84	4.57	06/10/69
		22.5	0.52	2.08	4.91	07/16/69

Source: Taylor and Levine, 1970.
* All blood histamine values are ng/ml.

TABLE 23-7.

The "D-M" Family, a Typical High-histamine Family. Only the middle daughter has a normal histamine level, 47. Mrs. M, the middle daughter, has had six miscarriages and four living children—all with high blood histamine levels. Note the high serum uric acid levels in the 8 and 10 year old children. This is an index of stress.

Family	Age	H	SPD	SP	SUA	Date
Normal values*		40–60	0.90	1.20	4.5	
Mr. D	60	63	0.68	1.50	8.64	8/16/69
Mrs. D	57	113	0.84	1.31	4.81	8/16/69
1 miscarriage						
3 daughters						
——, oldest	31		Not tested			
A.D., youngest	26	90	1.0	2.0	5.50	mean of 20+
Mrs. M., middle	28	47	0.79	1.33	5.15	8/16/69
6 miscarriages						
4 living children						
Tony M., male (cannot talk)	3	144	0.64	1.42	4.17	8/16/69
Larry M., male (cannot learn)	5	185	0.83	1.97	4.49	8/16/69
Philip M., male (allergies and infections)	8	189	0.88	1.96	7.25	8/16/69
		251	1.41	2.49	—	10/25/69
Ginger M., female (allergies and infections)	10	89	0.45	2.04	6.54	8/16/69

* Blood histamine values in ng/ml.

manganese therapy has aided in her complete remission. Birth control pill (started 3/7/70) caused high serum copper and return of psychiatric difficulties. Serum copper returned to control level only five months after birth control pill was stopped. (See Table 23-8.)

Low-Histamine Patient (R. R.)

Female patient, age 31. A sickly infant, an eight-month premature twin, lived in an incubator for three months (the male infant died 48 hours after birth). Had a congenital hip as a child, was delicate, a loner, and malnourished. She became an active horseback rider in her teens. She was mostly alone with horses, had paranoia, often felt people were following her. She was nervous and afraid of the dark. She was always a very poor student, could not concentrate, spelled words from right to left, and had no memory, not even for a phone number. She had bleeding gums, and in her late teens she developed rheumatoid arthritis. She was never suicidal. She always perspired so heavily that her clothes were ruined.

At the age of 27 she had a "nervous breakdown," going to the beach to rest and to cure the illness. The symptoms were constant crying and amnesia.

At 28 she married, and was under stress in her marriage. She never had a healthy sex life. She was beaten by her husband and gradually started to hear "stronger" voices and to see visions; she did not know they were unreal and began to act on the hallucinations and voices. She remained with no insight into her condition for eight months. During this period she was involuntarily committed to Bellevue Hospital in New York and then spent three weeks in a private hospital. She voluntarily signed herself out because she did not know she was sick and felt that her feelings of grandiosity were real.

After eight months of severe illness she started taking vitamin C. Two weeks after that she realized she was sick. She again went to a private hospital, stayed two days, then left to seek biochemical treatment, sensing her illness was chemical rather than "mental-environmental."

She started taking vitamin C in large doses. Her New York physician started her on megavitamin therapy; she did not respond to massive doses of niacin or niacinamide, but did respond to large doses of vitamin C. Blood tests showed a very low C level, 0.3 mg percent (normal is 0.7 to 2.0). Her P.B.I. was 7.2. Her T-3 was 17 (normal is 11 to 17). Her physician gave her the HOD Test. At the time of greatest disorder the total score was 159. With vitamin-C therapy the score fell to 43. She was prescribed folic acid and B12 and had a good response. She had had arthritis for three winters, and was bedridden for several weeks at a time, but for two years her arthritis has been in remission.

At the present time the patient has a good memory, is clear thinking with a

TABLE 23-8.

PATIENT'S NAME *R.B.* AGE *22* SEX *Female*

Date	MEC	CV	EWI	Medication	Hist	SPD	SP	SUA	LI+	Cu	Zn	Fe
1969												
3/8	97.4	15.6	20	Thyroid gr ii Stop Zn	75.0	0.98	1.71	5.81	0.80			
4/12	127	17.8	66	Thyroid gr ii NA/C	46.2	1.27	1.63	5.07	1.05			
5/31	93.5	15.5	18	ND–NA/C Tr-16 Thy D Li Mn	—	Lost Sample	—	4.41	0.80	1.36	0.66	0.88
7/5	—	—	13	ND–NA/C Tr-16 D Li Mn Thy	51.0	1.77	1.54	4.81	—			
8/9	139	17.7	18	ND–NA/C Thy Tr-16 D Mn Li+ E	87.7	1.36	1.44	7.36	0.80			
9/27	181	11.6	26	Stop Mn Thy ND–NA/C Tr-16 D Li+ E	63.1	1.22	1.52	6.21	0.50	2.30	1.18	1.18
10/18	158	32.9	8	ND–NA/C Tr-16 D Li E Thy	—	—	—	—	—			
12/6	153.8	19.6	14	Start Zn Thy Li B D Tr ND/C	43.9	1.98	1.67	6.37	0.85	1.52	0.76	0.94
1970												
1/24	—	—	—	Zn Thy Li B D Tr ND/C	—	—	—	*CPK*	—			
3/7	184	15.9	4	Start B.C. Pill	54.9	1.11	0.79	28		1.44	0.88	1.02

4/25	169	19.1	12	Li CMZ ND/C/NA	Tr-8	B	E	D(5)		39.5	0.92	1.10		1.00	3.24	1.34	1.52
6/6	139	26.3	66	Stop	B.C.	Pill				56.2	1.31	1.20		0.55	2.84	0.92	1.34
7/11	—	—	17	ZnMn	Tr	Li^+	D	B-12 B	E	Fo NA/C	—	—	—		0.50	2.96	0.94	1.40
8/22	179	14.2	25	ZnMn	Tr	Li^+	D	B	E	Thy NA/C	51.2	0.96	1.10		1.05	1.74	0.86	1.58
9/26			—	ZnMn	Tr	Li^+	D	B	E	Thy NA/C	—	—	—	*CPK*	1.35	1.56	0.90	1.60
11/7			15	ZnMn	Tr	Li^+	D	B	E	Thy NA/C	—	—	—	24	1.10	1.64	1.00	2.48
12/19			11	ZnMn	Tr	Li^+	D	B	E	Thy NA/C	—	—	—		1.15	1.48	0.98	1.45
1971																	
1/30	159	9.9	11	ZnMn	Tr	Li^+	D	B	E	Fo NA/C				31	0.80	1.54	1.20	2.12

Abbreviations

MEC = Mean energy content EEG
CV = Coefficient of variation of EEG
EWI = Experiential World Inventory
Hist = Total blood histamine ng/ml
SPD = Total blood spermidine μg/ml
SP = Total blood spermine μg/ml
SUA = Serum Uric Acid mg %

Li^+ = Serum lithium level m.e.q./l
Cu = Serum copper μg/ml
Zn = Serum zinc μg/ml
Fe = Serum iron μg/ml
CPK = Creatine phosphokinase
Thy = Thyroid
Zn = Zinc

NA = Niacin
C = Vitamin C
Mn = Manganese
ND = Niacinamide
Tr = Trilafon
Li = Lithium
E = Vitamin E 200 units

D = Deaner
B = Benadryl
Fo = Folic Acid
BC = Birth Control
CMZ = [Chromous acetate 0.1%
[Manganous chloride 0.5%
[Zinc sulfate 10.0%

cheerful personality, and is free from paranoia or hallucinations. She has normal sexual activity and normal sweat responses.

She states, "I now have a new body and mind that faulty body chemistry had denied me." (See Table 23-9.)

High-Histamine Patient (J. Z.)

Male patient, age 43, first seen in January 1969. He dated the onset of his mental illness to age 33 when he "came to" in a mental hospital. In all four hospitalizations he was diagnosed as schizophrenic. In the last hospital he stayed for a period of two months and had insulin and electro-shock therapy. On discharge he was placed on megavitamin therapy by the clinic psychiatrist.

His wife dated the onset of his illness to age 30 (in 1956), when he had exaggerated swings of mood, was abnormally argumentative and suspicious of people (including his wife), and had difficulty doing his work as a carpenter because of depression and suicidal thoughts.

The family history showed that he was one of six children. The oldest sister committed suicide while depressed. The oldest brother was diagnosed as a paranoid schizophrenic and died at the age of 39 of coronary heart disease. The youngest sister had had a postpartum psychosis after the birth of a boy. The mother had been in and out of hospitals for 40 years for the treatment of her schizophrenia.

Because of his high blood histamine, depression, and lack of response to antipsychotic medication he was treated with methadone and diphenhydramine, which relieved the depression and thought disorder but produced constant nausea and headaches. The methadone was discontinued after three months. Since then zinc, manganese, and calcium dietary supplement have been used. On this regime his EWI has decreased to a normal level and he is well maintained on the trace metals, Trilafon®, lithium, calcium, and megavitamin therapy. Blood histamine stays above normal. (See Table 23-10.)

High-Histamine Patient (D. L.)

Male patient, age 20, received psychiatric counseling through four years of high school. In January 1970 he had increasing spells of depression in which he talked of suicide. In one depression he attempted suicide with an overdose of anti-anxiety pills. He was hospitalized in a private mental hospital and given Triavil®, morning and night. In September he was transferred to a half-way house, where the medication was continued. At no time did he have hallucinations or a high degree of paranoia. Megavitamin treatment was started in November 1970. At that time his EWI was 77.

TABLE 23-9.

PATIENT'S NAME *R.R.* AGE *30* SEX *Female*

Date	EWI	Medication	Hist	SPD	SP	CPK	Cu	Zn	Fe
1970									
4/9	62	NA/C CMZ DBI	25.0	1.05	1.36		1.28	0.92	1.60
4/23	41	CMZ C E Vicol D Fo	46.3	1.17	0.97		1.34	1.02	0.76
5/28	21	CMZ Fo C E Thy D Ca Vicol	57.9	1.23	0.91	35	1.60	0.76	0.72
7/30	15	Zn Fo C E NA	66.3	0.83	1.67	23	1.42	0.94	1.48
9/21	6	Zn Fo C E NA	61.1	1.02	0.94	29	1.64	1.34	0.52
12/1	—	Zn Mn Fo C E NA	56.7	1.04	1.44	20	1.42	0.84	1.48
1971									
1/19	8	Zn Mn B-12 C E NA	79.2	0.66	1.33	20	1.70	1.04	0.80
3/5	10	Zn Mn B-12 C E NA	67.4	0.96	1.22	22	1.52	1.10	1.20
4/8	6	Zn Mn B-12 C E NA	61.6	1.37	0.92	24	1.58	1.04	0.88

Abbreviations

EWI = Experiential World Inventory
Hist = Total blood histamine ng/ml
SPD = Total blood spermidine μg/ml
SP = Total blood spermine μg/ml
CPK = Creatine phosphokinase
Li^+ = Serum lithium level m.e.q./l

Cu = Serum copper μg/ml
Zn = Serum zinc μg/ml
Fe = Serum iron μg/ml
NA = Niacin
C = Vitamin C
D = Deaner

E = Vitamin E 200 units
Thy = Thyroid
Ca = Calcium
CMZ = [Chromous acetate 0.1%
[Manganous chloride 0.5%
[Zinc sulfate 10.0%

Vicol = B-Complex
Fo = Folic acid
Mn = Manganous chloride

TABLE 23-10.

PATIENT'S NAME *J.Z.* AGE *43* SEX *Male*

Date	MEC	CV	EWI	Medication	Hist	SPD	SP	SUA	Li^+	Cu	Zn	Fe^+
1969												
				Direct from Hosp. Thor	75							
1/11	38.2	6.5	38	Start Lithium NA/C	124	0.44	1.40	7.76	—			
2/2	—	—	26	Thor. 75 Li NA–ND/C	96.6	1.26	1.28	5.47	0.75	meq/l		
2/15	44.7	21.4	23	Thor. 75 Li NA–ND/C	89.7	0.74	1.68	6.54	0.80	meq/l		
3/8	48.8	10.6	29	NA/C D Li^+ 900	135.5	0.64	1.09	6.70	0.65			
3/29	49.0	5.75	14	NA/C D Li^+ 900	128	0.73	1.08	7.76	0.65			
4/26	42	9.1	22	1 Wk Dol-5 Li^+ 1200 NA/C D	76.5	0.84	1.60	6.37	0.70			
5/10	47.6	5.9	26	Dol-5 Tr-8 Li-1200 Thy B-6	129.8	0.88	1.02	4.81	1.00			
6/7	59.7	10.1	28	Dol-10 Tr-8 Li-600 B	145.5	1.09	1.02	4.65	0.85			
6/21	51.9	10.5	18	Dol-15 Tr-8 Li-600 Thy	143	0.70	0.50	7.84	0.40			
7/5	53.2	10.7	15	Dol-15 Tr-8 Li-600 Thy	102	0.76	0.92	5.39	0.35			
8/9	55.9	15.1	15	Dol-15 Tr-8 El-25 Li-600	123	0.57	0.75	5.89	—			
9/13	46.6	10.5	—	NA/C Tr-8 B + Dol Li	122.4	0.63	1.23	5.89	0.25			
11/8	57.3	10.4	—	NA/C Tr-8 B + Dol Li Ziman (3)	145.3	0.70	1.13	6.37	—	0.96	1.36	1.20

1970												
1/3	54.5	14.0	9	NA/C Tr-8 B Li Mo	155.9	0.96	1.45	6.54	0.45			
2/21	46.4	12.8	30	Mo Zn NA/C B Li Ca NA/C	115	0.44	0.87	CPK 60		0.88	0.84	1.40
3/21			9	Mo Zn Tr-4 B Li-600 Ca NA/C	66.3	0.84	1.12		0.45	0.84	0.80	1.00
5/9	53.8	7.6	12	CMZ Tr-4 B Li^+ NA/C	70.1	0.45	1.05		0.55	0.82	0.80	0.70
6/27			14	CMZ Tr-8 B Li^+ 900 CA B NA/C	116.6	0.57	1.01		0.60	0.76	0.74	1.02
8/22	53.3	13.9	15	CMZ Li^+ 900 Ca NA/C B	141.2	0.69	1.39		0.40	1.18	0.78	0.52
10/10			7	CMZ Li^+ 900 Ca NA/C B	—	—	—	84	0.35	0.88	0.88	1.04
12/5	59.2	13.6	18	CMZ Li 900 Ca NA/C B	—	—	—	42	0.55	1.24	0.88	0.84
1971												
1/16	—	—	12	ZnMn Li 900 NA/C B	139	0.40	1.56	77	0.90	1.08	0.87	0.87
2/20	44.8	6.7	25	ZnMn Li 900 NA/C B	108.3	0.75	1.64	64	1.0	1.38	0.98	1.36

Abbreviations

MEC = Mean energy content EEG
CV = Coefficient of variation of EEG
EWI = Experiential World Inventory
Hist = Total blood histamine ng/ml
SPD = Total blood spermidine μg/ml
SP = Total blood spermine μg/ml
SUA = Serum Uric Acid mg %

Li^+ = Serum lithium level m.e.q./l
Cu = Serum copper μg/ml
Zn = Serum zinc μg/ml
Fe = Serum iron μg/ml
Thor = Thorazine
NA = Niacin
ND = Niacinamide

C = Vitamin C
D = Deaner
Dol = Dolophine
Tr = Trilafon
B = Benadryl
Thy = Thyroid
El = Elavil

Ziman = Zinc + Manganese
Mo = Molybdenum
Ca = Calcium
CMZ = Chromium-Mn-Zn

After five months of treatment this rating fell to a normal of 12. The patient obtained employment. His last serious contemplation of suicide was in January 1971. The rise and fall of creatine phosphokinase is of interest as is his elevated serum copper level. Serum zinc was initially at the lower limit of normal. (See Table 23-11.)

Histidine is not considered to be an essential amino acid for the adult human, although animals and infants seem to require a regular dietary supply. Presumably, adult man can synthesize histidine as needed. If this is true, then the lowered histamine levels in the schizophrenic may be due to (1) increased utilization (as by stress), (2) faulty decarboxylation of histidine, (3) inadequate storage, as in zinc deficiency, (4) inadequate synthesis, (5) increased histamine activity, (6) increased methylation of histamine or histidine, (7) deficiencies of folic acid or vitamin B12, (8) continued antigen-antibody reactions, (9) excess spermidine, which is a histamine releasing agent, and (10) trace metal abnormalities. These and other possibilities need study and clarification. In regard to methylated histamine, we have found N,N-dimethylhistamine to be a better stimulant in the rabbit brain than histamine. We have also found the Schiff's base addition product of acetaldehyde with histidine to be a stimulant. Thus, both histidine and histamine may be unavailable because of abnormal alkylation or methylation processes.

Summary

Two distinct types of schizophrenia are described. The largest group (H−) is characterized by a low incidence of allergies, a low blood histamine, and a low basophil count. The patients may also be free of head colds and slow to achieve ejaculation or orgasm. These patients respond to the usual anti-schizophrenic therapy, including EST. The main psychiatric symptoms are thought disorder, paranoia, and sometimes hallucinations. These patients may respond dramatically to folic acid therapy plus vitamin B12. The folate antagonist Dilantin® (Reynolds, 1968) makes these patients worse.

The second type of schizophrenia (H+) occurs in about 20 percent of the outpatient population of patients and is characterized by a normal or high incidence of allergies, a high blood histamine, and basophil count above 0.6 percent. These patients are also "schizophrenic" but are obsessed with suicidal depression, which may result in many unsuccessful suicide attempts by methods such as slashing or the ingestion of sleeping tablets. They are made worse by folic acid and do not respond to the usual anti-schizophrenic therapy, including EST and insulin therapy. Such patients accumulate in psychiatric treatment centers or are referred for newer therapies. Since their blood histamine is high they do respond to methadone, which is a histamine-releasing agent. This can be given with diphenhydramine at bedtime as part of their sleep packet. They also respond to zinc and manganese supplementation of their diet, and respond slowly to Dilantin® therapy.

TABLE 23-11.

PATIENT'S NAME *D.L.* AGE *20* SEX *Male*

Date	EWI	Medication	Hist	SPD	SP	CPK	Li^+	Cu	Zn	Fe
1970										
11/9	77	Tri 2/10 NA/C B-6 ZiMn E D	104.5	1.01	1.03	27		1.40	0.80	1.12
11/30	52	Tri 4/25 Li+ NA/C B-6 ZiMn E Ca D Li	—	—	—	80	0.10	1.18	0.84	0.68
12/14	—	Tri 4/25 NA/C B-6 ZiMn E B D Li	—	—	—	41		1.34	1.16	1.44
1971										
1/15	31	Tri 4/25 NA/C B-6 Li ZiMn E D	90.5	0.80	1.66	41	0.50	1.32	1.10	1.97
2/12	22	Tri 4/25 NA/C B-6 Li ZiMn E D	59.9	0.71	1.30	41	0.40	1.56	0.90	1.12
3/12	12	Tri 4/25 NA/C B-6 Li ZiMn E D	80.1	0.81	1.18	33	0.30	1.30	0.94	0.72
3/26	11	Tri 4/25 NA/C B-6 Li E D ZiMn	56.5	0.94	1.05	32	0.35	1.12	1.08	0.56

Abbreviations

EWI = Experiential World Inventory
Hist = Total blood histamine ng/ml
SPD = Total blood spermidine μg/ml
SP = Total blood spermine μg/ml
CPK = Creatine phosphokinase

Li^+ = Serum lithium level m.e.q./l
Cu = Serum copper μg/ml
Zn = Serum zinc μg/ml
Fe = Serum iron μg/ml
Tri = Trilafon

NA = Niacin
C = Vitamin C
D = Deaner
E = Vitamin E 200 units
ZiMn = Ziman (Zinc + Manganese)

Li^+ = Lithium
Ca = Calcium
B = Benadryl

With effective therapy, the blood histamine level of both the H− and H+ types moves to the normal level of 40 to 60 ng/ml and the basophil count to 0.5 percent. Hyperarousal and overregulation of the quantitative EEG is characteristic of both types, and severe insomnia may also be present. Controlling this insomnia may tax the ingenuity of the therapist.

TRACE ELEMENTS

The following comment on trace elements in nutrition is from *Nutrition in a Nutshell*, by Roger J. Williams (1962, pp. 99–100).

> Because the development of biochemistry has been recent, there has been a lag in identifying biochemists as the experts who are to be trusted in nutritional matters. The Food and Drug Administration requires that on certain labels it must be stated with respect to various items contained in the package: Need in Human Nutrition not Established. Among the items so designated is zinc. The question arises, "Who needs to be satisfied on this point before it can be said to be established?" Obviously, the experts. Clearly the man in the street is not one of those who should be consulted. Neither should those self-styled experts who have no scientific standing. A lawyer would not know the answer. The real experts are the biochemists who know most about the chemistry of living things and are perfectly at home with such problems.
>
> Zinc, to discuss this particular example, is an indispensable constituent of an enzyme, "carbonic anhydrase." This enzyme is in our bodies and needs to be there to hasten the decomposition of carbonic acid. The enzyme has to be made in our bodies, it cannot be made without zinc, and the only way we can get the zinc is through nutrition. Therefore the need for zinc in human nutrition has been established. Perhaps it has not been established in the eyes of untutored individuals; if it is established in the eyes of the experts this should be enough. No competent biochemist can be found who has any doubt about the need for zinc in human nutrition.
>
> One way to establish the need for zinc in human nutrition would be to feed human individuals a diet lacking zinc until illness overtook them, and then administer zinc as an effective cure of the illness. But this direct method is unnecessarily inhumane as well as very expensive. This direct demonstration is quite unnecessary to convince an expert, though it might be required to convince one who knows little about biochemistry. The need for phosphate in human nutrition (which everyone accepts) has never been demonstrated by feeding human beings everything but phosphate until they become ill, and then curing them with phosphate. This could be done, but it is not necessary in view of all that biochemists know about phosphate biochemistry.

Trace Element Studies in Schizophrenic Patients and Normals

Many elements are needed by the body in trace amounts for specific enzyme action (Table 23-12). Probably the two best known trace metals are cobalt (in vitamin B12)

TABLE 23-12.
Enzymes That Require Selected Trace Metals

Zinc	
Carboxypeptidase	Leucine aminopeptidase
Carbonic anhydrase	Pyruvate carboxylase
D-lactic-cytochrome reductase	Liver transmethylase
Alkaline phosphatase	Carnosinase
Ethanol dehydrogenase	High molecular weight RNA synthetase?
Glutamic dehydrogenase	Pyridoxine phosphorylase
Manganese	
A number of phosphate transferases	Carboxypeptidase
Isocitric dehydrogenase	Mono-amine oxidase
Enolase	Liver arginase
Pyruvate kynase	Hydrogenase
Chromium	
Phosphoglumutase	Glucose tolerance factor
Succinic-cytochrome C dehydrogenase	
Cobalt	
Glutamic isomerase	Pyruvate carboxylase
Coenzyme B-12	Carboxypeptidase
Acid phosphomonoesterase	Carbonic anhydrase
Aminopolypeptidase	Methyl-malonyl CoA mutase
Glycylglycine dipeptidase	Diol dehydrogenase
Arginine desimidase	Phosphatases
Molybdenum	
Aldehyde dehydrogenase	Hydrogenase
Xanthine dehydrogenase	
Copper	
Dopamine B hydroxylase	Cytochrome oxidase
Hydrolysis of amino acids esters	Polyphenol oxidase
Amine oxidase	Ascorbic acid oxidase
Tyrosinase	Galactose oxidase
Carnosinase	
Iron	
Tyrosine hydroxylase	Pyrocatechase
Ferrochelatase	Liver arginase
NADH cytochrome-C reductase	Choline dehydrogenase
Succinic dehydrogenase	Aldehyde oxidase

and zinc (in insulin). The elements that are essential to man show definite levels with a normal distribution curve when the organs from autopsied patients are assayed. For those elements that are considered to be extraneous or environmental poisons (lead, mercury, cadmium, and arsenic) the analytical values show a skewed distribution curve, fortunately with most values at or close to zero. (Liebscher and Smith, 1968.)

CNS POISONS

Lead, and especially mercury, may produce mental symptoms similar to those of schizophrenia. This has been known since the work of Neal and Jones (1937), who studied the use of mercury salts in the felt hat industry. The psychotomimetic effects of mercury poisoning gave rise to the expression "mad as a hatter." With the more toxic methyl mercury from fish and the organic mercury fungicides the populace at large can be insidiously poisoned, thereby developing a degree of schizophrenia which may defy accurate diagnosis. Mercury is not excreted in urine, but a physician testing for mercury poisoning may find evidence of it in the hair. The points to keep in mind are:

1. Is there a history of exposure to mercury or fungicides? One of our patients raised African violets in her basement. The organic mercurial fungicide Panogen remained in an open dish on her work bench for five years. These compounds have a definite vapor pressure; they poison the atmosphere, and basements are not well ventilated.
2. Does the patient have unexplained tremor of the hands? The degree of tremor varies and may be so severe as to interfere with writing. The African violet grower signed her checks in advance on her good days. Decreased peripheral vision may be present. Ataxia may be present and intermittent.
3. In fluctuating degree all the symptoms of schizophrenia occur, so the patient may have paranoia, hallucinations, thought disorder, lack of affect, insomnia, and waves of suicidal depression in a 24-hour period. This varying symptomatology perplexes and exasperates the patient, the relatives, and the attending physicians. Even the biologically oriented physician may erroneously say that the patient is acting out, or role playing, and thus making an exaggerated bid for attention. The psychic symptoms (ugly mood) also vary in a 24-hour period.
4. Taste disperception may be present so that excessive salt and sugar may be used. The patient frequently complains of a metallic taste, and that foods taste the same.
5. An elevated serum copper level may be present which does not decrease with zinc therapy. In the renal impairment of cystic fibrosis an infant's nail clippings

show 50 to 200 ppm of copper, compared with 2 to 30 for normals. We therefore suspect that these patients also have a slight kidney impairment which makes the excretion of copper difficult. Zinc and penicillamine therapy is indicated.

6. Urinary analysis may show intermittent traces of albumin.

The feathers of birds collected in Sweden in 1940 contained four times more mercury than those collected in 1900. This increase indicates the public health menace with which we may now be confronted. In a group of 200 outpatient schizophrenics we believe that four suffer from mercury poisoning. This may mean that 2 percent or more of our hospitalized mental patients may be there because of mercury poisoning. Accurate surveys and human hair studies are needed to provide prevention and prophylaxis, since diagnosis and cure may be difficult if not impossible.

Has there ever been a "Sword of Damocles" in medical history such as methyl mercury (MM) and the other organic compounds of mercury?

1. MM enters the body in food.
2. MM affects the brain, causing loss of memory, tremor, ataxia, confusion, and/or madness.
3. MM produces symptoms which mimic natural diseases.
4. The presence of MM cannot be diagnosed by ordinary laboratory methods.
5. The effects of MM are mostly irreversible after the brain damage occurs.

If the threat were measurable we could discount the occasional occurrence of MM in foods. At present MM is a silent fifth column.

COPPER AND IRON AS TISSUE ENZYME POISONS

A trace element which is definitely high in the blood serum of some schizophrenics (Holmberg and Laurell, 1951; Angel et al., 1957; Ozek et al., 1957; Horwitt et al., 1957). Most (93 percent) of the serum copper is contained in an alpha-2-globulin protein, ceruloplasmin, which varies normally from 20 to 40 mg percent. Serum copper rises steadily during pregnancy because of increased estrogen activity, and the contraceptive pill with its high estrogen activity is yet another factor in producing elevated levels. Normal males have an average level of 1.0 μg/ml and normal females a mean of about 1.1, depending on the day of the menstrual cycle (see Figure 23-5). The highest copper level occurs with the highest estrogen-progesterone levels one week before the menstrual period, which coincides with the time of greatest psychiatric depression. The lowest copper level occurs one week after the period. Schizophrenic patients have a higher copper level when on the pill than do normal controls. In fact, the serum copper level is higher than in the ninth month of

pregnancy. One of our schizophrenic females on the pill had a level of 5.65 μg/ml! From our experience most female patients will worsen mentally and get depressed with the pill.

Thus far only the *serum* copper and ceruloplasmin have been determined in schizophrenic patients. Tissues which should be tested are hair, nails, skin, and leukocytes. Perhaps more important is the tissue level of both copper and iron, since in many enzyme systems the active trace metal can be interchanged with

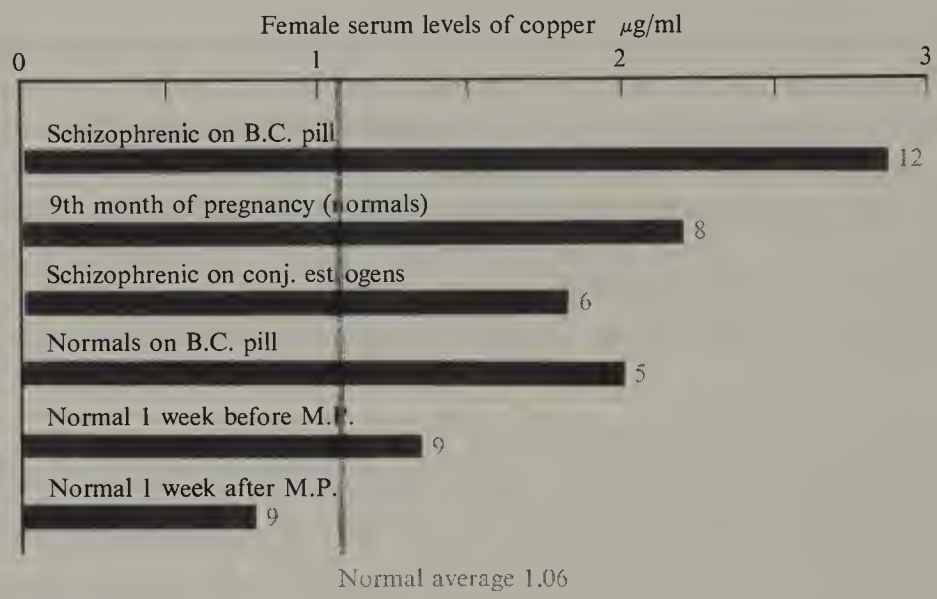


FIGURE 23-5.
Serum copper levels of various categories of schizophrenic patients and normal females. The numbers at top of bar graphs indicate number of patients or normals. The schizophrenic on the contraceptive pill has a great increase in serum copper which is greater than in the ninth month of pregnancy in normals. Both rises are ascribed to estrogens, which indicate the great estrogenic potency of the contraceptive pill. Before menstruation is also different from after menstruation because of the normal variation in estrogen level. The high copper level coincides with the time of greatest depression.

resultant changes in enzyme activity. Simpson and Vallee (1969) have shown that alkaline phosphatase, a tissue enzyme, is more active when the cobalt ion is substituted for the normally occurring zinc ion.

Excess copper and iron can destroy vitamin C. Several studies have shown that large doses of vitamin C can be given to schizophrenics without any spillover in the urine (VanderKamp, 1966; Ozerengin et al., 1968). Anxiety and excitement have been shown by Maas et al. (1961) to increase the breakdown of vitamin C, and in schizophrenics this process may be exaggerated by abnormal epinephrin metabolism (Briggs, 1962). Milner (1963) found sub-scurvy to be present in many of the 40 male patients tested. Patients with high iron as in siderosis have a decreased level of

leukocyte vitamin C (Wapnick et al., 1968). We find that many patients who have normal serum copper or iron levels will have a rise in these levels for several months after zinc (or zinc and manganese) trace element supplements (Tables 23-13 through 23-25). For the present, we interpret these findings to indicate that Zn (and particularly Zn with Mn) displaces excess iron and copper from the tissues.

The Akerfeldt test (1957) measured the oxidative effect of ceruloplasmin in schizophrenic patients. The test was criticized as being nonspecific, but the logical study of abnormal copper and iron levels in the schizophrenic has received little or no attention. With the ease of determination of Cu, Fe, and Zn by atomic absorption spectrophotometry these data can now be more available and act as guide lines for therapy.

BIOLOGICAL ANTAGONISM BETWEEN ZINC AND COPPER

The trace metals are known to compete with each other in biological systems, so an excess of copper could block other more effective trace metals from an active enzyme site (Habermann, 1969; Nicolson et al., 1966).

Cox and Harris (1959) summarized studies on the displacement of copper from tissues by excess dietary zinc. They also studied rats that were given a diet containing 0.6 percent zinc, which, within three weeks, produced copper-deficiency anemia. The anemia was corrected by adding 0.01 percent Cu to the diet, but an addition of 0.08 percent Fe was less effective than the Cu. Liver and kidney Cu levels were not reduced by this large zinc intake, but iron levels were significantly reduced.

Lee and Matrone (1969) found that in rats high zinc diets produced a precipitous drop in ceruloplasmin levels within one week which was restored toward normal by copper or copper/iron injections. The diet contained 1.4 percent zinc carbonate, which is an enormous dose. Studies by Rimai and Hyde (1970) show that adenosine triphosphate combines with Ca^{++} and Mg^{++} at the phosphate ionic bond while Zn^{++} and Mn^{++} complex both with the phosphate bond and the adenine base. McCormick et al. (1969) report the stability constants of Fe and especially Cu with tridentate amino acids to be much higher than those of Zn or Mn. If these amino acids are involved in trace metal enzyme action, one could predict that excess copper would dominate Zn and Mn in tissue enzyme action.

The copper chelating agent penicillamine (P) has been given to the treatment-resistant schizophrenic in an attempt to decrease the copper level. Careful checks on serum levels and urinary excretion of copper are routinely made on the patient with Wilson's disease who receives P in therapy, but it is given to schizophrenics without the benefit of objective trace-metal tests. Fister et al. (1958) suggested that the patient on P therapy be given extra trace metals (except copper) once each week. This regime was also followed by Nicolson et al. (1966), but others have ignored the finding that P chelates and removes zinc as well as copper (Affleck et al., 1969). One of the side

TABLE 23-13.

Placebo, 13 Normal Subjects. Changes in serum, zinc, copper and iron after a starch placebo tablet. The zinc levels decrease significantly in the six-hour test period while copper and iron remain much more constant. This may indicate the need for regular zinc intake with each meal.

Metal	0 hours	6 hours
Zinc	1.05 ± 0.05	0.83 ± 0.11 −21%*
Copper	0.93 ± 0.09	0.93 ± 0.14 0%
Iron	1.40 ± 0.4	1.33 −5%

* Change significant at the 95% level of confidence. Means in μg/ml ± S.D.

TABLE 23-14.

Human Quantitative EEG after Zinc Sulfate 50 mg Orally. In patients Zn decreases MIA and increases CV, which changes occur with antianxiety drugs. In the normals where the CV is higher no significant change occurs. This may indicate that zinc is needed in the schizophrenic because of deficiency. The addition of pyridoxine (B6) accentuates the response of the patients to zinc sulfate. Zinc is needed for the normal action of B6.

Trials†		Control	Hours after dietary supplement					
			1	2	3	4	5	6
Patients	MIA	100	92	83*	90	93	85	85
(11)	CV	9.0	12.6	16.9*	14.1	12.4	17.0	11.7
Normals	MIA	100	102	100	102	96	95	96
(10)	CV	20.8	18.7	21.9	16.1	22.8	26.4	21.0
			$ZnSO_4$ 50 mg+B6 50 mg					
Patients	MIA	100	97	87*	85*	94	95	96
(15)	CV	12.0	14.1	19.1*	18.9*	13.1	14.7	14.0

* Significant change from control level $P < 0.05$.
† MIA = Mean Integrated Amplitude; CV = Coefficient of Variation.

TABLE 23-15.

E.E. (Normal?) Male, age 27; $ZnSO_4$ + B6, 50 mg of Each per Day. The zinc dietary supplement raises serum zinc level. The rise in histamine and polyamine levels is also of interest, in that this (normal ?) subject had abnormally low levels.

Date		Serum			Whole blood		
		Cu	Fe	Zn	H	Spd	Sp
7/14	0 hr	0.92*	1.38*	0.82*	21.7†	0.62	1.08
7/14	6 hr	0.94	1.04	0.64			
7/15	6 hr	0.94	1.04	0.64			
7/16	6 hr	0.80	1.04	0.78			
7/17	6 hr	1.02	0.88	1.04			
7/18	6 hr	0.96	1.64	1.00			
7/20	6 hr	1.06	0.96	0.92	30.8	1.09	1.63

* μg/ml. † ng/ml.

TABLE 23-16.

Zinc Dietary Supplement—24 Males and Females with Low Zinc. Note that the serum zinc level rises and stays up for the 6-month period covered by the six visits, Serum copper and iron also rise. The EWI decreases.

	Visit						
	C	1	2	3	4	5	6
EWI	52	52	43	29	34	47	36
Cu	1.22*	1.29	1.37	1.31	1.43	1.44	1.53
Zn	0.73*	1.10†	0.97†	0.99†	1.09†	0.92†	0.88†
Fe	1.05*	1.23†	1.16	1.18	1.45†	1.20	1.28†

* μg/ml. † Significant change from control level $P < 0.005$.

TABLE 23-17.

Zinc Dietary Supplement in High Copper Male Patients (14). The high serum copper level (normal 1.0 μg/ml) may decrease promptly in high copper patients. This is accompanied by improvement in psychiatric symptoms (EWI).

	Visit					
	C	1	2	3	4	5
EWI	60	66	56	58	35	47
Cu	1.44	1.25	1.19	1.26	1.30	1.32
Zn	1.23	1.31	1.06	1.08	0.96	1.05
Fe	1.18	1.22	1.26	1.21	1.25	1.11

TABLE 23-18.

Zinc Dietary Supplement Rising Copper Response, 28 Subjects. While no significant changes from the control occur, the copper rises for three months and then falls. This is accompanied by a decrease in the EWI. The normal zinc level does not increase.

	Visit				
	C	1	2	3	4
EWI	43	45	46	43	34
Cu	1.10*	1.34	1.38	1.35	1.28
Zn	1.06*	1.10	0.96	0.98	1.01
Fe	1.31*	1.24	1.15	1.26	1.35

* μg/ml.

TABLE 23-19.

Rising Copper and Iron after Zinc Dietary Supplement in 72 Outpatient Schizophrenics. With this type of serum trace metal change the individual patient may get worse mentally before getting better. This may account for the slow decrease in the EWI.

	Monthly visit						
	C	1	2	3	4	5	6
EWI	49	46	42	42	42	36	40
Cu	1.13†	1.21	1.24*	1.27*	1.27*	1.31*	1.32*
Zn	1.05†	1.15*	1.01	1.00	0.98	1.03	1.04
Fe	1.18†	1.42*	1.42*	1.40*	1.29	1.28	1.38*

* Significant change from control level ($P < 0.05$). † μg/ml.

TABLE 23-20.

Zinc Dietary Supplement—16 Subjects with Low Iron. Note that Zn supplement increased iron level of the serum. Over a longer period (five months) the copper reached a peak. Zinc levels did not change.

	Visit						
	C	1	2	3	4	5	6
EWI	51	65	62	65	60	59	29
Cu	1.25†	1.39	1.23	1.22	1.45	1.61*	1.43
Zn	0.90†	1.13*	0.87	1.04	1.01	0.89	0.90
Fe	0.55†	0.78*	0.97*	1.06*	1.00*	1.04*	0.84*

* Significant change from control level ($P < 0.05$). † μg/ml.

TABLE 23-21.

Summary Blood Serum Trace Metal Studies of 240 Schizophrenic Outpatients. Only 11% + 20% = 31% of the patients could be classified as low in zinc or high in copper, but with zinc supplementation the rise in copper or copper and iron indicates many more may have excess copper and iron in their tissues.

Low zinc $>$ 0.80 μg/ml	27 (11%)
High copper $<$ 1.20 μg/ml	47 (20%)
Low iron $>$ 0.60 μg/ml	18 (8%)
High iron $<$ 1.50 μg/ml	29 (12%)
Changes after zinc dietary supplement	
↑ Copper and iron	76 (32%)
↑ Copper	43 (18%)
No change	48 (20%)

TABLE 23-22.

Six-hour Urinary Excretion in μg of Zinc, Copper, and Iron after Small Doses of Trace Metals, in Comparison to Placebo. Cu excretion of schizophrenics is about one-third that of normals. Zinc acetate in schizophrenics increases this Cu excretion as does Mn, but Zn/Mn allows greatest excretion of Cu. Magnesium chloride increases excretion of Fe in both schizophrenics and normals.

Compound	Dose	Schizophrenic Patients				Normals			
		Trials	Ce	Zn	Fe	Trials	Cu	Zn	Fe
Placebo		(18)	1.7	152	16	(26)	4.6	147.5	19.9
$CuSO_4$	5 mg	(16)	2.5	126	36	(15)	1.4	151	42
$ZnSO_4$	50 mg	(11)	2.3	204	20	(16)	2.1	115.4	13.2
Zn Acetate	30 mg	(13)	3.69	107.5	22.5	(10)	3.6	138	15
$ZnSO_4$ $MnCl_2$	3 mg	(14)	20.0	224	16	(13)	3.0	186	6
$MnCl_2$	3 mg	(11)	5.5	137	47	(10)	1.2	325	12
$MgCl_2$	200 mg	(13)	2.54	136.1	26.6	(10)	3.1	116	34
$FeSO_4$	900 mg	(15)	3.50	140.9	36.4				

TABLE 23-23.

Six-Hour Urinary Excretion in μg of Copper, Zinc and Iron after Various Inactive Trace Metals. Calcium acts like magnesium to increase the urinary excretion of iron. Note that copper excretion in the schizophrenic is consistently below that of the normal.

Compound	Trials	Dose (g)	Cu	Zn	Fe
		Patients			
Placebo	18	—	1.7	152	16
Calcium lactate	9	2.0	1.5	163	33
Chromium acetate	8	0.005	1.4	155	14
Ammonium molybdate	12	0.005	1.2	146	10
		Normals			
Placebo	26	—	4.6	148	20

TABLE 23-24.

Important Trace Element Losses in Bread Making. Note that each of these trace metals may be decreased in the milling process. Since doughnuts are made from cake flour, which is lowest in important trace elements, anyone who tries to get by on a "coffee and doughnut diet" is headed for nutritional deficiencies and mental health problems.

Food	Parts per million			
	Mn	Cu	Zn	Mg
Wheat, common hard	38	5.0	24	1800
Wheat, common soft	35	4.5	22	1590
Wheat, durum	32	4.8	30	1860
Processed wheat foods				
Cake flour	1.7	0.8	2.3	220
White bread	5.5	2.1	8.9	420
Whole wheat bread	41.0	5.1	27.0	1950
Doughnuts	3.5	1.7	6.5	320

Source: Selected data from the report of Zook et al. (1970).

TABLE 23-25.

Zinc Content of Various Megavitamin Tablets Including a Large Starch Placebo. Magnesium stearate and zinc stearate are sometimes used as dry lubricants in the manufacture of tablets and capsules. The zinc present in niacin may come from the manufacturing utensils. Megavitamin therapy may in part be zinc therapy.

Compound	Zinc
Magnesium stearate	36 μg/g
Niacin, Merck	28 μg/g
Niacinamide, Wolins	120 μg/g
Placebo	12 μg/g
Niacin, IDE	4 μg/g
Hexanicotol	7 μg/g
Nicotinamide USP (powder)	undetectable

effects of P therapy is the loss of the sense of taste, which is a sign of zinc deficiency (Henkin et al., 1969). We can confirm the fact that P chelates zinc and copper out of the body, but urinary iron excretion is decreased (Table 23-24, Figures 23-6 and 23-7). This confirms the findings of Walshe and Patston (1965), who found no effect on serum iron. P also complexes with pyridoxine (B6), so that many workers have recommended 50 mg of B6 per day as a supplement. If the P is given after meals (to prevent nausea), then 25 mg of the B6 should be given before breakfast and an additional 25 mg before supper to minimize interaction with the P.

Very few studies of trace metals, other than indirect copper studies, appear in the literature on schizophrenia. In fact, the story of trace metals as a possible factor in schizophrenic behavior began in 1929. At that time Dr. W. M. English of Brockville, Ontario, used manganese chloride intravenously in 181 schizophrenic patients and found that half of them showed improvement. English (1929) reported a weight gain in those patients who responded to manganese therapy, similar to the gain with CPZ and reserpine therapy. He also found that the intravenous manganese produced a cutaneous flush like that of niacin. This study was repeated by R. G. Hoskins of the Worcester Foundation (1934), but instead of using manganese chloride intravenously he used for the most part suspended manganese dioxide given intramuscularly. In the first instance the intravenous route was unnecessary with water soluble and easily absorbed manganese chloride. In the second instance manganese dioxide in a nonabsorbable form was deposited intramuscularly, where it probably stayed for a very long time. Hoskins found no improvement in the schizophrenics injected with manganese dioxide.

Of the trace metals which theoretically should produce some benefit in the schizophrenic, manganese is a likely prospect since it increases the activity of acetylcholine

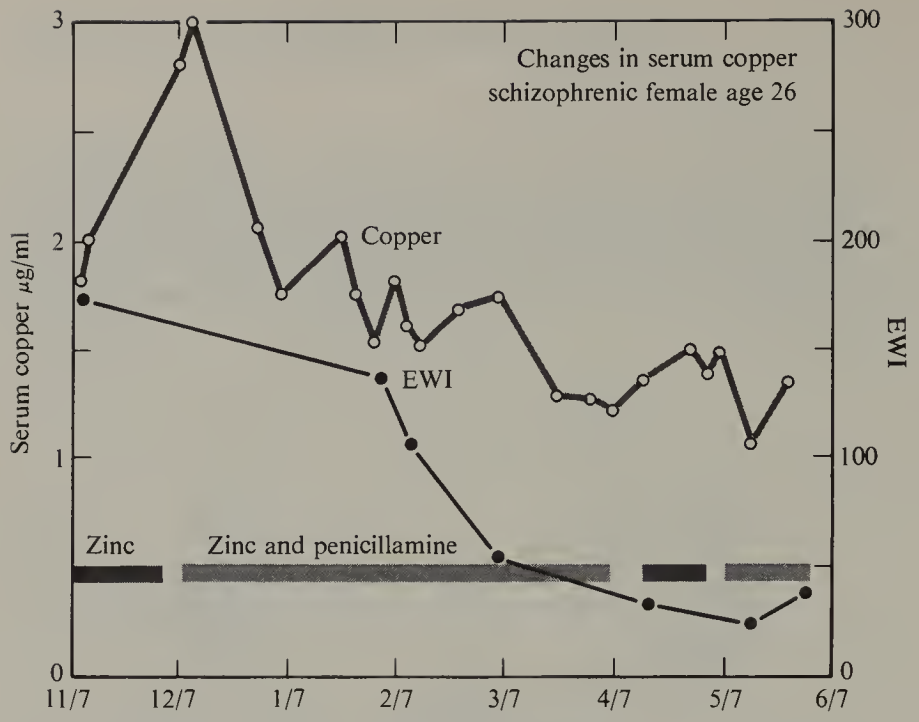


FIGURE 23-6.
Female patient (A.D.), age 26. Change in EWI with change in serum copper level. Mercury poisoning is the suspected etiology of disorder. Note that zinc alone raised the serum copper level. Penicillamine plus zinc dietary supplement reduced the serum copper. A concomitant drop in the EWI occurred.

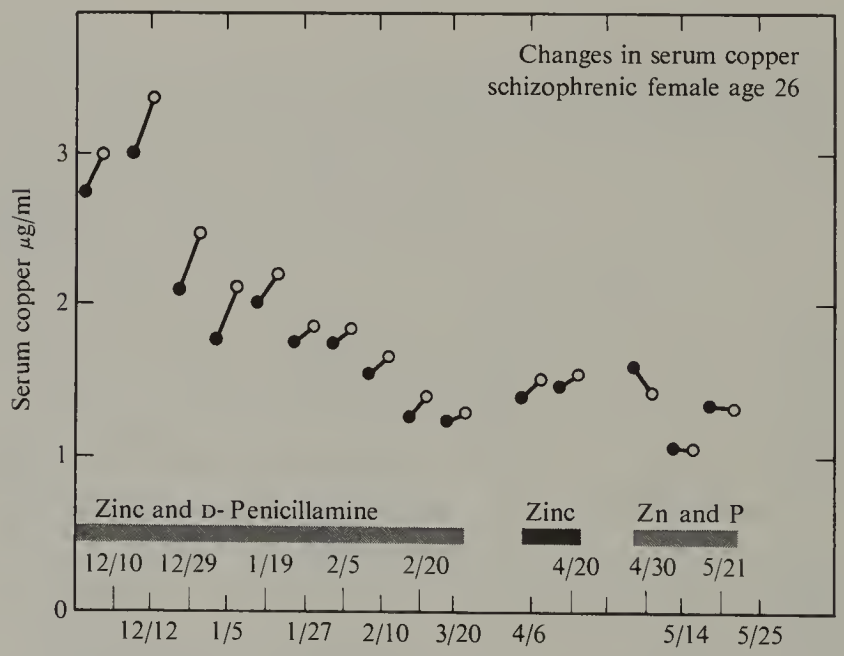


FIGURE 23-7.
Changes in serum copper from 0 to 6 hours after administration of zinc dietary supplement and zinc and D-penicillamine therapy. Zinc causes a rise in the serum zinc presumably because of displacement from tissues. This rise is less and less as the copper level returns to the normal range. Patient probably has poor copper excretion because of chronic exposure to mercury.

acetylase. We know that other chemical therapies that increase the acetylcholine effect in the brain will also be of benefit. For example, reserpine, which produces symptoms of acetylcholine overdosage and also increases acetylcholine in the brain of animals, might be called the prototype of compounds which have a specific antischizophrenic effect.

Considering porphyric schizophrenia as one of the schizophrenias (it is frequently overlooked), the discovery of zinc deficiency in schizophrenia can be traced back to 1929 when Derrien and Benoit, working at Montpelier in France, discovered that

TABLE 23-26.

Effect of Placebo or D-Penicillamine on Six-hour Urinary Excretion (μg) of Copper, Zinc, and Iron. Means ± S.E. The normal excretes more copper and less zinc. Penicillamine greatly increases copper excretion, but zinc excretion is more than doubled. Iron excretion is decreased.

Metal	Normals (8)	Schizophrenics (11)
	After placebo	
Copper	4.46 ± 1.69	0.2
Zinc	128.00 ± 24.78	143.90 ± 27.28
Iron	31.12 ± 7.03	16.18 ± 2.39
	After 500 D-penicillamine	
Copper	178.00 ± 37.96	174.00 ± 37.37
Zinc	299.71 ± 41.27	525.87 ± 132.66
Iron	9.28 ± 3.86	11.62 ± 3.08

uroporphyrin chelates zinc and thus removes it from the body. They postulated that some psychic and neurological symptoms could be precipitated by zinc deficiency. The excess loss of zinc via uroporphyrin was confirmed by Watson and Schwartz (1941). Nesbitt (1944) also suggested that the mental symptoms of porphyria might be caused by a zinc deficit. Peters (1961) found an increase in zinc excretion and occasionally copper in patients with acute attacks of porphyric schizophrenia. Perhaps the main cause is added copper ingestion or absorption; the copper displaces zinc and both are excreted excessively. Peters also suggested another trace metal deficiency, which might be manganese. Pyridoxine deficiency as suggested by Meltzer (1961) could also be a precipitating factor. In any event, the mauve factor is now known to be a pyrrole derivative (Irvine et al., 1969), which may come from the breakdown or abnormal synthesis of myoglobin or hemoglobin; thus, mauve-positive patients may be mild porphyrics. This pyrrole should be tested as a potential chelator of zinc and manganese.

In 1965 Kimura and Kumura found that brain autopsy specimens from schizophrenics had less zinc than did brains of patients who died of other causes. As cited previously, Henkin et al. (1969) found zinc deficiency to be one of the etiological factors in loss of normal taste, which sometimes occurs after a severe virus infection such as "Hong Kong Flu." The taste disperception can be relieved by therapy that includes 100 mg of zinc sulfate per day. Pecarek and Beisler (1969) found that endotoxins will produce a quantitative reduction in serum zinc levels of rats. Pories (1967), Henzel et al. (1967), and others have found that zinc is necessary for maximal healing of wounds, and that the stress of an operation frequently depletes the body's stores of zinc. Caldwell et al. (1970) found that offspring born of zinc-deficient rats and mice have learning deficits. Hurley (1969) found birth anomalies in zinc-deficient rats, and reports that rats on a zinc-free diet will have a 38 percent drop in serum zinc levels within 24 hours. Since this indicates a lack of easily mobilized zinc reserves in body tissues, the daily intake of zinc is of great importance.

Plasma or serum zinc levels do not, in our experience, provide a valid index to the tissue zinc levels, or to the degree of deficiency which may exist. Plasma zinc levels are significantly reduced, however, in serious liver disease, active tuberculosis, indolent ulcers, myocardial infarct, Down's Syndrome, cystic fibrosis, growth retardation, and pregnancy, and by oral contraceptive therapy (Halsted and Smith, 1970). When zinc therapy is attempted, zinc sulfate $.7H_2O$ has usually been given in oral doses of 50 to 200 mg. This is one-sixth zinc, so more than the usual dietary level of 17 mg Zn/day is given. Such doses occasionally produce nausea, vomiting, and diarrhea. The role of the sulfate anion as a factor in these side effects is not known. Certainly more studies are needed in the oral absorption of various zinc salts to determine the optimal anion conditions for maximal absorption and if there is a need for more than 17 mg Zn per day. We have compared zinc sulfate with zinc acetate in equimolar concentrations in normal volunteers (Table 23-22).

TRACE METALS IN THE BRAIN

Several other studies have been made on trace metals in the brain, Harrison et al. (1969) studied Cu, Zn, Fe, and Mg distribution in the human brain. They found Cu to be highest in the caudate nucleus, Zn and Mg highest in the hippocampus, and Fe highest in the globus pallidus. The zinc was distributed as follows: frontal gray, 95 ± 31 μg/g; frontal white, 45 ± 12; hippocampus, 95 ± 38; caudate, 81 ± 21; putamen, 75 ± 13; globus pallidus, 69 ± 16; corpus callosum, 49 ± 30; and thalamus, 58 ± 9. The frontal cortex and hippocampal areas of the brain contain higher levels of zinc than any other parts tested. Ibata and Otsuka (1969), using histochemical techniques, found Zn to be present mainly in the terminal vesicles of the nerve endings of the mossy fibers of the hippocampal formation of rabbits and rats.

Since zinc occurs with histamine in both basophils and mast cells, one can speculate that the mossy fibers of the hippocampus may be histaminergic. McLardy (1970) has used hydrogen sulfide to inactivate this zinc in the mossy fibers of rats. These rats could still learn and retain their ability to run a complex maze, which led McLardy to believe that these fibers are not involved in recent memory and consolidation. Wong and Fritze (1969), who give trace metal values for calf, cow, and pig brains, found that the hippocampus has the highest level of both copper and zinc in each species; the pineal body has a slightly higher level.

A possible relationship between serum polyamines and trace metals may exist and be reflected in changes in RNA synthesis (Dawson et al., 1969). Swenerton et al. (1969) ascribe congenital malformations after zinc deficiency to impaired DNA synthesis, and Weser et al. (1969) found that zinc increases thymidine incorporation into DNA in zinc deficient rats. Cox (1969) determined that zinc is necessary for RNA synthesis and is also needed for adrenal corticoid action involving protein synthesis. Gregoriadis and Sourkes (1970) found an accumulation of copper in the liver of adrenalectomized rats; thus, severe adrenal insufficiency may be accompanied by increased tissue copper.

Since hypoglycemias occur frequently in psychic disorders and are often misdiagnosed as schizophrenias, one should always consider carefully the possibility that the patient may be zinc deficient, as both insulin and pancreatic action require zinc.

The second most likely trace metal which might be low in the hypoglycemic patient is the trivalent chromium ion. This metal rises in the plasma with the usual glucose tolerance test, so the possibility exists that excess starch may dissipate the body's stores of chromium. The recent comprehensive review by Mertz (1969) not only emphasizes the role of Cr in carbohydrate metabolism but also implicates ATP and histidine complexes with chromium as the possibly bioactive form of the element. Mertz has called this bioform of Cr the "glucose tolerance factor" and has data to show that "old age" diabetes may well be a chromium deficiency. Man's usual diet is very low in chromium, so low in fact that a mother of many children has a steady decrease in the chromium content of her hair with each pregnancy as she shares her body's store of chromium with her offspring (Hambridge and Rodgerson, 1969). This can be restored by adequate chromium supplementation in the diet.

THE SOIL AND TRACE ELEMENTS

Why does a well-rounded diet not always provide adequate amounts of the two trace metals, zinc and manganese, which seem to be most important in combating excesses of copper and iron in the schizophrenias? Let us begin at the beginning.

Plants grown on well-fertilized soil should contain all of the trace elements vital to life. The flesh of animals eating these plants should contain adequate trace elements.

When fresh vegetables, nuts, and meat are eaten by man, he should have a good intake of trace elements. However, not all soils are adequate. Areas of Iran and Egypt lack zinc, and the genital development of young men who live there fails to take place at puberty: zinc sulfate by mouth cures this deficiency (Prasad, 1963). Grains grown in South Dakota may be high in selenium; grain from Ohio is too low. The sandy soil of Florida requires the addition of many trace elements to produce an abundant citrus crop: at present, zinc, manganese, cobalt, molybdenum, iron, and copper salts are added. The first trace metal deficiency of the Florida sands (discovered around 1900) was copper, so some of the older citrus groves are loaded with it. Copper was blindly added year after year in an effort to produce a bigger crop. This excess copper is now a problem which is countered by adding more zinc to the soil.

The loams and shales of the northern United States were originally adequate in trace metals, but they have been cultivated for a century with fertilizers consisting predominantly of nitrate, phosphate, potash, calcium, and magnesium. These fertilizers will grow plants that are luxuriant but do not contain adequate amounts of the trace metals needed by man. Furthermore, nitrates, phosphates, and ammonia tend to solubilize zinc and manganese, so that these can be leached from the soil by rain water. The use of organic fertilizer or compost provides more of the trace elements. Chemical analysis, as in scientific farming, will show what is lacking, and the deficit can easily be corrected by addition of the missing elements. Total scientific farming will eventually be accomplished, and we will grow yeast and algae or sprout soybeans in a completely enriched culture medium.

VEGETABLE PROCESSING

Fresh vegetables grown on an adequate soil should be most nutritious if cooked lightly or eaten raw. In the commercial process, vegetables to be frozen are scalded with the chelating agent EDTA (ethylenediamine tetra-acetic acid) and the trace metals are in part removed. This makes the peas and broccoli greener when cooked whereas the home frozen vegetables are less green when cooked. The processors say the deep green color *is more wholesome* but we know and say *such peas are less nutritious*!

Nuts are a good source of trace elements, but the metals promote rancidity so the peanut butter will not have as long a shelf life if the trace metals are allowed to remain in it. Our modern hydrogenated peanut butter never turns rancid! What happened to the trace metals?

Nutritionists calculate that man may eat as much as 100 mg—perhaps even more—per day of the chelating agent EDTA because of its present widespread use in foods. Over 44 sequestrants are officially approved for the removal of trace metals from our foods (New York Times, 1969).

THE WATER WE DRINK

Homes were once provided with zinc-coated (galvanized) water pipes but these rusted at the joints after 15 to 20 years of use. Our most popular replacement, and most new piping, is copper. The water coursing through the piping early in the century dissolved zinc and iron, but now the water dissolves copper. This amount is sufficient to poison a patient on an artificial kidney whose blood is being dialyzed against running tap water. Patients with zinc deficiency may have taste disperception so that they cannot taste normal levels of salt. They then oversalt their food up to the new elevated salt threshold. With added salt intake they must drink more water to relieve their excessive thirst—and that water contains copper. Thus, a vicious cycle is established. Some of our patients with houses on local well water will not return to a normal serum copper level until their fluid intake is limited to distilled water. Well water has more sulphurous acid and carbonic acid than city water. These acids react with copper to form salts that are then ingested.

THE VITAMINS WE TAKE

Those widely advertised multivitamins plus minerals sound great but they are relatively loaded with copper and iron, and low in zinc, manganese, and magnesium, so much so that the patient does much better on one regular multivitamin plus the proper trace metal supplement for his particular needs. The patient frequently does not realize that the letter "M" after a vitamin brand name means that unwittingly extra copper and iron are being offered and absorbed. (Vitamin C promotes the absorption of iron.)

Our protection against excess iron depends on the ferritin content of the intestinal mucosa. The Bantus of South Africa brew a beer in iron kettles which ends up very high in iron (Bothwell and Charlton, 1970). Some who drink this beer ingest 50 to 100 mg of ionic iron per day and end up with serious siderosis (excess iron in all tissues). A similar disorder—excess copper in the tissues and liver cirrhosis—can result from extra copper ingestion when copper cooking vessels are used. In this instance the ceruloplasmin of the tissues and blood tend to limit our copper absorption. The effectiveness of ferritin for iron regulation and ceruloplasmin for copper regulation are only relative so excess ingestion of either iron or copper can be harmful. It is best to avoid iron and copper unless analysis of the blood shows that levels are abnormally low.

SUMMARY OF EXPLORATORY STUDIES ON TRACE METAL BALANCE STUDIES IN SCHIZOPHRENICS

1. Serum zinc levels of normal subjects decrease significantly in a six-hour period, but copper and iron levels do not.

2. Zinc, with or without pyridoxine, produces an EEG "anti-anxiety effect" in schizophrenics but not in normals.
3. Urinary copper excretion is consistently less for schizophrenics than for normals.
4. Zinc increases urinary copper excretion, as does manganese, but Zn/Mn in dietary doses is most effective in increasing copper elimination.
5. D-Penicillamine increases urinary excretion of zinc and copper, therefore, dietary supplement of zinc should be provided during P therapy.
6. Approximately 11 percent of 240 schizophrenic outpatients had a low serum zinc level (less than 0.80 μg/ml), 20 percent had elevated copper levels (greater than 1.20 μg/ml), 8 percent had low iron (less than 0.60 μg/ml), and 12 percent had high serum iron (greater than 1.50 μg/ml).
7. The serum level may not reflect the tissue level; with Zn/Mn dietary supplement, 50 percent of the patients had a rise in serum copper and iron over a period of four to five months.
8. Of the dietary supplements used in the schizophrenic outpatients, the best results were obtained with zinc sulfate 10 percent, plus manganous chloride 0.5 percent.
9. The lowest serum copper level occurs one week after the menstrual period, and the highest level occurs the week before the period. Estrogens raise copper levels and the schizophrenic appears to be more susceptible to this hypercupremia since copper levels may exceed those found in the ninth month of pregnancy. Hypercupremia can aggravate depression and other symptoms in the schizophrenic.
10. Trace metals which have not been explored adequately in the schizophrenias are manganese, chromium, molybdenum, and selenium.
11. Because of zinc metal contamination (or addition in tableting) megavitamin therapy may in part be zinc dietary supplement.
12. Patients who show high serum copper levels, tremor of the hands, ataxia, and intermittent schizophrenic symptoms with wide mood swings should be studied as possible victims of mercury poisoning.

OBSERVATIONS ON THE THERAPY OF THE SCHIZOPHRENIAS

The Histapenic (H−) Patient

1. These patients are over-stimulated—so don't use the usual drug stimulants such as amphetamines, Ritalin, or tricyclic compounds such as Vivactyl®, or

Tofranil®. Elavil is safe to use since it has antipsychotic as well as antidepressant effect, exceptions are Thyroid or Deaner®—both of which are naturally occurring substances. The dose of desiccated thyroid can be started at 120 mg per day, and any increments in dosage must await careful evaluation of the patient for tachycardia, tremor, etc. The dose of Deaner® can be 100 mg each morning with the patient evaluated at each visit for unusual emotional outbursts or excessive appetite.

2. Give enough of a potent antipsychotic medication to produce some muscle symptoms before deciding that the dose is adequate or the drug is ineffective. Start with a small dose and increase gradually at 3-day intervals. In this way the patient will have a minimal of side-actions so that the usual antidotes Cogentin® or Kemadrin® may not be needed.
3. These patients turn night into day and usually request some type of sleeping medication. We suggest the use of Benadryl® and/or Mellaril®. These compounds are relatively suicide-proof in the adult and have enough atropine-effect to reduce the muscle symptoms of the Trilafon® or Prolixin® therapy which is used in the daytime. Dosage of Benadryl® may be as high as 100 to 200 mg at bedtime. If this is ineffective then Mellaril® should be started at 25 mg and increased to as much as 200 mg with or without Benadryl®. If the patient cannot tolerate Mellaril®, then Thorazine® must be used at bedtime.
4. Use niacinamide/vitamin C plus Deaner® in children. *Megavitamin therapy is usually effective!* As the child becomes more normally active and mischievous Haldol Concentrate® (1 to 4 drops each AM) may be needed. Each drop contains 0.1 mg Haldol®. Since Haldol® Concentrate is odorless and tasteless this preparation can be used for covert treatment of the paranoid withdrawn patient.
5. Use niacin/vitamin C in treatment of the adult because niacinamide may cause psychiatric depression. The skin flushing produced by niacin is reduced as therapy continues. Always start with no more than 50 to 100 mg niacin as the first dose. Niacin may occasionally produce insomnia and may precipitate attacks of gout (rapid rise in the serum uric acid) with nausea and vomiting. These attacks are self limiting because of the vomiting. Vitamin C does not produce a rapid rise in the serum uric acid level.
6. Drugs which may produce the side effect of psychiatric depression in the adult are niacinamide, Haldol®, Stellazine® and Prolixin®. We have not seen psychiatric depression with Mellaril®, Trilafon® or niacin. We have seen postural hypotension with Mellaril®, Navane®, Sinaquan® and of course reserpine.
7. Elavil® is the most useful antidepressant in that it does elevate mood and has

a strong atropine-like effect to prevent the muscular side-effects of the antipsychotic therapy. The initial dose should be no more than 25 mg and should be started at bedtime. As tolerance develops, daytime doses can be added.

8. Dilantin® therapy is not effective in most schizophrenias although it is useful to prevent seizures which may be precipitated by the antipsychotic drugs or folic acid therapy.
9. Folic acid therapy (2.5 mg orally per day) may provide dramatic improvement in the H— patient. This improvement may continue for several months, when a plateau of improvement will occur unless the patient also gets an adequate supply of vitamin B12. This B12 dose can be as little as 1.0 mg given subcutaneously each month. Folic acid in doses of 5 mg or more daily can produce myoclonic jerking and even seizures when combined with antipsychotic drug therapy.
10. Because of its rapid oral absorption, Mellaril is preferable to Thorazine for calming the acutely agitated patient. A dose of 50 to 100 mg orally will usually suffice. Side effects may be postural hypotension as evidenced by "black-outs" if the patient stands up suddenly. Male patients may complain bitterly about Mellaril therapy since ejaculation may be prevented, and with larger doses penile erection may be impossible.
11. When all else fails lithium therapy should be tried. Almost every adult will tolerate two 300 mg lithium carbonate tablets per day (total 600 mg/day). The serum level can then be determined after 2 weeks and the dosage adjusted (usually upward) to attain the therapeutic serum level of 0.50 to 1.2 mEquiv.
12. The treatment schedule after a week for an adult histapenic patient might be:

Niacin	1 gram 3 × per day
Vitamin C	1 gram 3 × per day
Trilafon®	8 mg AM and PM
Mellaril®	25 to 50 mg at bedtime
Benadryl®	50 to 100 mg at bedtime
Vitamin E	200 units each AM
Pyridoxine	100 mg AM and PM
Deaner®	100 mg each AM
Folic Acid	2.0 mg each AM
1 Multivitamin capsule without minerals[1]	
B12 by injection	1.0 mg per week
Rutin	50 mg AM and PM

[1] These patients are frequently high in both copper and iron so that vitamins *with minerals* may add insult to injury since these preparations are too high in copper and iron and low in zinc and manganese.

In addition the patient should have a high protein diet and the intake of caffeine-containing beverages—coffee, tea and cola drinks—should be limited to one each morning.

13. Should the patient develop a head cold or influenza attack (which event is a sign of a higher histamine level) he may be treated with aspirin, Bufferin® or Tylenol® for reduction of fever. Polycillin® or the tetracyclines may be used for bacterial infections without stopping the regular doses of vitamins and tranquillizers.

The Histadelic (H+) Patient

1. These patients are also overstimulated and the control of their insomnia may be most difficult. Again the only antidepressants to be used are Thyroid, Deaner® or Elavil®. Some of the daily Elavil® dose can be put in the sleep drug packet which can be provided nightly by a reliable member of the family from a locked steel cabinet. The sleep packet might include (2) Benadryl® 50 mg capsules, (1) Mellaril® 50 mg tablet, (1) Haldol® 1 mg, (2) pentobarbital 100 mg, and (2) Buffered aspirin. This packet may produce 6 hours sleep for these patients! With adequate sleep they are less depressed the next day.
2. Dilantin® therapy provides a mild but persistent degree of antagonism to folic acid and B12 vitamins. The usual 100 mg capsule should be used 3 times per day. Relief of symptoms should appear after 3 to 4 weeks of continued therapy.
3. The known histamine-releasing chemicals (which will pass from the blood to the brain) are calcium, adenosine monophosphate, and the potent analgesics. The male patient should routinely have calcium lactate 0.5 g AM and PM. The female patient should have one tablet per day since she may develop symptoms of renal colic on calcium therapy. Calcium helps to relieve the constant or frequent headache which occurs in these (H+) patients. Of the potent analgesics methadone has the longest duration of action. In severely suicidal patients methadone can be used with Benadryl® or Phenergan® at bedtime to release and eliminate the histamine. (The anti-histamines are only effective against released histamine; they do not decrease the stored histamine—hence the combination.) These patients and their relatives are very reliable and do not increase the prescribed dose of methadone. The highest bedtime dose we have used is 20 mg. After 1 month of treatment the symptoms of the patient's suicidal depression may disappear and the bedtime methadone dose can then be reduced by 5 mg each 3 days. Methadone is not used again unless the suicidal depression recurs. Postural hypotension from histamine release causes nausea

and occasional vomiting which is the main morning side-effect of this bedtime therapy.

4. If facilities are available for trace metal studies the research procedure of a zinc and manganese supplement to the diet can be used. The patient is provided with a solution of zinc sulfate 10 percent combined with 0.5 percent manganous chloride in a dropper bottle with directions to take 3 drops AM and 3 drops PM. This provides approximately 33 mg of zinc sulfate (6 mg zinc) and 2 mg of manganous chloride (0.5 mg manganese)—this dose level only supplements that which should be present each day in a good diet—namely 10 to 15 mg of zinc and 3 mg of manganese. The effect of this supplement is only evident after 3 to 6 weeks of therapy.

5. Megavitamin, antipsychotic drugs, ECT, and insulin therapy may be disappointing in these (H+) patients. When carefully studied some of these patients. have a high insulin level of the blood after a glucose tolerance test and all are "hypoglycemic." Some of them do well on DBI–TD® (Phenformin) 50 mg AM and PM. We believe the insulin level and hypoglycemia may be due to high copper and iron with a relative deficiency of zinc and manganese. As with the (H−) patient, the use of lithium therapy to produce a therapeutic level of 0.5 to 1.2 mEquiv. in the blood serum is sometimes effective in producing sleep and reducing depressive symptoms.

6. The treatment schedule after one week for an adult male histadelic patient might be:

Dilantin®	100 mg 3 × per day
Niacin	100 mg AM and PM
Vitamin C	1.0 g AM and PM
Vitamin E	200 I.U. each AM
Mellaril®	50 mg 4 × per day
Calcium Lactate	500 mg AM and PM
Chlor-trimeton	12 mg Spansule each AM
Mellaril® 100 mg and Benadryl® 100 mg at bedtime	
Methionine	500 mg each AM

Chloral Hydrate or Pentobarbital (Nembutal®) at bedtime in a sleep packet with Mellaril® and Benadryl®. Occasionally Methadone at bedtime.

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SECTION III

TREATMENT

24

High-Dosage Levels of Certain Vitamins in the Treatment of Children with Severe Mental Disorders

BERNARD RIMLAND

BACKGROUND

Although numbering perhaps only 3 or 4 per 10,000 among their peer age group, children afflicted with the severe behavior disorders of childhood, such as infantile autism and childhood schizophrenia, are victims of perhaps the most disabling illness known (Rimland, 1964). The most common means of treatment, based on psychoanalysis or related forms of psychotherapy, have been evaluated in numerous controlled studies, and have invariably been shown to be of no discernible benefit (for reviews, see Levitt, 1963; Lewis, 1965). My own data, based on the case histories of over 2,000 such children in the files of the Institute for Child Behavior Research, support this negative evaluation of psychotherapy.

Drugs have also been widely used in the treatment of children with severe behavior disorders, and in some cases have proved to be of major benefit in making the child less disruptive, but few believe that the drugs currently available provide more than stop-gap assistance.

Because the Institute receives communications from professional workers and parents in virtually every state in the Union, as well as from Canada, England, and nearly a score of other countries, we have become aware of an extraordinary range of innovative treatment techniques. Our files include reports from professionals and parents on such approaches as operant conditioning; the "talking typewriter" and other computer approaches; "patterning"; play, shadow, and music therapies; rage reduction; sensory deprivation; visual and motor training, tactile stimulation; LSD and other hallucinogenic drugs; steroid injections; spine adjustments; and colonic purges, to name but a few.

Exposure to this diversity of approaches, most of which are presented as "breakthroughs" by enthusiastic proponents, citing dramatic clinical material, engendered a certain skepticism on my part about their effectiveness. But, despite my initial skepticism, one method of treatment was reported to us to be effective so frequently by both physicians and parents that I decided to evaluate it in a carefully designed study. This method consists of giving the child vitamins in doses much larger than those needed by normal children.

Like most professionals, my training had led me to believe that one's normal everyday diet contains all the vitamins and minerals required for good nutrition, and that anyone advocating the use of larger quantities was probably a food-faddist, charlatan, stockholder in a vitamin manufacturing concern, or simply naïve. I have since become convinced that my original training and most traditional thinking on this matter have been seriously misguided.

It may be true that most people do not require supplementation of their vitamin intake. The general rules about how much of each vitamin is needed, such as the official "minimum daily requirements," are probably widely applicable. They are clearly, however, not *universally* applicable. It is individuals who are highly atypical, who may be possible exceptions to these rules, that concern us. In terms of behavior, we are concerned with the three or four *most* abnormal of each 10,000 children.

A substantial body of scientific evidence has developed in the past decade showing that mentally ill children and adults do in fact tend to have markedly atypical metabolism with regard to vitamins. I shall present some of these studies shortly. First, let us look at the background of the "megadose" vitamin approach and at some of the data which led this Institute to engage in its systematic study of vitamin therapy as a means of treating children with severe behavior disorders.

THE MEGAVITAMIN APPROACH

A major impetus for the current interest in the megavitamin approach was provided by the provocative work of Abram Hoffer and Humphry Osmond. They have been using massive doses of niacin and ascorbic acid on adult mental patients, primarily

schizophrenics, since 1952, and have reported encouraging results. The generally favorable outcome of their treatment with megadose vitamin therapy has been documented in numerous papers and several books published by Hoffer and Osmond (for example, 1964, 1966), as well as by other contributors to this volume. Their work has been the subject of much controversy, but unfortunately there have been virtually no replications of it by others. Mosher (1970) cites some studies said to be supportive and others not supportive of Hoffer and Osmond, but the four negative papers cited deal with NAD and DPN, substances biochemically related to niacin, rather than with niacin itself, and only one of the eight positive studies was not authored by Hoffer and Osmond.

An interesting study cited by Mosher but incorrectly not listed among those showing positive effects of niacin was conducted by Ananth et al. (1970) under the auspices of the Canadian Mental Health Association. Twenty adult schizophrenics were used in a double-blind crossover study of the effects of 3 g per day of niacin. Despite the small sample size, the limited duration of the treatment, the use of a rather small dosage of niacin, and the failure to use vitamin C in combination with the niacin, significant clinical improvement was seen in the patients ($P < .02$). Although this carefully controlled study clearly demonstrates the utility of niacin in the treatment of schizophrenia, it failed in its original purpose, which was to determine if niacin could control the adverse effects of 20 g of methionine given each day to the patients. Since the investigators, who were not associated with Hoffer and Osmond, observe that it would have taken 16 to 17 g per day of niacin to counteract this quantity of methionine and only 3 g per day was given, the only (and inescapable) conclusion to be drawn from the study is that niacin has been shown to benefit schizophrenics.

A second study conducted by essentially the same group (Ramsay et al., 1969, written commun.) produced results at variance with the first one. Three groups of ten adult schizophrenics, each treated with niacin, niacinamide, or a placebo, in addition to phenothiazines given to all three groups, showed no differential improvement, although 29 of the 30 patients did show improvement. The failure of these investigators to replicate their original findings is puzzling. It is regrettable that they used only 3 g of niacin or niacinamide per day, inasmuch as Hoffer recommends dosages ranging from 3 to 18 g per day, adjusted to the patient's requirements.

A SURVEY OF VITAMIN USE ON MENTALLY ILL CHILDREN

Because of articles appearing in the public press in the late 1960s concerning the controversy over Hoffer and Osmond's studies on vitamin use in adult schizophrenia, a number of the more venturesome parents of schizophrenic and autistic children

began experimenting with various combinations of the water-soluble vitamins to see if they could bring about some improvement in their children's condition. Many of these parents, aware of this Institute's role in serving as an information clearing house, began sending us reports of their experimentation and its results.

Over a two-year period our initial skepticism was modified by the remarkably parallel reports trickling in from the parents and physicians of some twenty children in such widely separated places as California, New York, Massachusetts, Georgia, Washington, Canada, and England. In early 1968 the information available was encouraging enough to cause this Institute to send a form letter of inquiry to the approximately 1,000 parents and professionals then on its mailing list to locate additional children on high-dosage vitamin treatment.

This survey resulted in our obtaining detailed case reports on the use of vitamins on 57 children, and summaries from seven physicians who had used vitamins in treating children with severe behavior disorders. Most of the parents had experimented independently. Some had used as many as nine individual vitamins (not taken as part of a multiple-vitamin preparation). We were struck by the extent to which the trial-and-error efforts so often converged to the same group of three or four vitamins—the same vitamins that biochemical research studies have indicated as being of greatest relevance in mental disorder: niacin, ascorbic acid, pyridoxine, and, to a lesser extent, pantothenic acid. Well over half of the children for whom we received reports showed significant improvement, irrespective of diagnosis, and children given various combinations of these four vitamins in particular often showed remarkable improvement.

As might be expected, we found enormous diversity in the combinations and in the range of dosages used by the parents and physicians who had sent us reports. Thus niacin or niacinamide, used with 40 of our 57 cases, had been given at levels ranging from 30 mg to 6 g per day. Ascorbic acid, used in 27 cases, ranged from 100 mg to 6 g per day. Pyridoxine (24 cases) ranged from 5 mg to 400 mg per day, and pantothenic acid (11 cases) ranged from 25 to 900 mg per day. In most cases in which the vitamins appeared beneficial, increase in dosage beyond a certain value did not bring commensurate improvement, although the dosage levels that appeared best were markedly above the usual levels.

The individual case reports submitted by our correspondents included a number of striking examples of behavioral improvement or deterioration which appeared to be clearly associated with the use or cessation of use of the vitamins.

An especially interesting case is the son of Professor J. Noakes, who teaches in an English university. We have corresponded with Professor Noakes for several years, since he wrote in 1966 to inform us of the steady progress his child has made as a result of daily administration of 30 mg of B6. This child had been one of 19 "autistic" children studied by Drs. A. F. Heeley and G. E. Roberts at Park Hospital, Oxford (1966). Eleven of the 19 had been found to exhibit an abnormality of their tryptophan

metabolism, so the researchers gave each of them 30 mg of B6 orally, then re-examined their urine. Heeley and Roberts reported that the abnormal response of the enzyme system was corrected by B6 administration. Dr. Roberts has advised this Institute that of the 11 psychotic children given the B6 experimentally, only Professor Noakes' child continued to take it after the brief laboratory experiment. Professor Noakes attributes his child's continuing improvement to the B6. The following is taken from a letter by Professor Noakes which appeared in *The London Observer* in early 1965:

> AUTISM—Sir . . . Our child . . . was diagnosed as autistic by two different specialists at the age of two-and-a-half and went into hospital for a year, though he came home at weekends.
>
> A biochemical test showed that he lacked Pyridoxine (Vitamin B6). A number of other autistic children were tested at the same time and the same was found to be true of some of them, though not of all. Since then we have been giving him the vitamin daily in pill-form. About three months after we started, he said his first word (Bus!). Since then his improvement has been rapid and steady. He now has a vocabulary of approximately 400 words, he can use short sentences to express his wants and observations, understands the use of letters and numbers, and above all is beginning to appreciate other people. He will be five in December. His behavior is still autistic in many ways, but his progress judged by any standards, seems remarkable.
>
> At the time, our doctor was careful not to commit himself on there being a necessary connection between Oliver's improvement and the vitamin treatment, but he has published a preliminary report on his work in *Developmental Medicine and Child Neurology* for February, 1965—"Tryptophan Metabolism in Psychotic Children," by A. F. Heeley and G. E. Roberts (our doctor)—and a full report is due to appear in the December issue of the same journal. *Jeremy Noakes.*

Of course one must be cautious, and even skeptical, in evaluating therapeutic claims. Since the parents, and in some cases the physicians, who administered the vitamins were also those who judged the child's improvement, "placebo effect" would appear to be one source for the positive findings reported here. However, it is our opinion that "placebo effect" has little bearing on the favorable results. There are a number of reasons for giving credence to the reports we received. Among them:

1. Many of the cases represent single clinical experiments conducted on a trial-and-error basis and largely independent of each other, yet they have shown consistency in converging toward niacinamide, B6, and C (and possibly pantothenic acid).
2. The children manifest such gross behavioral disturbances that the range in which improvement may show is enormous. That is, unlike normal children, in whom behavioral improvement might approximate and thus be indistinguishable from mere day-by-day variation, the present cases are so grossly atypical that they provide the opportunity for observing very marked improvement.

3. Most of the children had already been tried on quite a number of psychoactive drugs, with negative results or results that were not comparable to that gained from the vitamins. The psychiatric literature and our case files show few cases of dramatic response by children to drugs. In view of the disappointment the parents have so often experienced with earlier chemotherapy, one might almost postulate a *negative* placebo effect, where *no improvement* is the most expected effect. (Although the responses to our questionnaire show a large variety of drugs to have been tried, Mellaril was the only drug used for any substantial part of our 57-child sample, and only 2 of 9 children on whom Mellaril was reported to have been used showed significant improvement.)
4. A number of our respondents had curtailed or stopped the vitamin therapy either deliberately as a check on efficacy or as inadvertent "natural experiments" which occurred for such reasons as the mother's forgetting to buy a new vitamin supply. Often the child's regression in behavior without the vitamins was sudden and dramatic. There was often an equally dramatic improvement when the vitamins were reinstated.

These several instances of "natural experiments" involve children whose response to the presence or absence of the supplemental vitamins was unusually prompt. In most cases the response was much more gradual and in many other cases no improvement was observed. However, in many of the cases where no benefits were observed, combinations of vitamins and dosage levels departed markedly from those which the most improved children had been given.

OTHER VITAMIN STUDIES WITH CHILDREN

The only published report of the use of megavitamin treatments on behaviorally disordered children known to me prior to our own mail survey was the study by Heeley and Roberts already cited. Several relevant studies have come to light since that time, however, and these will be reviewed briefly.

Bönisch (1968) reported his experience with B6 treatment of 16 children diagnosed as autistic, out of a larger group of 200 brain-damaged children. Twelve of the 16 were reported as becoming more interested and accessible. Three children spoke for the first time under the B6 treatment, and language development reportedly improved for two others. Nine children grew restless and showed disturbances of sleep until the B6 dosage was reduced. Bönisch used 100 to 600 mg of B6 per day, with most of the dosage at the 300 to 400 mg level.

Cott (1969) has reported favorably on his use of nicotinamide, vitamin C, B6,

calcium pantothenate, Deanol, and several other drugs on childhood schizophrenics.

Although most of Hoffer's work has been with adults, he has recently published a report of his experiences in treating several groups of children with niacin and niacinamide (Hoffer, 1970). One case, a girl with childhood schizophrenia, is reported in detail from age 9 to 17.

An interesting letter by Green (1969) describes his experience with the use of several grams each of niacinamide and ascorbic acid per day, along with a high-protein, low-fat diet, in treating reading disability in school children. Only children who showed signs of perceptual instability were so treated. Green reports encouraging results on the thirty children he had treated, and states that they began to show improvement within two weeks. This problem is so common and the treatment is so safe and inexpensive that one would think it would be quickly seized upon for evaluation in reading clinics.

Fifty-seven schizophrenic children were studied by Greenbaum (1970) in a double-blind comparison of niacinamide, niacinamide plus a tranquilizer, and a placebo. No statistically significant differences were observed. A report in *Newsweek* magazine (August 24, 1970, pp. 69–70) describes a paper by L. E. Rosenberg of Yale in which an undisclosed number of children afflicted with homocystinuria and diagnosed as autistic or schizophrenic prior to the discovery of homocystine in their urine were successfully treated with vitamin B6. Homocystinuria is described as being about as common as phenlyketonuria, with an incidence of perhaps one per 15,000 to 20,000 births. In his paper "Vitamin Dependent Genetic Disease" Rosenberg (1970) states that dosage levels of up to 500 mg per day of vitamin B6 are needed for homocystinuria, in contrast to the 1.2 mg per day considered to be a normal requirement. Rosenberg points out that of the dozen known disorders involving genetic vitamin dependency B6 is involved in no fewer than five.

Of the ten forms of mental retardation listed by Carter (1970) as treatable through large dosages of vitamins, five require high levels of B6. The others require vitamin D (3 syndromes), niacin (2), and B12 (1).

Dr Henry Turkel (1969, personal commun.) of Detroit has for some years advocated the use of high-dosage levels of certain vitamins and minerals as a way of partially remedying the mongoloid child's very poor mental and physical functioning. I have made no attempt to evaluate the large body of data he has accumulated to document his claims (including many before-and-after x-rays), but I have been interested in the abuse he has received from authorities who are convinced he is wrong. Dr. Turkel recently sent me a copy of a letter from a U.S. Food and Drug Administrative official asserting that his treatment *could not* be effective because mongolism is a genetic disease(!). He also sent a copy of a report from Japan (Tanino, 1966) verifying the efficacy of large dosages of vitamins in treating mongoloid children.

BIOCHEMICAL STUDIES

I have cited a good deal of the research demonstrating that clinical improvement in some severely disordered adults and children can be achieved by use of massive dosages of certain vitamins. Having discussed this matter with many people (most of them skeptical), I am aware that such strictly empirical evidence leaves many unconvinced. The skepticism is often accompanied by the assertion that there is no theoretical or scientific basis for vitamin use in mental illness. This is not true. In this section I shall briefly review some of the relevant evidence.

It has been known for many years that one form of severe mental illness, pellagric psychosis, is caused by a deficiency of niacin, and that the sick person quickly returns to normal upon being given the niacin his body needs. To the question "Are there other mentally ill persons whose mental illness may similarly be corrected by adding niacin or some other vitamin to their diet?" the stock answer has been that giving niacin to a person psychotic with pellagra helps him only because his diet *lacks* niacin. A person with a normal diet gets enough niacin to prevent mental disorder, it is argued, and so will not be helped by additional amounts of the vitamin. The error in this argument becomes obvious when we consider atypical individuals such as a child with vitamin-D-resistant rickets. Only *massive* quantities of the vitamin will help.

I use vitamin-D-resistant rickets as an example only because it is so widely known, but examples involving behavioral abnormality are readily available. I have already mentioned the study by Heeley and Roberts, which showed 11 of 19 psychotic children to exhibit an abnormality of tryptophan metabolism that responded to supplemental vitamin B6. The work of Rosenberg on homocystinuric children diagnosed as autistic was also cited in this connection. Nutrition manuals tell us that the daily requirement of B6 in childhood is 0.5 to 1.5 mg per day. Twenty times this amount served to normalize the tryptophan metabolism in the Heeley and Roberts' sample, and about 400 times this amount was needed by Rosenberg in the treatment of homocystinuria.

Roger J. Williams (1956) points out in his book *Biochemical Individuality* that even among clinically *normal* persons tenfold variation in need for B vitamins is common. In another study Williams and Deason (1967) demonstrated that thirty-two times the putative "minimum daily requirement" of vitamin C for guinea pigs brought about increased growth and longevity in some members of a sample of guinea pigs—a species whose diversity is distinctly smaller than man's.

Reference has already been made to the work of Hoffer and Osmond on the use of ascorbic acid and niacin in schizophrenia. A number of other writers have recently published papers showing a highly consistent and quite strong tendency for schizophrenics to fail to excrete ascorbic acid when it is given in multigram quantities. VanderKamp (1966) found that it required an average of 40 g (about 1,300 times the "minimum daily requirement") per day of oral ascorbic acid before it appeared in

the urine of a group of chronic adult schizophrenics, while a control group of normal individuals began to excrete ascorbic acid after only 4 g per day (average) had been taken. This study was replicated by Herjanic and Moss–Herjanic (1967), who found essentially similar results. In addition to his ascorbic acid excretion test findings, VanderKamp reported, "All the patients who received this vitamin in these large doses made a definite clinical improvement." In an earlier study, Milner (1963) had also reported both clinical improvement and low excretion rates in psychiatric patients given vitamin C, although Milner had used only 1 g per day of ascorbic acid.

The possibility that vitamin C may play a role in the effectiveness of the phenothiazines in treating schizophrenia is raised in a study conducted by Sainz (cited by Kalinowsky and Hippius, 1969): " . . . the phenothiazines also increase the blood level of ascorbic acid, and it was found that the higher the increase, the greater the clinical improvement."

Theoretical considerations linking ascorbic acid, niacin, and thiamine to acetylcholine and catecholamine metabolism in mental illness have recently been elucidated by Galzigna (1970).

Siva Sankar (1969) has reported the findings of thirty biochemical tests for groups of children classed as autistic, schizophrenic, and nonschizophrenic. The blood levels of four vitamins, C, folic acid, B6, and B2, were among those tested. Sizable differences between the groups in vitamin levels as well as in other blood constituents related to vitamin metabolism were found.

Unfortunately, Siva Sankar did not give his criteria for the diagnosis of autism and schizophrenia. As I have shown (Rimland, 1968, 1970, unpub. data), such diagnoses are subject to such great interdiagnostician variation that little reliance can ordinarily be placed upon them.

An objective means of diagnosing infantile autism, which I had developed, was used by Boullin et al. (1970), who were able to report highly significant abnormalities in platelet 5-hydroxytryptamine (5HTP) efflux in autistic children, as compared with normal controls. In a second study (Boullin et al., 1971), the abnormality was found in all cases diagnosed as autistic, but in no case diagnosed "psychotic but not autistic." The laboratory work was done without knowledge of the diagnoses.

A serotonin abnormality in a group of children labelled as having "early infantile autism" has also been reported by Ritvo et al. (in press). These authors report a "significantly greater variability" in their putative "autistics" than in the normal controls—a finding which I would attribute to the heterogeneity of their sample.

The foregoing studies are of particular significance because of the important role vitamin B6 plays in the metabolism of 5HTP. Friedman (1969) has provided some astute conjecture on the role serotonin may play in the symptoms shared by children with such disorders as autism, schizophrenia, and PKU. His description of the similarity between autistic and phenylketonuric children, barely touched on in my own book on autism (Rimland, 1964), is striking.

Watson (1965) has reported an unusually interesting study in which treatment of mentally ill patients with various vitamins and minerals was found to permit division of the patient population into two groups, according to their response to the nutrient treatment. "Blood studies revealed statistically significant differences between *Ss* classified as Type I or as Type II, the greatest differences being found in the plasma *p*H and in the dissolved $O_2 + H_2CO_3$."

The foregoing was intended to provide only a sampling of some of the more relevant studies implicating vitamin metabolism in mental illness. Additional references may be found in Pauling's already classic paper "Orthomolecular Psychiatry" (1968a).[1] Another recent source is the chapter on "Psychologic Disorders" in *Diet and Disease* by Cheraskin et al. (1968).

SAFETY OF THE VITAMINS EMPLOYED

It is widely accepted that with the exception of vitamins A and D (fat-soluble vitamins that are not readily excreted) there is no serious toxicity problem even when vitamins are taken in very large quantities. Nevertheless, because of their anticipated use on children, and especially on children who are usually unable to communicate to report side effects, the Institute has made an intensive review of the possible toxicity of the vitamins selected for use in our study: niacin (or niacinamide), ascorbic acid, pyridoxine, and pantothenic acid. (We did not similarly review the evidence on toxicity for vitamins B1 and B12, biotin, and folic acid, which Pauling mentioned in addition to niacin, B6, and C as likely prospects for vitamin research on mental illness, nor for vitamins B2 and E, calcium, potassium, or magnesium, for which we have seen suggestive but as yet noncompelling evidence.) Pauling says of the vitamins mentioned in his review that they are quite safe and nontoxic (1968b). Pauling and many others have observed that these vitamins are far safer than the synthetic drugs that are widely used for mental patients.

We could find no evidence for serious side effects in the vitamins which our investigation leads us to believe are most promising for the psychoses of childhood. The safety and side effects of *niacin* and *niacinamide* have recently been thoroughly reviewed by both Hoffer (1967) and Mosher (1970). Our data suggest that dosages of 1 to 2 g per day, and possibly up to 4 g per day in some cases, are sufficient for use in

[1] The reader may also wish to see the paper on biochemical research on mental illness by Kety (1966), in which Kety describes the work of Hoffer and Osmond on nicotinamide as an "ingenious" approach to testing the transmethylation hypothesis of mental illness, and describes research of his own as being supportive of the hypothesis. Oken (1968), then Head of the Clinical Research Branch of the National Institute of Mental Health, wrote a highly critical letter to *Science* concerning Pauling's article on "Orthomolecular Psychiatry" in which he referred to a 1959 paper by Kety which is often cited to discredit the vitamin approach but did not refer to Kety's far more favorable 1966 paper.

children. There certainly appears to be no danger from these dosages, nor even from dosages much higher. Hoffer refers to two patients who were given 25 g per day for three months, and states that his usual dose range for adults is 3 to 18 g per day. There is some indication (though not apparent in our own data) that niacin may be slightly more efficacious in mental illness than niacinamide. However, the flushing of the skin and the itching which may occur for a few days after niacin is started can be distressing to many people, so our decision was to use niacinamide. Periactin (4 mg) has been reported to control the niacin flushing (Robie, 1967), and hexanicotol (niacin plus inositol) is reported by some to have the efficacy of niacin without the flushing, but niacinamide seems to work well enough. Niacinamide does bring about nausea in some cases and vomiting in still fewer cases. Fortunately, the B6 which also seems helpful for childhood psychosis appears to confer the additional benefit of preventing nausea. Our data suggest that 15 to 20 mg of B6 per 100 mg of niacinamide may be an effective ratio in preventing nausea.

Two parents in our survey group reported allergic-like side effects to niacinamide. One mute 13-year-old boy began scratching his skin and wrinkling his nose with the use of niacinamide. These effects promptly disappeared upon the cessation of use of the vitamin. The parents thought they might have seen minor behavioral improvement but could not be sure. Another boy, age 18 and mute since birth, showed such extraordinary improvements in many ways upon being given several of the vitamins, including large amounts of niacinamide, that his parents placed a telephone call across the continent to tell us of the improvement. A hive-like skin reaction was mentioned but was not thought serious enough to require cessation of the treatment.

One caution in the use of niacin (not niacinamide) is that it inhibits the drop in blood sugar level in hyperglycemic conditions, and therefore diabetics may require regulation of their insulin dosage if niacin is used.

Ascorbic acid is very safe, only occasionally causing minor side effects. One of the patients in the Herjanic and Moss–Herjanic study cited earlier was given 110 g per day, and seven others were given over 60 g, with no ill effects reported. Glatzel (1966) has reported diarrhea to have followed the use of large amounts of vitamin C in some very young children. We have also encountered several cases in which diarrheal disorder may in some cases have been due to lactose intolerance. Hoffer advises us that pure vitamin C can, in some cases, bring on temporary diarrhea, and that for these patients he gives 1 g per day less than the amount causing diarrhea.

Correspondence with Paul György, who discovered B6, and our own intensive search of the literature indicate *pyridoxine*, vitamin B6, to be quite safe, even at high dosage levels. A review published by the American Academy of Pediatrics (1966) presented the same conclusion: "To date there has been no report of deleterious effects associated with daily oral ingestion of large doses of vitamin B6 (0.2 to 1.0 g per day)."

Pantothenic acid is reported by Williams (personal commun.), its discoverer, to be

nontoxic even in very large doses, and we have found no evidence to the contrary. Williams (1968) reports monkeys to have been given calcium pantothenate for six months in amounts up to about 500 times their normal intake, with no adverse effects. He reports the life span of mice given supplemental pantothenic acid daily to have averaged 645 days, as compared with 549 days for mice treated alike but given only a good commercial laboratory mouse diet. Healthy human adults given 10 g per day, 500 times the normal therapeutic dose of pantothenic acid, for six weeks and then placed under stress were reported to have displayed many "physiological advantages" (Ralli and Dumm, 1953).

On the basis of this evidence, we concluded that there was little or no danger of consequential adverse side effects in the planned experiment.

THE INSTITUTE FOR CHILD BEHAVIOR RESEARCH EXPERIMENTAL STUDY OF HIGH-DOSAGE VITAMIN THERAPY

After we had considered all the data available to us and consulted various interested researchers and practitioners, the regime shown in Table 24-1 was decided upon. The dosages shown are for a child under 75 pounds body weight. Children weighing 75 to 125 pounds took four rather than two of the vitamin C, niacinamide, and B6 tablets, and children over 125 pounds took six tablets of each. Thus each child daily took two multiple B tablets, 200 mg of pantothenic acid, and from 1 to 3 g of ascorbic acid and niacinamide, plus 150 to 450 mg B6, depending on body weight.

The multiple B was used to provide a high background level of the B vitamins as a safeguard against B-deficiencies which large doses of the single B vitamins might otherwise produce. Niacinamide was used in preference to niacin to avoid loss of cases due to the flushing and itching of the skin which often occurs during the first few days of niacin use.

The vitamins were produced for us in the form of flavored tablets by Kirkman Laboratories of Portland, Oregon, and were made available at near cost. The niacinamide proved very difficult to flavor properly because of its bitter taste, and many problems were experienced because a large proportion of the children would not readily accept it. Since children as severely afflicted as those in our study are even less readily moved by reason and persuasion than normals, the availability of candy-flavored vitamins was essential to the conduct of the study.

The subjects of the study were the approximately 300 children of parents who had expressed interest in participating in the study when responding to our questionnaire survey on the use of high-dosage levels of vitamins. Each parent was required to obtain the cooperation of the child's physician or another local doctor to provide on-site medical supervision and to complete monthly reports on the child's status

TABLE 24-1.

Institute for Child Behavior Research Vitamin Study. Vitamin Regime and Schedule Sheet. Numbers Refer to Daily Quantity of Tablets: Half given at Breakfast and Half at Supper. Table for Child Weight "A" (Under 75 lbs)

Day of Study	Week[a]	Parent Report	Doctor Report	Cherry	Orange	Pink	Yellow	Choco-late
1–7	1		[b]	2[c]	2			
8–14	2	×		2	2			
15–21	3			2	2	½[d]	½[d]	
22–28	4	×		2	2	1	1	
29–35	5		×	2	2	2	2	
36–42	6	×		2	2	2	2	2
43–49	7			2	2	2	2	2
50–56	8	×		2	2	2	2	2
57–63	9		×	2	2	2	2	2
64–70	10	×		2	2	2	2	2
71–77	11			2	2	2	2	2
78–84	12	×		2	2	2	2	2
85–91	13		×	2	2	2	2	2
92–98	14	×		2	2	2	2	2
99–105	15			2	2	2	2	2
106–112	16	×		2	2	2	2	2
113–119	17		×	2	2	2	2	2
120–126	18	×						
127–133	19							
134–140	20	×			No Treatment Period			
141–147	21							
148–154	22	×[e]	×[e]	2	2	2	2	2
155–161	23			2	2	2	2	2
		×[f]	×[f]					

Tablet Contents: Cherry: multiple B: 10 mg iron, 30 mg choline, 30 mg inositol, 2.5 mg B_1, 2.5 mg B_2, 2.5 mg B_6, 7.5 mcg biotin, 0.05 mg folic acid, 15 mg niacinamide, 25 mg pantothenic acid, 5 mcg B_{12}, 15 mg para-aminobenzoic acid.

Orange: vitamin C, 500 mg Pink: niacinamide, 500 mg Yellow: vitamin B_6, 75 mg
Chocolate: pantothenic acid, 100 mg

[a] "Week" means early in week; i.e. Sunday, Monday, or Tuesday.
[b] Dr.'s appointment at beginning of study for baseline observation of child.
[c] Numbers indicate *total* tablets per day. Give half at breakfast, half at supper.
[d] Give fraction of tablet first day; more second day, etc., until full dosage reached at 10 days.
[e] Parent and Dr.'s report due at end of "No Treatment Period." This period may be less than 30 days if parents and doctor agree that treatment should be reinstated earlier.
[f] Final report when vitamin supply depleted.

under the vitamin treatment. Many parents encountered great physician resistance to participation in the study, and a number of families were forced to withdraw as a result of being unable to find a local doctor willing to cooperate. The cost to the parents for participation in the study was $40 (about $10 per month) for the vitamins.

Participation in the study was to be for 24 weeks. A few families started at the very beginning of the study and finished 24 weeks later, but most were enrolled after some delay because of the problem of finding a doctor, the desire to start the study after school vacation to avoid confounding school-produced changes with vitamin effects, or some other reason.

Six weeks before the end of each child's study participation period, the schedule called for a one-month no-treatment period during which the vitamins were to be discontinued to permit observation of any effects of the discontinuance. Use of the vitamins was to be reinstated at the end of the no-treatment month, or earlier if the decision had been reached jointly by the parents and physician that the child's behavior had deteriorated significantly.

The rating sheets on which the parents were to record their observations semi-monthly and the physician's observations monthly provided for separate ratings of change in speech, alertness, eating, sleeping, tantrums, and several other aspects of behavior.

The criteria of vitamin efficacy were to be: (1) parent reports during the vitamin-treatment period; (2) parent reports during the no-treatment period; (3) physician reports during the vitamin-treatment period; (4) physician reports during the no-treatment period; and (5) whether or not vitamins were reordered.

Problems Encountered

By far the most serious problem encountered—apart from the difficulty the parents experienced in finding physicians willing to cooperate—was the unwillingness of over half the children to take the niacinamide. Although the laboratory had tried several methods of masking its bitter taste, the product still left so unpleasant an aftertaste that great resourcefulness was required to keep many of the children in the study. Kirkman Laboratories generously agreed to provide unflavored niacinamide free of cost to all participants requesting it. Most of the parents whose children balked at the oversize flavored tablets were ultimately able to work out a means of administering the unflavored tablet, either by crushing it and mixing it with a preferred food (ice cream, apple sauce) or by teaching the child to swallow the whole tablet. Unfortunately, a significant number of children dropped out of the study, or took all vitamins except niacinamide as a result of the taste problem. (In further work we shall probably use the more easily flavored niacin, despite the skin flushing that it causes.)

In one way the problems with niacinamide conferred an advantage. A number of the children in the study had been institutionalized, and their enrollment in the study was usually accomplished only through great effort on the part of their parents. The superintendent or director might acquiesce, but the actual ward workers were often not cooperative. It was quickly apparent to us that most of the children in

institutions were only nominally in the study—reports were not submitted or were completed in a perfunctory manner, inconsistent reports were received as to the child's status, depending on which of several persons signed the forms, etc. When it was realized that 54 percent of the children given the vitamins at home had refused the flavored niacinamide, according to parental reports, yet only a few institutionalized children had refused it (if one were to credit the absence of complaints from institutions), it was decided to place the twenty-six institutionalized children in a separate group for later analysis. The data to be disclosed below are thus based only on home-reared children.

Only four children were removed from the study as a result of apparent adverse reactions to the vitamins. Three of these became wild (or wilder) and unmanageable soon after the B6 and niacinamide were started. The fourth became even more distant and withdrawn. In each case the child's behavior returned to its original status within 10 days of the discontinuance of the vitamins.

A substantial proportion of the children showed such adverse effects as increased activity level, irritability, and sleeplessness, especially at the onset of the B6 and niacinamide, but these effects usually subsided spontaneously after a week or two. In these cases the parents were encouraged to reduce the dosage levels of B6 or niacinamide for week-long periods in order to find the optimum level for the child. Sleep problems were controlled in some cases by giving the vitamins earlier in the day.

A few children showed deterioration of behavior when the last vitamin, pantothenic acid, was added. A few others, who showed no behavioral response to the earlier vitamins, appeared to improve dramatically when the pantothenic acid was added. Parents of children showing problems on the initiation of pantothenic acid were advised to discontinue giving it, since the first several children showing the pantothenate-induced irritability did not improve until the vitamin was withdrawn.

Although our instructions advised the parents to continue for a time whatever medication the child was taking, then try to taper it off, many parents removed the tranquilizers abruptly, with ensuing problems. These problems could usually be resolved over a few weeks time by adjusting dosages of the drugs or vitamins.

In addition to the above-mentioned adverse effects, there were a considerable number of entirely unexpected beneficial side effects. A number of children who had acne or other skin problems were reported to show sudden and dramatic improvement. Several cases of highly aberrant appetite were corrected by the vitamins, food ingestion being either raised or reduced toward normal quantities. (In one case compulsive overeating was increased, however.) Three mothers reported their children's hair to have begun to curl upon the use of vitamins. One mother of a 20-year-old boy had taken snapshots before and after the vitamins; the hair curling was quite evident in the photos. One child who showed no other change in response to the vitamins stopped grinding her teeth. By experimentation the mother found that it was the multiple B which helped, and she discontinued the other vitamins.

Vitamin Study Data

Every report for each child in the study was coded and punched into an IBM card. Including the parents' and doctors' reports, plus the final summary parent report and our own overall evaluation of the case, this amounted to 20 cards per child. Every side-effect, change in dosage, and supplemental drug used, in addition to the behavioral description of the child, which was our primary focus, has been recorded. A body of data this large requires a good deal of time (and money!) to analyze, and

TABLE 24.2
Distribution of "Overall Improvement" Ratings

Effect and score	Description	No. of cases
Definite improvement (45.3%)		
90–99	Maximum improvement in all areas	3
80–89	Very good improvement	38
70–79	Significant (definite) improvement	45
Possible improvement (41.0%)		
60–69	Some improvement	41
50–59	Possible improvement	37
No improvement (10.5%)		
40–49	No change	20
Adverse effect (3.1%)		
30–39	Some behavior deterioration	4
20–29	Much deterioration	2
10–19	Great deterioration	–
Total		190

the present report must be considered only a preliminary one, based on a rather gross overall behavioral criterion of improvement during the vitamin-treatment period and deterioration during the no-treatment period. Later reports will cover the more detailed findings.

As of May 25, 1970, relatively complete data were on hand for 233 cases. Approximately 70 additional cases were incomplete and still outstanding.

To arrive at the single global improvement score analyzed below, two judges inspected all the data available for each case, including both the parents' and physician's reports. Each judge arrived at a two-digit numerical score for each case, using the scheme shown in Table 24-2 for scoring. To receive a score above 80, the child had to show not only strong improvement while on the vitamins, but also significant deterioration during the no-treatment period.

After the two judges had independently scored each case, the two ratings were

compared to resolve discrepancies. Most discrepancies were of only a few points, and these were resolved by averaging. Where discrepancies of 10 points or more were found, an attempt was made to resolve them through discussion among the judges. In a number of cases the results were so conflicting from one report to the next, or contained such gross inconsistencies within a single report, that one or both judges felt unable to assign a meaningful single score. Most of these, as it turned out, were reports on institutionalized children, and when it was realized that almost none of the institutions had complained about the niacinamide the decision was made to exclude all 26 institutionalized cases, as well as the 17 ambiguous home-treated cases, from the analysis. This left a total of 190 cases for the present analysis. (In the ensuing three-month period 17 additional cases have reached the final report stage.)

Statistical Analysis

The design of our study represents a marked departure from the traditional concepts of therapy-evaluation research. In my opinion the usual double-blind and placebo design is greatly overvalued. There is such wide acceptance of the double-blind design that it is not generally recognized that such a design has, in addition to its many advantages, certain severe disadvantages. (For critiques of the double-blind design, see Altschule, 1964 and Barsa, 1963.)

One of these disadvantages is that it is usually difficult, if not impossible, to find an adequate placebo. Most potentially therapeutic substances, such as drugs or vitamins, have side effects in addition to their main effects, and these side effects, which usually cannot be duplicated in the placebo, serve to "unblind" the participants. The flushing usually produced by niacin, for example, or the gastro-intestinal upset sometimes caused by large doses of niacinamide, would be hard to reproduce in a placebo.

Another problem with the double-blind design is that it is inefficient in its use of subjects when the population to be studied consists of a mixture of types of disorders. If the treatment being evaluated is effective for only part of the group, the double-blind design is likely to lead to an erroneous negative evaluation of the treatment unless very large numbers of subjects are used in the study. It seems probable that, because of the difficulty in diagnosing psychiatric populations accurately, most double-blind studies of psychiatric patients have involved heterogeneous samples. In the case of the childhood psychoses, I have repeatedly emphasized that the diagnostic methods are poor and that most of the research done on groups of autistic children is for this reason meaningless (Rimland, 1964, 1968, 1970, unpub. data). The experimental design used in the present study was chosen to avoid the above problems.

Each parent who wished to enroll a child in the vitamin study was required to

complete two detailed questionnaires concerning the child's medical history, symptoms, previous diagnoses, and related matters. One of these, Form E-2, was designed for statistical analysis to provide a means of identifying the various homogeneous subgroups, syndromes, or clusters of similar children in any large sample. Form E-2 contains 80 multiple-choice questions which are readily amenable to computer analysis.

The design of the vitamin study assumed that if the Form E-2 data were subjected to computer cluster analyses, so that children who resembled each other in terms of medical histories and behavioral symptoms were grouped together by the computer into small homogeneous clusters, the clusters would then be found to differ significantly from each other in terms of response or non-response to the vitamin treatment, if the vitamins were in fact of benefit to part of the sample.

Even without the use of a placebo group it would thus be possible to determine if the vitamins had a statistically significant effect on the condition of the children. There appears to be no way for bias—experimenter bias, patient bias, or rater (parent and physician) bias—to influence the results. Even if the parents wished strongly to see improvement in their child, and consequently rated them as more improved than was warranted, this would have no effect on the significance of the findings, except perhaps to *lower* the likelihood of positive findings (by adding "noise" to the data). The parents, who had completed the diagnostic check lists some time before the child started the vitamins, had no way of knowing which other children in the sample would be found by the computer to resemble their child, and whether the similar children were or were not improving.

Data Analysis

There is no "right way" to cluster-analyze data. There are a variety of methods, several of which were applied to the E-2 diagnostic check lists for the children in the vitamin study. The methods used employed a series of scores derived from the E-2 form in earlier studies. One set of 10 scores had been derived from the E-2 form by factor analysis by James R. Cameron, using data I had provided. Another set of 7 "rational" or "a priori" scores had been developed by the present writer for research purposes. (Some of these are described in Rimland, 1968.)

Normix Analysis

Normix is a system of cluster analysis developed by John H. Wolfe (1970) of the U.S. Naval Personnel and Training Research Laboratory, San Diego. Wolfe was provided

with a deck of 190 IBM cards, each punched with the 17 E-2 scores for a child who had completed the vitamin regime. Using program Normix on an IBM 360–67 computer, Wolfe arrived at a clustering solution which produced six subgroups of children, ranging from 72 children in the largest group to 5 children in the smallest. For each group the score profile, or pattern of scores, tended to be more similar for the children within that group than for any pair of children from different groups. It is important to note that Wolfe, like Cameron and Hoffman, whose analyses are described below, used only the scores derived from the E-2 forms to construct his groups. He had no knowledge of how any of the children had fared under the vitamin treatment.

After the children had been classified into the six groups, the vitamin improvement score was entered into the computer. The mean improvement score was then determined for each group and an analysis of variance was done to determine if the group means differed significantly from each other. The means, which ranged from 69.00 to 46.71, yielded an F ratio of 2.70, which was significant at the .02 level with 5 and 183 d.f. Thus, the vitamin treatment may be seen to have been definitely more effective on some children than others, and the differences found were too large to be attributable to chance factors.

BC TRY Analysis

A second computer cluster analysis of the same data was performed by J. R. Cameron of Napa State Hospital, California, using the BC TRY cluster program on the IBM 7090 computer at the University of California at Berkeley.[2] The BC TRY method involves different mathematical assumptions than the Normix program, and Cameron for technical reasons preferred to use only the 10 factor scores in his analysis, rather than all 17 scores used by Wolfe. Cameron produced eight homogeneous clusters of children, ranging from 10 to 39 children. Nine children could not be classified in any of these groups. The mean vitamin improvement score was then determined for each group. The range of means was from 57.83 to 78.23, and an analysis of variance yielded an F-ratio of 2.49 (7 and 172 d.f.) which was significant again at the .02 level. Thus again there was found a correlation between the symptomatology and the degree of improvement which was too great to be explained as a chance relationship.

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[2] Since cluster analysis is a developing technology, cluster analysts are pleased to be able to try their various methods on the same body of data, as a means of comparing the methods. The present data are of special interest from the methodological standpoint since they include an "outside" criterion, the vitamin improvement score. Other cluster analysts have also been invited to use our data.

Hierarchical Analysis

A third computer cluster analysis was performed by Paul J. Hoffman at the Oregon Research Institute, using a hierarchical clustering program on the ORI-IBM 360–91 computer. Hoffman, using all 17 E-2 scores, produced 14 subgroups (the 14th group consisted of only one child). The thirteen other groups ranged in size from 4 to 33 children, and the means ranged from 58.83 to 71.22. The analysis of variance yielded an F-ratio of only 1.32, however, which is not significant.

Discussion of Cluster Analysis Results

Two of the three analyses yielded results significant at the .02 level, and one failed of significance. The reason for the discrepancy is inherent in the differences in the methods.[3] The hierarchical method, as its name implies, yields a pyramidal structure of subgroups, ranging from a single group at the top, containing all cases in the sample, to a large number of subgroups at the bottom, with each "subgroup" consisting of a single case. Perhaps if the fractionation process had stopped at a higher stage, with 6 to 8 subgroups, the results would have resembled the others.

This problem, as well as such matters as the correlation between the groupings provided by the different methods, is under discussion among the methodologists and need not concern us at this point. It will be seen that our proposed follow-up study, in which we plan to *predict* the degree of vitamin improvement in children not yet tried on the vitamins, may be of great interest from the cluster-methodology standpoint.

AID Analysis

When the vitamin study was first conceived, it was planned to depend solely on clustering procedures such as those described above. Recently, however, I learned of Program AID (Automatic Interaction Detector) developed by John R. Sondquist, now of the University of California at Santa Barbara. Unlike the clustering programs, which arrive at subgroups without "knowing" what outside criterion they will be used to predict, Program AID constructs its subgroups so as to maximize the prediction of whatever criterion it has been instructed to maximize. While AID is thus clearly a useful program, its dependence upon an outside criterion would seem to

[3] Perhaps it should be pointed out that mathematical cluster analysis is not different from "real life" clustering in sometimes lacking a unique or best solution. If one were subgrouping retardates, should all mongoloids be considered alike, or should the trisomy-21 cases be a separate group? Should a PKU child with an inactive thyroid be classed with the PKU or the cretin group?

preclude it from the present purpose, which requires that the improvement score be predicted on a "blind" basis, using only data independent of the criterion.

But Raymond E. Christal and Janos Koplyay of the Personnel Research Division, Lackland Air Force Base, Texas, have devised an ingenious improvement of AID which makes it ideal for our purposes. The improved AID program randomly divides the sample of subjects into halves, develops a grouping procedure on half "A" designed to predict the criterion, then applies the grouping procedure (or "scoring key") to half "B" to determine how accurately it can predict the criterion in the independent sample. It then constructs a key on half "B" to be tried on half "A". It then recombines the groups into the whole sample, divides the whole again into two new random halves and repeats the process as often as desired. Each cycle (each random division of the sample) produces two unbiased validity coefficients—each is the product-moment correlation between the actual criterion scores and the scores predicted through use of the "key" developed on the other half of the sample.

Christal and Koplyay used the Lackland version of program AID on our vitamin study data through four of the above prediction cycles. The eight independent and unbiased validity coefficients so produced ranged from .315 to .480. Each coefficient is significant well beyond the .01 level. This confirms beyond doubt that the effectiveness of the vitamin treatment for a child can be predicted from knowledge of his symptomatology—that is, from the information provided on the E-2 form by his parents. Prediction is far from perfect but far better than chance.

Follow-Up Study

The files of the Institute for Child Behavior Research contain over 2,000 completed E-2 forms. The next step in our program for experimental evaluation of vitamin effects on psychotic children entails using the keys already provided by program AID to classify the remaining 1,800 children into subgroups varying in terms of their predicted likelihood of benefiting from the vitamin treatment. We propose then to use the computer to identify the 200 children designated as most likely to benefit and the 100 least likely to benefit. Half of each group will randomly be assigned to vitamin treatment, and the other half to a placebo. The design of the study will then be explained to the parents of all the children, and they will be asked to participate in a 90-day trial of the vitamins.

Further Findings from Vitamin Study

As noted earlier, a great deal of highly detailed data, occupying some 20 punched cards per child, has been collected and awaits analysis. The analysis will be especially

concerned with such questions as: Are there specific vitamins among those tried that seem particularly appropriate for any given subgroup of children? Which specific symptoms are remediable by which vitamins?

Although we have established through statistical tests that the combination of vitamins as used does effect improvement in identifiable subgroups, little else by way of firm further conclusions can be forthcoming until the more detailed analysis can be completed. However, there are several findings of sufficient saliency to warrant their being mentioned pending more formal statistical analysis.

Vitamin Effect on Autistic Subgroup

The subgroups of children identified by the cluster-analysis procedures may on further analysis prove to be interesting from an etiological standpoint, apart from their present usefulness in evaluating the outcome of the vitamin study. Cameron (1969), whose doctoral dissertation consisted of an intensive analysis of the clusters derived from a BC TRY clustering of Form E-2 data, was able to show a number of significant differences between the subgroups in the medical histories of the children and their mothers, using questionnaire data I provided.

One subgroup of the children, however, has been recognizable as a distinct syndrome ever since its delineation in 1943 by Kanner—the subgroup of children with classical infantile autism. Form E-2 has an autism scale designed to identify such children that can be used without the employment of computer clustering techniques. Through the use of the scale, 37 cases of classical infantile autism were identified among the 190 children who had completed the study. The vitamins appeared to be strikingly effective for this group. Twenty-two (59 percent) of the autistic group had been assigned improvement scores of 70 (definite improvement) or higher, as against 63 (41 percent) for the remainder of the sample. If one used a more rigorous cutoff score of 30 points or higher on the autism scale, instead of the usual score of 20, the percentage of autistic children showing "definite improvement" increased to 77 percent (10 out of 13 children).

Among the children in the study who showed the greatest improvement were the six autistic children who were taking Dilantin along with the vitamins. The Dilantin had been prescribed mainly for its tranquilizing properties (usually not for convulsions) and had been continued, as our instructions suggested.

One mother of an autistic boy provided an especially relevant report:

> Joey finished his vitamins on August 12. He has been extremely upset for these three weeks. His pediatrician took him off Dilantin in the middle of July and he just went back to biting himself and having tantrums repeatedly. I started giving him Dilantin again August 4 and he calmed down again, but the same thing has happened since he

> is not on the vitamins. He hits himself and screams all day long, the slightest frustration completely throws him. It seems he does very well on both the Dilantin and vitamins. Many people have commented on how much his behavior improved in the past 3 months.

The children in the sample taking Mellaril also showed unusually good improvement on the vitamins, but, unlike Dilantin, Mellaril showed no special interaction with the autism diagnosis. No other drugs seemed beneficial.

Specific Vitamin Effects

It will be remembered that the children were given a multiple B tablet plus vitamin C for two weeks before B6 and niacinamide were added to the regime. Pantothenic acid was added two week after that. Judging from the time certain effects were observed, and from the consequences of the parents' experimental modification of the dosage level, a number of the beneficial side effects such as skin and appetite improvement resulted from use of the rather high potency multiple-B tablet.

The main effect of vitamin C seemed to be an increase in alertness, social awareness, and sociability. On reading the clinical reports of researchers such as Milner (1963) and VanderKamp (1966) several years ago I was surprised to find them report that ascorbic acid had brought about improved personality and especially sociability in their schizophrenic patients. It seemed unlikely that a trait like sociability could be significantly affected by a vitamin. Yet such descriptions have come from the parents of our group of children, seemingly as a consequence of 1 or more grams of vitamin C per day.

It is difficult to characterize accurately the effects of niacinamide at this point. It may have an antipsychotic effect; that is, it seems to have quelled bizarre behavior in some children. On the other hand, it seemed to produce irritability and hyperactivity in others.

As was mentioned earlier, pantothenic acid also seemed to benefit some children while disturbing others. Those benefited seemed to have become more alert, calmer, and more accessible. It will be interesting to see if the differential effect of these vitamins correlate with different cluster membership.

The most obvious and dramatic changes attributable to a single vitamin were brought about by B6. Very often the effects were seen most clearly after the parent had doubled the 150 mg per 50 lbs body weight initial dosage of B6. For example, we received the following report from a mother who doubled pantothenic acid with no results, but who then doubled B6:

> Now this has made a difference . . . [she is] very eager to do things . . . at slight suggestion ready for almost anything. Eager to play basketball in front of house. Hasn't

> printed her name or numbers for over a year, but doing it now. I can't emphasize enough that she has refused to do anything these past months . . . even my husband who is a disbeliever says she has improved these past 4 days.

Another parent wrote

> Elsie has been on the doubled dosage of B6 and has shown great improvement . . . she is sharper and more aware of the outside world . . . we lit our Chanukah candles and she surprised us all by singing a Chanukah song from beginning to end.

And another,

> There was a definite improvement in most aspects of Sammy's behavior. The improvement started the same day he started niacinamide and B6. Words and sentences (3 or 4 noticed) have taken the place of much of the humming noises . . . much more aware of people . . . spends noticeably longer time with his story books.

One of the most interesting findings to emerge from the study is the surprisingly specific effect of B6 on speech. It will be recalled that Bönisch reported noticeable speech improvement and initiation of speech in the children given B6. Several of the foregoing quotations also demonstrate this phenomenon. Following is an earlier letter from Elsie's mother (note that this appears in a letter, not the formal report).

> We are in the 31st day of the vitamin study and I want to discuss the changes that have taken place the last three days. I am too excited about it to wait until the next report period. For the past two days Elsie has been doing a lot of talking—initiating conversation, answering questions, commenting on everything she hears around her!

Earlier, when the child had just started on B6, the mother had written, ". . . quite remarkable was the spilling out of so many thoughts without interruption as compared to her usual sporadic type speech."

It is interesting that in these cases where B6 seems to have stimulated speech it is not merely the *capability* for speech which has changed—there seems also to be a pressure to talk.

The No-Treatment Period

For a child to have received a very high improvement score in our study, he not only had to improve during the three months of treatment, but also to regress during the one-month no-treatment period (NTP).

Many children regressed within a matter of days. Others took nearly the whole month before showing any signs of regression, and still others, usually those in whom no improvement had been seen during the treatment period, showed no change during the NTP.

Some parents who felt that their child may have been improving on the vitamins saw no deterioration during the NTP, and decided not to reinstate the vitamins at the end of the month. However, we later heard from some of these parents, who said that the month's NTP had not been long enough, and that after two or three more weeks had elapsed they had realized that the child was indeed deteriorating, and was behaving as he had before being on the vitamins.

These findings suggest that there may be several processes operating. When the child deteriorates rapidly, one might assume a deficiency process that is quickly remedied, or partly remedied, by the added vitamin(s). In the slowly responding children, the process might instead be one of gradual accretion of some toxic product of metabolism.

Following are examples of positive NTP reports. They demonstrate the rapidity of change in some cases and the diversity of the changes.

> Frustration level extremely high without the vitamins. Much yelling and irritability. Has to be given direction three times instead of once. Changes were evident after 3 days of no vitamins and grew worse each subsequent day . . . I resumed vitamins on 14th day.

> On August 5th [tenth day of NTP] both parents, who had been keeping separate notes, agreed that marked deterioration of behavior had occurred. William seemed to have withdrawn into himself; he no longer exhibited the lively interest in the world around him that had marked the previous month. His new-found willingness to cooperate and to obey such directions as he understood disappeared rapidly. His old repertoire of mannerisms and bizarre hand motions and positions, which had been waning, reasserted itself with a vengeance.

> Harriet seems to be progressively less social with us. She is starting to retreat to her room for longer periods as she did before she started the vitamin therapy.

> Mary has been off the vitamins two weeks. Her speech hasn't deteriorated but all the annoying noises . . . have returned. Her skin tone isn't as good and the slightly bluish transparency to her facial skin is again noticeable. She is having trouble focusing her eyes and the pupils appear dilated and her expression is far off and dreamy, jaw slack.

> He stopped taking the vitamins exactly five days ago. I never expected the definite reaction that has gradually shown up without a doubt during these last five days—slowly at first and then increasing at an amazing rate. His doctor is on vacation and we cannot see the substitute doctor until next Thursday. However, I took it upon myself this morning to start him again on the complete dosage. I only hope it will relieve his present symptoms soon, symptoms that cannot be traced to anything short of not having the vitamins for these few days. He gradually showed improvement in every area on the checklist—even those I may have noted as no behavior improvement, because now in those areas he has badly regressed. He is agitated and crying practically all the time, shaking nervously, hiding under blankets, tapping on things with spoons, getting into things he hasn't been getting into and that he shouldn't get into, eating poorly and away from the family table, making continuous odd noises and seems to

> be suffering physically from some internal misery. Without a doubt I trace his former improvement to the vitamins. He became calmer, seemed normal in public, didn't make noises, verbalized sensibly, socialized more, was really much, much better. Excuse me if I've been overly verbose. I just want to explain fully the sudden change when the vitamins stopped.

Such reports—and the above are merely a sample of those in our files—are indeed encouraging. But our elation must be tempered; most of the children in our study showed much less improvement, and some none at all.

CONCLUSION

It seems clear from both the statistical analysis of our data and the clinical reports of those who have observed the children that a substantial proportion of psychotic children can be expected to benefit from treatment with high dosages of the vitamins used in this study. Other vitamins, and perhaps minerals, may also be effective for a further proportion of such children, and should be investigated.

The findings in this paper represent a skeletal overview of the results of the study. Subsequent analysis of the data collected will add some of the detail and depth necessary to an understanding of the role of orthomolecular psychiatry in the treatment of children with acute behavior disorders.

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25

The Use of Parenteral Vitamins in the Treatment of Schizophrenia

ALLAN COTT

The use of parenteral vitamins described in this paper was begun in 1968 with adult schizophrenic patients who had suffered one or more relapses requiring hospitalization and/or ECT. The technique was later modified and extended for use in the initial treatment of schizophrenic patients who were responding slowly to biochemical treatment that included the use of vitamins orally. In those patients who had previously suffered relapses, the parenteral use of the vitamins in a sample of 33 prevented rehospitalization of 31 patients. The vitamins used were nicotinamide (200 mg/ml), ascorbic acid (500 mg/ml), and thiamine-pyridoxine mixture (100 mg each/ml). One ml of each vitamin was used combined in a single 3-ml syringe and administered by deep intramuscular injection three times weekly. When improvement was established the frequency of injection was reduced to twice weekly and finally to a maintenance schedule of once each week for several months. Throughout the course of parenteral treatment the oral medications were maintained and their use was continued after the injections were discontinued.

Initially 10 mg of Elavil was added to the injection of the first week's treatment for

those patients in whom depression was overwhelming. The use of Elavil was discontinued when it was determined that the clinical response was not improved by its addition. During alternate injections the thiamine-pyridoxine mixture was replaced with vitamin B12 (1,000 μg/ml). Clinical response was seen in most patients by the end of the second week of treatment. In many patients a favorable response to treatment was noted earlier. The oral use of vitamins in megadoses was continued throughout the course of parenteral therapy.

The parenteral use of the vitamins was then extended to the initial treatment of schizophrenic patients who were being treated with megavitamins and were responding slowly. This group of patients, many of whom were hospitalized because of the severity of their illness, showed a more rapid clinical response than that achieved in similar patients prior to the use of parenteral vitamins. In those patients requiring ECT the response to treatment was in most instances more rapid, and maximum response was achieved with a smaller number of electroconvulsive treatments. Gould (1953a, 1953b) reported there were indications that, where parenteral vitamin therapy had been given for some time before ECT, memory impairment was reduced or absent and tension did not arise in connection with the treatment. Gould's initial premises for the use of parenteral vitamins in the treatment of delirium tremens were simple: delirium tremens was considered to be a B1 deficiency-disease-equivalent due to poor food intake and, since spontaneously occurring vitamin deficiency disease was rarely single, he gave "very large" amounts of several vitamins by intravenous administration, by drip or directly into a vein, of 3 to 10 g glucose, 1.5 g vitamin C, 1.0 g B1, 200 to 400 mg nicotinamide, 20 mg B2, and 0 to 25 mg pantothenic acid. Gould extended the use of his techniques to the treatment of acute alcoholic psychoses, post-operative confusional psychoses, deliria due to drugs, barbiturate coma, psychoses following continued narcosis, and drug withdrawal syndromes. In many of the above cases he reported restoration to normality within twenty minutes to four hours.

Poor alimentary absorption of nutrients is a factor in the development of illness, and interference with absorption of medications taken orally is, in some cases, a significant factor in those patients who respond poorly to treatment or who do not respond at all.

Vitamin insufficiency may be brought about by decreased intake and/or absorption of vitamins, increased body demand due to increased metabolism, inactivation of the B-vitamin enzyme systems due to narcotics, and intracellular derangement of metabolism by toxins. Attention was drawn to the probability of the factor of malabsorption of megavitamins administered by the oral route in the case of the first patient to receive the parenteral vitamin treatment. This patient had been ill for seven years and had been hospitalized many times, once for a period of several years. For two years he had been taking the megavitamins orally with marginal improvement; his relationship with his parents was stormy and his occupational adjustment was

poor. He remained in a constant depression and frequently entertained suicidal ideas. In the year prior to the use of the parenteral vitamins he had daily been taking 12 to 15 g niacin, 10 g ascorbic acid, 300 mg pyridoxine, 3 g thiamine and various antidepressants and psychoactive drugs. Despite this regimen he had four major relapses, which required two periods of hospitalization and the use of ECT. Two relapses responded to courses of ambulatory ECT. His serum ascorbic acid level was investigated and found to be 0.5 (N = 0.6–2). Parenteral vitamins were begun according to the technique described above and the patient made significant improvement at the end of the second week of vitamin injections. The injections were continued for four months for a total of 22 injections. Six months later, when depression began to recur, another series of 12 injections sufficed to end the relapse. The patient has now maintained his improvement for the past year. The above experience has been repeated in the 31 patients in the group treated by the parenteral vitamins.

A report by Hoffer (1970, written commun.) reveals similar success with many patients who had a history of numerous relapses which required ambulatory ECT or hospitalization. Two patients who were awaiting admission to hospital were deteriorating rapidly and were started on the parenteral vitamin treatment. There was no evidence of improvement during the first week's treatment, but by the end of the second week they had both made such significant improvement that neither hospitalization nor ECT was necessary. Similar reports have been received from others who have begun to include the parenteral vitamins in the treatment of relapsing patients or in patients whose improvement on megavitamin treatment was slow. The use of parenteral vitamins in schizophrenic patients who show signs of relapse following the use of marijuana or other hallucinogens has been extremely valuable.

Vitamins have been commonly regarded as tissue catalysts and as such remained unchanged by the metabolic reactions they facilitated. The small daily requirements of vitamins are held to support the view. Catalyst and enzyme are terms often used interchangeably. Yet vitamins undergo chemical change (phosphorylation, for example, in the cases of vitamins B1, B2, and nicotinamide) on absorption before combination with a complex protein molecule whereupon enzymatic status is attained. They also undergo degradation and excretion in an altered form (for example, uroflavins and nicotinuric acid). The daily requirement of vitamins is a significant proportion of the total body stores. Vitamin C is considered by some investigators to function in metabolic synthetic processes and to be present in amounts proportionate to the metabolic activity of the nervous tissue, whereas the B group serves tissue respiration. It has been shown that recovery rates in vitamin deprivation experiments depend directly on the size of the replacement dose. Gould summarizes the rationale for the parenteral use of vitamins as follows:

> If, indeed, one regards vitamins as metabolic agents, whose relation to cellular respiration mirrors in some measure the law of mass action, and remembers that the body stores of some of these substances are not only meagre, but are readily inactivated or

rapidly reduced in certain circumstances, then the use of parenteral intensive mixed vitamin therapy in certain groups of clinical conditions becomes reasonable on grounds other than clinical observation. Furthermore, the value of high blood concentrations of vitamins may be seen to reside in the possibility of influencing rapidly the equilibria between the various phases through which the vitamins are built up in the tissues to the enzymes in which they function within the cell, contributing to its metabolic integrity.

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26

A Review of Ten Years' Experience Utilizing Niacin in Treating Schizophrenia with an Evaluation of Metabolic Dysperception as a Clarifying Diagnostic Term

THEODORE R. ROBIE

My absorption with the confusing psychiatric disorder known as dementia praecox began in my junior year in medical school in 1924 and has continued throughout my 40 years of psychiatric practice. This enigmatic mental disorder seemed like the veritable hydatidiform-mole of psychiatry with a different face on each of its many pedicles. In the course of those 40 years, I surveyed a huge volume of literature, and each writer, in attempting to add further insight into this illness, only added confusion to a very cluttered diagnostic entity. Each seemed to illuminate only certain facets, and I also published a number of papers on the riddle of schizophrenia (Robie, 1927a, b, 1937). From all of this, there was little that could be conveyed to either the patient or family that was particularly helpful or clarifying. This was amply demonstrated by my colleagues' confusion over what to tell the patient suffering from this illness. None of the things that could be said were particularly enlightening, clinically accurate, or therapeutically encouraging.

In 1967, Dr. Bella Kowalson of Winnipeg minted the term "Metabolic Dysperception" to describe this baffling illness. The term combined the clinical picture, the biochemical basis, and the patient's symptoms in such a clarifying way as to remove confusion and by-pass the cumbersome label of schizophrenia.

For years, patients refused to accept that their symptoms were delusions or hallucinations, but now were able to understand them as symptoms of an illness when they were described as dysperceptions. When the patient observed that the doctor understood that he was suffering from dysperception, rapport was greatly increased as he felt he was being truly understood for the first time. It also gave the doctor a tool whereby he could point out certain things being experienced by the patient in an acceptable way. To the patient, a dysperception is naturally experienced as a real event. No other explanation for it is ever truly accepted, although patients will give lip service to the doctor that they "imagined it." The prefix "dys" implies at once that this event being experienced is in error. The term "metabolic" immediately implies to the patient that what he is experiencing is a result of improperly functioning body chemistry. He begins to learn that these dysperceptions are reporting errors and his critical faculties become enhanced. He then becomes a sick patient rather than a psychotic one. This salutary effect was noticeable even in patients whom I had successfully treated for over ten years, utilizing niacin successfully in their therapeutic regimen.

I had the good fortune, from the beginning, of having had encouraging results with niacin therapy, and in several cases the remissions had lasted for over ten years. At the time I began using niacin, there was no other chemical or therapeutic method known that would maintain a schizophrenic in remission for such a long period of time. The main difficulty, which dissuaded a number of my colleagues from using it and also dissuaded a number of patients from staying on niacin, was the unpleasant niacin flush. With the discovery that cyproheptadine (Periactin®) counteracted the flush (Robie, 1967), niacin treatment became acceptable to patients and clinically feasible, so that I was the first psychiatrist in the United States to begin using niacin in the treatment of schizophrenia. The unpleasantness of the niacin flush greatly interfered with the acceptance of the niacin treatment, and then scant notice was paid to it because of the sudden rush of interest and literature concerning the phenothiazines, which were introduced in the mid-fifties. During the years before we found that niacin in a four-times-per-day divided dosage, with or without the addition of cyproheptadine (Periactin®), eliminated the recurrent flush, a number of my patients bravely persisted because the recurrent flush was less unpleasant than the symptoms of their illness, which niacin controlled.

I would like to report two sets of contrasting cases. The first two are patients who, although successfully treated with niacin, did not have the psychological benefit that ensues from the use of the term metabolic dysperception.

Case No. 1

In 1951, a 44-year-old man with a diagnosis of schizophrenia-paranoid type was committed to a state hospital because of delusions of persecution. He believed that a thousand communist eyes watched him when he left the house, and to protect himself he tore up many documents of value. In addition, he believed his wife was trying to poison him. While hospitalized he received electroshock therapy but soon after release from the hospital the paranoid ideation returned. In 1956, when I began treating him, he had not responded to chemotherapy and he was, therefore, given electroshock therapy on an outpatient basis over a prolonged course of maintenance ECT for two years, during which time he received 39 treatments. In 1958, ECT was discontinued and he was started on niacin, although promazine hydrochlorid (Sparine®) was used for sleep at night. He continued on niacin and has had no recurrence of psychosis. He is still in good remission on this regimen and has become a responsible citizen, actively participating in community affairs, with a variety of outside interests. He accepted with appreciation that he must continue to take niacin regularly if he is to remain mentally well.

Case No. 2

A 35-year-old married male with a diagnosis of schizophrenia-paranoid type began treatment with me in 1957. ECT was necessary because of his homicidal impulses toward his wife which accompanied his strong paranoid trend. He received 42 ECT treatments over a 15-month period. In 1958, maintenance ECT was discontinued and he was placed on niacin, subsequent to which there has been no recurrence of his former psychosis and he has remained in good remission since.

These results were impressive in those years because until that time electroshock treatments alone remained the only effective treatment for controlling these patients' dangerous impulses, and shock therapy seemed to offer the only hope for the preservation of life in many potentially worthwhile patients. Contrast these cases with the following two treated in more recent years as metabolic dysperceptives (Robie, 1971).

Case No. 3

This 54-year-old man had bizarre delusions of infidelity about his wife and she, in turn, found these persistent accusations totally abhorrent. His paranoia was perhaps potentiated by partial deafness and his accusations could be easily interpreted as a defense and projection because of his own partial impotence. Prior to the use of

the term metabolic dysperception, it would have been impossible to point out to the patient the paranoid nature of his altered thinking. However, I now found it easy to describe the erroneous nature of his thoughts to him by explaining metabolic dysperception in terms of its possible biochemical basis. I simply explained to him that because of faulty biochemistry that affected his brain function he was perceiving incorrectly, and that, although we do not know how, in detail, the abnormal biochemistry actually produces illusions, hallucinations, or delusions, niacin would help correct the abnormality. His acceptance of this explanation brought about an acceptance of the necessity for taking niacin and a remission of his paranoid symptoms. This then effected a reconciliation with his wife, which I ascribed to the combined effect of an adequate explanation (to the patient) and therapy by niacin alone.

Case No. 4

This 26-year-old unmarried woman, college graduate, complained that peoples' features were undergoing alterations. In addition, she perceived alterations in perceptions of her body parts expressed as hypochondriasis. In addition, she felt that her mind was all mixed up. She was unable to read any more, although she had previously been a researcher. She complained that because of mental confusion she was no longer able to make decisions. In addition, she was having visual hallucinations. This patient developed good insight into her illness from the first interview through my explanation of her biochemically induced dysperceptions. This case was early and had not yet gone on to delusion formation, and the explanation made sense to her. She found from experience that niacin favorably altered or dispelled these dysperceptions. The first thing that she noticed was that the distortion of people's features disappeared, and, as the dosage was increased, the visual hallucinations disappeared.

In the use of psychoanalytic interpretation, it is said that the correctness of an interpretation is affirmed by the patient's response to it. If that is the case, then certainly we have clinical verification that we are getting closer to the truth when we interpret the patient's symptoms to him as metabolically based dysperceptions. The content of the patients' symptoms in any of the four cases cited lent themselves readily to analytic interpretation and the dynamics were relatively obvious. (Thus, although the hungry man dreams of food, it is not the hunger that causes him to dream in the first place, but it is another metabolic process that is responsible for the dreaming state.) As an example, the last patient had the hallucination of the entire Rockette troop, all in the high kick-in-unison position. She makes a quick slash with a sword, amputating the leg of each one of the girls in a single act. She

admitted that she meant to defeminize them, and she readily recognized the narcissistic competitive element, as she is a very attractive young woman who has shapely legs. Her illness weakened her attractiveness as compared to the Rockettes and the hallucination demonstrated the hostility. Although she readily knew the meaning of the hallucination, what actually impressed her was my explanation that the reason she had the hallucination in the first place was her altered brain chemistry. The term demonstrates how we can dovetail a chemical or a metabolic therapy with a psychodynamic understanding of the patient's illness.

As a result of my experience in utilizing this term with many patients, I would like to urge that the term metabolic dysperception replace schizophrenia. This demonstrates a great step forward in improving our understanding of this complex and baffling disorder, which maybe is characterized in a considerable proportion of cases by an elevated score on the Hoffer-Osmond Diagnostic Test or may display delusions, hallucinations, dysperceptions, or apathy, and who usually respond favorably to large doses of niacin. This term is more accurate medically and more acceptable to patients and their families, and does not carry any "evil" label. The connotation does not bring about a feeling of nihilism which all too often accompanies the use of the word schizophrenia. When the correct term is used, parents do not feel the massive guilt that a diagnosis of schizophrenia causes because of the universal myth accompanying it that the parents are responsible for the illness. It is because of this massive feeling of guilt that denial is utilized by so many families and therapy is sought too late. My belief is that since 1967, when I was first introduced to this concept by Dr. Bella Kowalson, I have done more good for my patients with this illness than in all my previous 40 years of practice.

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27

Halfway Houses: Their Role in the Orthomolecular Treatment of Schizophrenia

H. B. PEARL

In the decade just ended, it was possible for the United States to design, build, launch, and direct a vehicle (and its passengers) to an orbiting satellite 250,000 miles away in space, and then to land it with fantastic mind-boggling accuracy, and return spacecraft and men safely to earth. We were able to watch all this on a television screen in the comfort and security of our own living rooms.

Surely the people of a nation capable of producing and providing the men, the program, and the billions of dollars required for such a superlative technological and organizational achievement must be capable of achieving the relatively minor goal of rooting out the cause and finding the cure for the last few remaining illnesses that continue to plague the family of man on earth.

Chief among these is mental illness, which is possibly the most neglected of all illnesses in terms of priorities and availability of funds to sponsor and support research into its causes and cure. In this connection it should be borne in mind that:

1. Mental illness is the nation's No. 1 health problem.
2. More than half of all the mentally ill are schizophrenic.

3. One of every ten children born this year—and every year—will sometime during his or her lifetime require psychiatric and/or mental hospital treatment.
4. Mental illness occurs at all ages, although schizophrenia is most likely to show up first in childhood, the adolescent years, or during early maturity.
5. Some 15 years after psychotropic drugs were first used in the United States on a massive scale for the treatment of mental illness, more than half (approximately 750,000) of all hospital beds in the United States continue to be occupied by mental patients, principally schizophrenics.
6. More people are being treated for mental illness than for polio, cancer, diabetes, tuberculosis, heart disease, and all other illnesses combined.

It is sad but nonetheless true that the schizophrenic frequently cannot—or should not—live at home with parents or other close relatives at some stage of his illness, or at least until his recovery or improvement has progressed to a point where more normal function, and his re-entry into the mainstream of living, has been assured.

It is my intent to focus attention on the fact that at this time in the world's wealthiest and possibly most scientifically advanced nation there exists such a shocking lack of (and lack of understanding of the need for) living facilities for post-hospital schizophrenics and for those who are either unable or unwilling to enter or to continue to live in hospitals (notwithstanding their obvious need for care or treatment) as to constitute a national disgrace.

It is also a sad fact that the families of many schizophrenics inevitably reach a point (after months or years of futile, ineffectual, back-breakingly expensive, traditional psychotherapy and/or private hospital treatment) where they are virtually stripped of funds and can no longer pursue any treatment that involves a major expense. Most hospital plans such as Blue Cross or other private insurance company programs cover either no part of, or only a very small part of, such costs, and coverage seldom includes psychiatrist's fees. Thus private hospitalization is barred to all but a small, affluent segment of the mentally ill. For the vast majority of patients the halfway house may be not only valuable but a virtual life-saver.

If the patient is admitted to a public institution, such as a state hospital, the cost will be low, or there will be no cost at all, but in the past the stay was usually long, and too often unrewarding. However, because of the substantial use of psychotropic drugs at most public (state) hospitals, there is now a good likelihood that the patient may be discharged at a reasonably early date, sedated, tranquilized, de-agitated, less depressed, less paranoid, less suicidal—but not well. For such a person, the halfway house may be invaluable.

For the schizophrenic patient whose principal reason for frequent visits to his doctor or staying on in a hospital is to receive supervision of the regular, daily

taking of prescribed medication, the expense of this procedure can be prohibitive, and for these persons the halfway house is of considerable value.

The doctor who feels that hypoglycemia may well be a substantial contributory factor in his patient's illness will specify a controlled, well-balanced antihypoglycemic, low-carbohydrate, high-protein diet as essential to a substantial reduction of symptoms or complete recovery. For all patients on such a diet, a halfway house at which it can be maintained may be extremely valuable.

Apart from the economic aspects of hospitalization, there is the question of the effect on the patient of any extended stay in a "total institution." He may enter the hospital seeking accurate diagnosis, proper treatment, and cure for his crippling ailment, but apart from the merits of the treatment made available to him, and apart from the question of whether, after a reasonable period in the hospital, he actually feels better or worse, the real problem that may confront him is his status and role as a mental hospital patient. Despite the universally accepted injunction that "the first rule of a hospital is that it must not do the patient any harm," there is growing evidence that this may not always be the case.

Goffman (1961) puts it plainly:

> Mental patients find themselves in a special bind. To get out of the hospital, or to ease their life within it, they must show acceptance of the place accorded to them and the place accorded to them is to support the occupational role of those who appear to force this bargain. This self-alienating moral servitude, which perhaps helps to account for some inmates becoming mentally confused, is achieved by invoking the great tradition of the expert serving relation, especially its medical variety. Mental patients can find themselves crushed by the weight of a service ideal that eases life for the rest of us.

Jones (1968) takes up where Goffman leaves off:

> To begin with, it is difficult to understand why one should talk about psychiatric hospitals at all. Goffman has drawn attention to many of the absurdities of the practice of psychiatry in large institutions. . . . Over the past ten years the hospital has ceased to be the only important place for the treatment of mental illness. The trend now is, wherever possible, to maintain the mentally sick person in the community rather than to incarcerate him in an institution.

In 1961, the Joint Commission on Mental Illness and Health declared:

> In the progress in the care of psychotics from moral towards scientific treatment these principles appear to have emerged:
>
> 1. The late nineteenth century medical dictum that schizophrenia is a hopeless, incurable disease requiring the person to be removed from human society for the rest of his life is baseless.
> 2. The widely held concept of "total insanity" likewise is without foundation.

3. The normal human being regards loss of liberty, forcible detention, removal from the community, and imprisonment as punishment for wrongdoing; the mentally ill, having grown up with the same viewpoints, are no exception.
4. The present state of scientific knowledge in the mental health profession does not permit as yet formulation of exact tests of "cure."

Earlier in the same report, the Joint Commission recommended, in connection with "aftercare, intermediate care and rehabilitation services," the following:

> The objective of modern treatment of persons with major mental illness is to enable the patient to maintain himself in the community in a normal manner. To do so, it is necessary (1) to save the patient from the debilitating effects of institutionalization as much as possible; (2) if the patient requires hospitalization, to return him to home and community life as soon as possible, and (3) thereafter to maintain him in the community as long as possible.

Raush and Raush (1968) summed up the trend toward providing a new transitional approach to the problems of the patient discharged from the hospital by relating the ever-increasing number of patients to the introduction and growing use of ataractic drugs:

> The major immediate circumstance precipitating the need for transitional facilities was the advent of drug therapies. With the introduction of ataractic drugs, such as chlorpromazine and reserpine, the number of patients in mental hospitals was reduced. In 1954, for the first time in over half a century, there was a drop in mental hospital population, even though admissions had increased. Further reductions have occurred each year since, always in spite of increased admissions. Few advocates of the drugs claimed that they "cured" and indeed it became apparent that if many of those released were to continue their stay out of the hospital, they had to be maintained on drugs. Still, the discovery of drugs which could, at least, inhibit the more disrupting aspects of psychopathology made possible the release of large numbers of mental patients, many of whom had been incarcerated for long periods of time. Since the tranquilizing drugs reduced the bizarre symptoms which people in an ordinary community found intolerable, it became feasible for the ex-mental patient to return to the community.

In any case, an extended stay at a psychiatric hospital is most likely contraindicated, on situational as well as economic grounds, for all those who are not (1) suicidal or homicidal; (2) agitated or paranoid to the point of potential violence or objectionable overt antisocial actions; (3) catatonic to the extent of complete withdrawal from environment; (4) fantasizing or so detached from reality as to be periodically unreachable through normal communication media; or (5) mentally retarded or unable to dress, feed, and care for themselves.

For all others, the halfway house may offer noninstitutional care, at a low to moderate cost, in a setting completely free of locked doors, dehumanizing living

conditions, loss of personal liberties, and all the other less favorable aspects of hospital life and treatment.

THE ORIGINS, CONCEPTS, AND DEFINITIONS OF THE HALFWAY HOUSE

Since 1877, the year in which the first halfway house in the United States opened in Boston, the movement has slowly grown and expanded. In the first 56 years only 3 halfway houses were established in the United States but by the end of 1970 there were approximately five hundred.

The three pioneer houses, Rutland Corner House (Boston, Massachusetts, 1877), Gould Farm (Monterey, Massachusetts, 1913), and Spring Lake Ranch (Rutland, Vermont, 1932), were created out of a knowledge, common to all three founders, that there was an urgent need for a transitional living facility for those who, as a result of mental illness or an overwhelming emotional disturbance, needed a place where, protected from the stresses and pressures of normal competitive daily living and working, they could regain their physical health, mental equilibrium, and spiritual strength.

The recovering schizophrenic often has to reshape his life style and set new limits and new goals for himself, but it is also true that the schizophrenic frequently cannot—or should not—live alone. He may have a deep yearning, frequently unspoken, for social contacts, though he may seemingly make little or no effort to reach out to others. He may not be able to express his need for friendship, companionship, or even human contact, yet these needs are no less real and necessary for him than they are for most of us. He frequently cannot show affection or love for others, nor, often, will he expect others to love him, so low is he in self-esteem, so lacking in a sense of self-worth. The very people who want to help him, encourage him, love him (his parents, husband, wife, siblings, others) seemingly are the least able to fill this role; perhaps because of emotional involvement, identification with his early "failures," preoccupation with the "square" world of normal living, or an inability, despite empathy, to pierce the veil and glimpse his distorted world.

Whatever the reasons, the schizophrenic may ambivalently and alternately avoid or reject the embrace of the family milieu, then suddenly veer in the direction of accepting, even demanding, familial attention and love in inordinate quantities. Or, though welcomed by him, the family's efforts may be contraindicated because the parental or home environment may be too accepting, too forgiving and understanding, too unstructured and undemanding; all resulting in a tendency for the chronically ill or recovering schizophrenic to backslide, to revert to old and perversely attractive (but disabling) habit patterns, to feel little or no need for even a minimum of effort at self-discipline, and possibly even resulting in an unconscious,

TABLE 27-1.
The Halfway House in Relation to Other Approaches—Comparative Study

Care or treatment modality	Availability of desired medication	Supervision of medication	Diet control	Structured work program	Individual psycho-therapy	Vocational rehabilitation
Patient–psychiatrist (1 to 1)	maybe	no	no	no	yes	no
Group treatment	no	no	no	no	yes	no
Private or public out-patient clinic or community health center	maybe	no	no	no	yes	maybe
Private residential psychiatric hospital	maybe	yes	no	no	yes	no
Private day hospital	maybe	yes	no	no	yes	no
Public residential psychiatric hospital	no	yes	no	no	maybe	no
Living alone or with family	yes	no	maybe	no	no	maybe
Halfway house	yes	yes	yes	yes	yes	yes

but no less disadvantageous effort to defeat the well-meant intentions of family members to effect the necessary structure, organization, and rehabilitation.

The orthomolecularly oriented halfway house, then, may well constitute the means, provide the facilities, and offer the opportunity for the recovering schizophrenic to throw off (or bring under control) his illness, re-evaluate his status, re-educate and retrain for a new role, and prepare to re-engage in a life of healthy involvement.

Can the schizophrenic be at ease and deal rationally with a situation where he is "a stranger in a strange land"? Can he find meaning or happiness in a noninstitutional setting without the support of family or friends? Possibly the more pertinent question is whether he can move from the overprotected, artificial, impersonal world of the psychiatric hospital to the "real world" of present-day, tough, competitive, stressful living without first going through a "decompression chamber" to effect the necessary and vital readjustment.

Toffler (1970) says that one aspect of what he describes as "future shock" is "the shattering stress and disorientation that we induce in individuals by subjecting them to too much change in too short a time." He goes on to quote Dr. Herbert Gerjuoy (1970) and his "situational grouping concept":

> A man required to adapt to a new life situation loses some of his bases for self-esteem. He begins to doubt his own abilities. If we bring him together with others who are moving through the same experience—people he can identify with and respect—we strengthen him. The members of the group come to share, even if briefly, some sense

Noninstitutional milieu	Opportunity for normal living	Opportunity for work	Freedom from stigma	No locked doors	Educational opportunity	Moderate cost
yes	yes	yes	yes	yes	no	no
yes	yes	yes	yes	yes	no	yes
maybe	yes	yes	yes	yes	no	yes
no	no	no	no	no	maybe	no
no	no	no	no	yes	maybe	maybe
no	no	no	no	no	no	yes
yes	yes	yes	yes	yes	yes	yes
yes	yes	yes	yes	yes	yes	yes

> of identity. They see their problems more objectively. They trade useful ideas and insights. Most important, they suggest alternatives for one another. . . . Membership in the group would, of course, be temporary—just long enough to help the person with the transitional difficulties.

Thus, the halfway house can well be the "decompression chamber" that helps to ease the individual back into contact and communication with the healthy world of productive activity, zestful living, warm and meaningful human contacts and, in general, a love of life.

There are almost as many definitions of such houses as there are variations in their size, function, and objectives. One of the early writers on the subject, Reik (1953), had this to say:

> Institutional psychiatrists have long been familiar with a group of patients whose progress in the mental hospital is at a standstill and whose continued hospitalization fosters dependency, loss of initiative and neglect of potentialities for healthy living. Patients in this group present paradoxical features. They are able to maintain equilibrium in the hospital but can not do so at home. They recognize their need to escape from the stresses of the outside world, but in the hospital they avoid and resist attempts to help them resolve basic conflicts. They take flight from home to hospital and in the hospital they occupy a position midway between sickness and health. Treated as invalids, they profess health; assumed to be well, they soon demonstrate inability to withstand the stresses of the outside world. . . . It seems logical to think that an environment intermediate between the hospital and outside world—a "halfway house"—would make an important contribution to the rehabilitation of properly

> selected patients. . . . Having moved from the restricted and dependent existence of the mental hospital to the more independent, but still relatively simple . . . life at a "halfway house," he would logically be better prepared to take his place in his own community again.

Landy and Greenblatt (1965) reviewed the literature and then formulated a concept and definition of the halfway house:

> The combined powers of modern psychotherapy, chemotherapy, and therapeutic use of the milieu have considerably brightened the prospects for many hospitalized victims of emotional disorder. The process of enabling the patient to mobilize resources and to move from hospital to community has been enhanced and shortened in recent years. But when the patient is ready to leave the hospital, what then? Is there a family to return to, a family willing and emotionally able to accept the patient as a functioning member? Is he able to withstand the pressures even in an accepting family? Or must he find the strength to operate alone and independently of family? As he makes ready to re-enter the outside world, what agencies exist for cushioning some of the trauma of social reintegration? He is moving from one subcultural world to another; how may he cope with the effects of this potential "culture shock"?
>
> For a patient who has no family, or whose family presents excessive or insurmountable hurdles, one attempt to bridge the cultural gap involved in rehabilitation has been that of the halfway house. The halfway house, a temporary residence away from the hospital, run by the hospital or by lay or professional organizations, attempts to offer the patient an accepting and understanding transitional environment immediately following hospitalization and before resumption of normal independent living.

Rothwell and Doniger (1966) refer to an article about halfway houses in the United States which appeared in 1958. Its author, Brete Huseth, defined a halfway house simply as

> a residential institution, designed to meet the needs of the ex-mental patient during the difficult transition from the sheltered environment of the mental hospital to the more rigorous life of the community.

My own thinking might add one more dimension to these concepts. I feel that to whatever extent there exists an "umbilical cord" between hospital and halfway house, it should be cut. The occupants of a halfway house are "residents," or "members," or "clients," or "guests," but they are not patients. They should receive care but not treatment. To the extent that their doctors have prescribed megavitamins and other medications, the halfway house staff must be absolutely certain that such medication is being faithfully taken. To the extent that an antihypoglycemic controlled diet may be a factor in reducing or eliminating certain aspects of schizophrenic behavior (or certain symptoms of schizophrenia), the staff must be certain that such a diet is rigidly adhered to. Further, an atmosphere of health should prevail in the halfway house, unlike the hospital, where the atmosphere of illness prevails. To the greatest extent possible, the work of running and

caring for and maintaining the halfway house should be done by the residents, as compared to the hospital, where frequently little or no effort by patients is either encouraged or permitted.

Above all, the halfway house is a transitional living facility where, from the day of entrance, a resident should be aware of and preparing for the day of exit. The halfway house is not a way of life (as many hospitals become), but an entry way to a life of involvement, conceptual clarity, and, hopefully, achievement of the full potential of the individual.

THE HALFWAY HOUSE AS AN ADJUNCT TO THE HOSPITAL

Quite apart from the human considerations, there are a number of practical, economic arguments in favor of the halfway house.

1. For the lack of suitable outside living and rehabilitation facilities, many state hospitals continue to retain as patients (for months and even years) large numbers of those who could otherwise be discharged. The cost to the various states may range anywhere from $5,000 to more than $10,000 annually per patient. A suitable halfway house can provide the necessary care and facilities for approximately half these amounts, resulting in a net saving to the community as a whole of from $2,500,000 to $5,000,000 or more per 1,000 persons so housed. As a practical matter, if self-supporting halfway house programs were to be funded through gifts from private foundations, plus moderate fees from residents able to afford such fees, then the state institutions would generate per capita savings equal to the former entire cost of the patient's hospital care.
2. If the state institutions could substantially reduce the number of patients cared for, they could reduce, or possibly eliminate their massive capital construction programs for new and more facilities, along with a major reduction in their substantial maintenance and repair budgets.
3. There could be substantial reduction of state hospital personnel, particularly in the categories of qualified doctors and nurses.
4. The halfway house, through the employment of a staff consisting largely, if not wholly, of paraprofessionals, would reduce the demands on the time of the relatively limited number of psychiatrists, thus freeing more of them for other essential tasks.
5. Through halfway house vocational rehabilitation programs, substantial numbers of individuals who would otherwise be nonproductive public charges

could once again be gainfully employed, self-supporting, and contributing to the nation's economic welfare.

THE ORTHOMOLECULAR HALFWAY HOUSE

Until the establishment of The Gateposts in Monterey, Massachusetts, in the spring of 1970, there was no halfway house for schizophrenics in the United States that had, as its cardinal principles of operation, the supervised consistent giving of megavitamins together with other prescribed medication, the maintenance of all residents on a controlled antihypoglycemic diet, and a structured work and living program.

When halfway house residents cover a wide range in age, and include those who have been chronically ill, either in or out of hospitals for varying and, in many cases, long periods of time, hope for "cures" cannot be high, and serious consideration must be given to a type of custodial or long-term care. If the house is set up to deal with youthful schizophrenics, it most likely will have to be able to deal with drug involvement as well. In addition, it has become apparent that such houses must also be prepared to deal with alcohol involvement on an ever-increasing basis.

The type of work and occupational programs that can be structured for the young residents may not be suitable or even possible for older residents and therefore much care must be given not only to the question of expectancy, but also to capability.

Aside from the supervision of the taking of medication and the dietary control aspects of halfway-house operation, one of the principal functions that such a house can perform is in the area of structured work, play, and environmental programs. A good deal of behavioral retraining is required, particularly with adolescent schizophrenics, because if the onslaught of the illness came during childhood or early adolescence, the illness may have interfered with or prevented the victim's acquisition of the type of learning and the basic patterns of normal living that would form the experiential background to which he could return upon being cured.

In this connection, Philpott (1970, written commun.) recently observed:

> I was a behaviorist before I began to practice orthomolecular psychiatry. I see the need for a combination of these two. It is my belief that responses become learned no matter how evoked, even though they may be chemically evoked originally. This is not 100 percent true but is true to a considerable degree. Therefore, you cannot depend entirely on chemistry to change responses but need to add sometimes the practiced methods for behavioral change. I believe that life circumstances, that is, the re-experiencing of success where before there was failure, do cause a great deal of therapeutic behavioral change once the organism is in proper energy balance. However, some responses are so severe and have become so strongly learned that life circumstances alone cannot be depended upon for the retraining, and specific behavioral practices can be used which will change these responses.

The one term that consistently appears in all definitions and discussions of halfway houses is "transitional" and this, of course, refers in part to the movement of hospital "patient" to halfway house "resident" on his way to becoming a community "member." One wonders whether this transitional period in the life of the recovering schizophrenic is, in itself, a traumatic experience. Certainly, the milieu that the halfway house constitutes, a substantial ingredient of which is the philosophy and the personality of the director and his staff, must play an important part —if not a major role in the transition being a beneficial one.

The Director should be a mature, understanding, empathetic, warm human being—firm of purpose and able to deal with the problems of resident and staff in a rational, consistent manner. The assisting staff should consist of one or more persons who, by education, training, and expressed desire to work with and be helpful to troubled people, have evidenced the inclination and ability to complement the Director's function. There is no need for the staff members to attempt consciously to influence or direct or shape the actions and attitudes of the residents to conform to a standardized or institutionalized concept of daily living. It is sufficient that they set a consistent example of reasonable and decent behavior and that they establish fair and workable rules and standards for individual as well as group conduct and performance. It is essential that the staff have a high expectation for the achievement potential of the residents, for it is only through goal-oriented programs, geared to high expectancy, that residents of the house will sense that there exists for each of them a potential for accomplishment that many may have felt was forever barred to them because of their illness.

Thus, it is apparent that the halfway house director and staff should be orderly, consistent, structured people who, by their everyday acts and their life-style, help to convey to the residents of the house a responsible and dependable approach in dealing with the needs and problems generated within the house.

Often the impact of the illness may cause conceptual changes so profound and so deep-seated that the victim's life style, his fundamental attitudes toward living in the world and with the people around him, may undergo semi-permanent alteration. It has been aptly said that there are no two schizophrenics exactly alike, to which a reasonable corollary might be that there is no uniform, standard way of dealing with and accommodating to the needs of the pre- or post-hospital schizophrenic.

Our experience has been that the most appropriate and manageable size of a half-way house resident group is in the range of 14 to 18 people, supervised by a resident staff of 3 or 4.

Others feel similarly, as evidenced by Rothwell and Doniger (1966):

> Experience with a halfway house group which has varied in size from two or three to twenty-two or twenty-three people has given the impression that an ideal number would be about twelve or fifteen people. A smaller group can be dominated by one

very depressed, very sick-behaving individual or by quarrels and dissensions among a few people. The larger group gives more flexibility to form and dissolve friendships and it can absorb troubles created by one member. If and when the group grows to about twenty, however, some disadvantages seem to emerge.

In a halfway house, all of the work of the house that can be done by the residents should be done by them. This includes all tasks, from making beds, sweeping floors, cleaning bathrooms, and so on, through repair and maintenance chores, including carpentry, automobile repair, and lawn and garden care. Additionally, residents should be encouraged to become proficient in the arts and crafts needed for personal and home use such as weaving, sewing, painting, cabinet work, rug hooking, furniture refinishing, photography, and so on.

The key essential is that the work of the halfway house be divided more or less evenly among its occupants and that each recognize his obligation to undertake his appointed tasks and be aware of the interdependency and interrelationship of his effort and the work of all of the other members of the household. Thus, any defection on the part of any one resident will throw an additional burden onto the others, with the result that there will inevitably be peer group pressure brought to bear upon the delinquent for his proper assumption of his portion of household tasks.

Because of the profound alterations that can occur in perception, mood, thinking, and behavior, it must be recognized that a schizophrenic is frequently unable to maintain a consistent interest in and willingness to work for a personal or a house-desired goal and, particularly in the early days of a resident's stay at the house, a reasonable tolerance for an illness-created apathy should be expressed by staff and older residents alike. Through empathy and patience, the other residents of the house can help to raise the interest and output levels of those who are at first unable to maintain a fair share of the work burden so that in time each will be able to do so.

The house should be a healthy one, and a prime requisite is that all the residents maintain a high level of personal cleanliness in a clean house. The bathrooms and the kitchen must be clean, and all of the house, both public and private rooms, should be well maintained. Token or superficial cleanliness is not satisfactory and should not be encouraged.

The house should be a happy one and there should be as few rules, regulations, and prohibitions as possible consistent with the maintenance of sanitary standards, adherence to fire, and other community required regulations, and application of such house standards as may be required for safety and health.

Music, recreational activities, the presence of pets, and any other kind of activity and facility that one would expect to find in a happy, healthy, loving, accepting family, should be encouraged and be a part of the living style.

If the resident population of the house is essentially young and if there are communities nearby offering the proper facilities, every effort should be made by the staff to encourage the residents to reinvolve themselves in the formal education process. Staff members with the proper academic credentials can tutor those not yet ready for outside instruction. Senior residents who may have completed all or even part of their higher education can teach younger residents. In fact, any resident who, regardless of age, possesses special knowledge, training, or skill, should be encouraged to teach others, for the benefit of both teacher and pupil.

A DESCRIPTION OF A HALFWAY HOUSE

The Gateposts, Monterey, Massachusetts

"A Country Guest House for rest—recovery—rehabilitation. A refuge, a peaceful haven, a jumping-off place to a new life; a place for learning, living, loving, contributing—and assuming life's responsibilities. A supportive transitional year-round living facility, coed, over-sixteen, non-sectarian, non-profit, and interracial. A warm, accepting, understanding (though structured and purposeful) home-away-from-home, yet free of the emotional stresses of family interaction. We are less concerned with the past than with the proper management of the present and a workable plan for the future." (From The Gateposts Brochure.)

Location

The Gateposts is on a state highway, approximately one mile from the center of a small New England village (population about 700) high in the Berkshire Hills (elevation 1,400 ft), midway between Boston and New York (140 miles to either). The house is set back from the road, on an 8-acre tract with ample room for gardening and sports. A state-owned lake nearby provides water recreation, and there are two popular ski areas within five miles. It is not far from Gould Farm, one of the oldest halfway houses in the nation.

Appearance

The Gateposts is a spacious 12-bedroom New England colonial central-hall home with a total of 19 rooms and $4\frac{1}{2}$ baths on three floors (plus basement). Heating is by a large oil-fired steam boiler. The main floor has four large public rooms, kitchen,

serving area, and office. There are seven bedrooms on the second floor and five bedrooms on the third floor. The executive director's 5-room cottage is about 100 feet away. A private roadway leads to the lakefront, about 1,500 feet from the main house. Ample water is supplied by an artesian well located on the property, and waste products are distributed scientifically over a large area by a septic tank system. The climate is excellent, cool and sunny in summer and briskly invigorating in winter.

The relative isolation of the house and area is one of the factors that enable the staff to maintain control over medication, diet, and possible drug involvement.

Residents

In 1971 The Gateposts had six female residents, ranging in age from 18 to 23, and ten male residents—nine between 18 and 25, and one who was 34.

All residents had been referred to The Gateposts by their psychiatrists, each of whom supplied necessary medical and personal information to The Gateposts Screening Committee, together with a positive statement that the patient was in a satisfactory condition to take up residence in a halfway house.

Many of the residents had had difficulty with formal education or had completely dropped out of high school or college as a result of their illness although a few had completed their courses.

Most of them had spent varying periods in psychiatric hospitals and many had had ECT treatments and psychotropic medication plus psychotherapy. Some had families that were devoted and secure but several came from broken homes. Many had been involved to some extent with hallucinogens and psychedelic drugs. Two had previously attempted suicide, and on entrance all were anxious, fearful, and apprehensive.

Staff

In 1971 the staff consisted of a house director, his wife, and two male assistants.

The director's age was 36, a university graduate with a B.A. degree (a philosophy major) and several recent years of experience as a psychiatric aide and staff member at a New York state mental hospital.

One male assistant was 22-years old, a recent university graduate with little professional experience in working with people with mental problems, but possessed of a strong desire to become deeply involved in this type of work.

The other staff member was 23-years old, a university graduate, with several

years of graduate work in architecture. In addition, he had skills in a number of arts and crafts and had done some work in the mental health field.

Staff Duties

The two assistants live in the main house, and the director and his family live in the adjacent executive director's cottage.

The staff is completely responsible for the residents, the proper and orderly running of the house, its cleaning, care, and maintenance, and food preparation. They eat, work, and play with the residents and share their lives as much as possible, yet always remain conscious that they are fully responsible for each resident's safety and well-being, and for his satisfactory achievement of the objectives that formed the basis for his becoming a resident.

The staff are the first to rise and the last to sleep, and are at all times alert to the fact that schizophrenia is a disabling illness, frequently causing perceptual and conceptual distortions that may prevent the victim from functioning or even trying to function normally.

How the House Functions

Residents are generally paired or grouped three to a room, and are expected to care for their rooms properly, including bed-making, vacuuming, and dusting.

Residents may come and go freely, but are expected to advise the staff if they plan to leave the grounds. They are expected to participate cooperatively in household cleaning, maintenance, and repair, and in food preparation, serving, and clean-up.

Residents go with the staff into town to shop for food, and supplies, and to run necessary personal and house errands. They may be asked to assist the staff in the management of the house and supervision of other residents.

All occupants of the house are expected to be in bed by a reasonable hour (11:00 P.M.), to be up by 7:30 A.M., and to appear dressed and ready for breakfast by 8:00 A.M. Residents are expected to take their prescribed megavitamins and medication every day *without fail.* A staff member is responsible for seeing that it is done, but on occasion one or another of the residents has assumed this responsibility. Recreation is varied and may include talk, music, drawing, painting, photography, ping pong, touch football, television viewing, rap sessions, dancing, group outings, movies—and, in season, "Tanglewood" concerts, skiing, tennis, summer theatre, and much more.

Meals are informal. Self-service is usual at breakfast and lunch. Dinner is served

family style. Cooking is done by residents and staff on a rotation basis, as is cleaning up and putting away after meals.

Night-time activities may run the gamut from attending evening classes at a nearby junior college to reading, listening to music, a trip to a movie, or whatever is desired. Planning activity is a mutual effort of residents and staff.

From all this it is apparent that The Gateposts provides care—but not treatment —for its residents. They are treated as family members would be in any large, loving, accepting, empathetic family group. There is a father figure, but a minimum of coercion or restraint: freedom, but not foolish permissiveness; structure, but not oppressive regimentation; love and care, but not mawkish sentimentality. A family. A home. A way-of-life—*transitionally*.

Where Residents are from and Length of Stay

The residents are from many parts of the country, of various religions, and with differing social, educational, and economic backgrounds. The Gateposts has no bias whatsoever as to color or national origin, but thus far it has had only white United States citizens as applicants. It would welcome others.

As to length of stay, it is too early in the life of The Gateposts to say, but it would appear from the records that an average stay of approximately 4 to 6 months may be typical. Residents are not required to state a departure date on entering (the Gateposts is not a hotel or a boarding house): one left in 10 days, one stayed more than 9 months. There is no specific time limit and there is no "House Rule" as to when a resident should leave. Most departures have been the result of conferences between the resident, his doctor and parents, and the house director. In at least three cases, however, residents deliberately violated fundamental house rules in order to precipitate discharge. At least three other residents departed abruptly (hitch-hiking to the nearest large community) without notice.

Costs of Care and Admissions Criteria

Rates are scaled in accordance with ability to pay, based on two guiding principles:

1. No one shall be refused entrance because of inability to pay.
2. Those-That-Have shall share with Those-That-Have Not.

The rate for those who are financially able to pay was $500 per month in 1971. For all others partial or full scholarships are available to qualified applicants. A screening committee, headed by professional social workers, passes on all applications and determines eligibility and order of entrance.

As has been indicated, neither sex, race, religion, nor social or economic background are criteria for admission. The determining factors are:

1. The psychiatrist's determination and recommendation that his patient would benefit by a stay at The Gateposts.
2. The applicant's visit to The Gateposts and an interview by the house director.
3. The decision by the house director and the chairman of the screening committee that the applicant would fit in well and would benefit by a stay at the house.
4. Conference between family and screening committee as to financial responsibility, waiver of liability, and other factors.
5. Availability of space.

Goals and Direction

It is the intent and purpose of The Gateposts to guide each resident through a learning and rehabilitation process with the ultimate goal of making his or her life a less painful, more fruitful, and more enjoyable experience. The basic concepts that motivated the founders of The Gateposts may best be described by quoting from the charter of the First Gateposts Corporation:

> To own, lease or otherwise occupy premises suitable for the purpose of operating and to operate, a residence or residences providing transitional living facilities and care but not treatment, for those who, because of emotional or other problems, are not willing or able to live alone or with family or friends. To aid such residents in resolving their problems, in making the necessary adjustments and adaptations required for normal family and community living; and in learning to provide for their own needs.
>
> To assist such residents in continuing their formal education; or in finding or providing facilities for vocational training or rehabilitation; or in finding employment.
>
> To provide such residents with an understanding of the essentiality of healthful living habits, doctor prescribed dietary supplements and a balanced nutritional approach in their dealing with and resolving their problems. To do all these things

necessary to provide help to those, regardless of race, color, religion, national origin, or income, who seek help of a type this corporation is equipped and able to provide.

Thus, The Gateposts is a manifestation of a determined effort on the part of an interested, informed, involved group of parents (working in close harmony with equally interested professionals), to prove that a schizophrenic can be helped back to a meaningful healthy life by a combination of orthomolecular psychiatry and a halfway house organized and run along orthomolecular lines.

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With a deep bow to Dr. Abram Hoffer and Dr. Humphry Osmond, a grateful nod to Dr. Philip May, and a puzzled glance in the direction of Dr. Ronald D. Laing.

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SECTION IV

A PRACTICAL CLINICAL MODEL

28

The Development of an Integrated Community System for the Effective Treatment of Schizophrenia

DAVID HAWKINS

At a time when health care—its quality and availability—is at long last being recognized as one of the nation's top priorities, Dr. Hawkins' report should have the attention of responsible medical and public officials.

There are too many closed doors, too many closed minds in our traditional approach to health care. We need the courage and the sense to strike out in new directions where the old ways have failed.

Dr. Hawkins describes a treatment system designed to enable millions of Americans afflicted with schizophrenia, and their families, to live more satisfying and productive lives without bankrupting themselves in the process. By integrating community resources for well-coordinated delivery of health services, his system points the way to more efficient use of scarce medical manpower. This can result in providing more effective treatment to many times over those who now receive it.

From personal experience with these and related problems, I can attest to the effectiveness of a number of the approaches Dr. Hawkins recommends. The overall concept, while startling in its simplicity and directness, makes sense to me.

Accordingly, I believe that mental health program administrators at every level owe it to their patients and their communities to investigate Dr. Hawkins' system and give it

proper trial. Considering the staggering emotional and economic burdens of schizophrenia, there is too much at stake to justify any other course.

Harold E. Hughes
UNITED STATES SENATOR

PROBLEMS IN HEALTH CARE DELIVERY SYSTEMS STEMMING FROM MIXED MODELS IN PSYCHIATRY

In recent years a great deal of attention has been paid to community and social psychiatry and the development of effective health care delivery systems. Because of the enormous cost of medical care in general, and psychiatric care in particular, the planning of such delivery systems has involved all levels of government, the insurance companies, labor, management, medical societies, and various regional planning boards.

The public has become more aware of the issues relating to health care, and many of these issues are being increasingly politicized. In most of this planning, psychiatry has trailed along behind so that psychiatric benefits are usually partial, limited, and late. Part of the reason for the limitations of psychiatric coverage or benefits in most health care plans is the nebulous quality of psychiatric disorders in the eyes of the providers of health care benefits, who end up paying the bills. The vague and unclear definition of major psychiatric disorders and the departure from the medical model, plus the indefiniteness of psychotherapy as a treatment modality, delays the placing of psychiatric illnesses on a par with illnesses whose medical nature is unquestioned.

This problem is most obvious in what Dr. Leo Hollister recently identified as the two major problems in psychiatry—alcoholism and schizophrenia (Hollister, 1971). Acceptance of these as treatable diseases has been greatly undermined and forestalled by emphasis on the motivational or psychodynamic aspects of both illnesses. Depiction of alcoholism as "just a symptom" and schizophrenia as "an alternate life-style," for instance, has brought little practical benefit to society or to the sufferers of these progressive illnesses.

The confusion arising from the mixing of the moral and other models with the medical model, well described by Osmond (1968, 1969, 1970, and oral commun.) and by Siegler and Osmond (1966, 1968, 1969), has serious consequences. In their series of papers Siegler and Osmond describe eight different models of psychiatric illness. These are the medical, moral, impaired, social, psychoanalytical, conspiratorial, family interaction, and psychedelic. They then explore the consequences of following each of these models, the confusion that ensues when these models are mixed, and the deleterious results of failing to follow the medical model.

Our society is historically unwilling to take on a major problem when there is an implication of moral culpability on the part of the sufferer. The public is unwilling to pay the bill when the true medical nature of an illness is still in question. It would seem that some clarification of the medical nature of both alcoholism and schizophrenia will have to be presented to the public by the psychiatric profession before truly successful and definitive health care delivery systems can be developed that are satisfactory to both the patient and the public.

In an effort to overcome some of these obstacles, patients, families, concerned professionals, and laymen have had to develop complex, interrelated, specialized treatment systems. In both alcoholism and schizophrenia the evolution of these systems has been based on the acceptance of both illnesses as primarily a medical problem for which outside help is necessary and essential. Oddly, it is only with the complete acceptance of the medical model that a truly humanistic approach becomes possible. Utilization of other models results in either subtle or blatant rejection. Expression of this moralistic rejection may take the form of refusal of general hospitals to accept patients with either disorder, refusal of insurance companies to provide insurance coverage for these illnesses, and a whole raft of consequences ensuing from the social stigma attached to them.

VARIETIES OF CURRENT PSYCHIATRIC TREATMENT SYSTEMS

Generalized Non-Specific Systems

A brief review of the major existing generalized or all-purpose psychiatric health care delivery systems may provide a helpful background, and place in context a later, more detailed description of a specialized treatment system for schizophrenia based on the medical model. Only a few comments will be made about the obvious advantages and disadvantages of each system, as these must, of necessity, be limited to only those which are pertinent to the subsequent description of a treatment system specifically designed for schizophrenia. It is obvious that an exhaustive analysis of the advantages and disadvantages of each system would, in itself, constitute a separate volume.

PRIVATE PRACTICE—PRIVATE HOSPITAL

Although the family doctor may treat some forms of mental illness, those patients who do not respond to reassurance and tranquilizers are usually referred to the private psychiatrist for treatment. Should the patient require hospitalization, the treating psychiatrist refers him to a private hospital where he is treated either by his

psychiatrist or by the house staff. The patient continues treatment with his private psychiatrist following discharge from the hospital. This has been the traditional pattern for the middle-class and upper-class patient. The advantages of this system are flexibility, convenience, humaneness, and great personal interest in the individual patients, who are the recipients of almost all of the treating psychiatrist's professional time and energy.

The disadvantages of this system are the obvious economic ones plus those that may ensue from what may tend to become a prolonged one-to-one treatment situation. The interest of the treating psychiatrist often becomes progressively focused on the details of the patient's history as an individual rather than on his specific disease. This is exemplified by the patient who stated "I really liked Dr. X. very much. He got to know everything about me. I only wish he had known more about schizophrenia."

Individual practitioners may become relatively isolated from each other and inadvertently become unaware that colleagues utilizing different approaches are getting much better results. This may even become a self-protective device in that the individual psychiatrist sometimes refuses to believe that colleagues are getting more satisfactory results. This is especially true in treating both alcoholism and schizophrenia. There are, for instance, many industrial medicine programs that achieve 80 percent recovery rates from alcoholism, and this same rate is achieved by a number of psychiatrists who specialize in alcoholism. Both of these groups use Alcoholics Anonymous as the mainstay of their treatment. These specialists, however, frequently run into colleagues who consistently refuse to accept their findings as valid. Alcoholic and schizophrenic patients have little way of knowing where to obtain a psychiatrist who has a specific interest in their illness. This, therefore, presents a problem for the public, in that selection of the "right doctor" becomes a considerable problem.

STATE AND VETERANS HOSPITALS SYSTEMS

The patient may enter a state hospital either directly or by involvement with some community agency. He may be referred by the family doctor or by the private psychiatrist if he cannot afford private hospitalization. This is also the treatment system which the former private patient enters when funds are depleted by the chronicity of the illness. The patient is treated in a large state hospital and referred afterwards to an after-care clinic for follow-up on a periodic basis. Should rehospitalization become necessary, this is effected by the after-care clinic, whose duty has primarily been with the schizophrenic, to see the patient periodically for adjustment of phenothiazine drugs. Family and social problems are usually handled by a social worker who may or may not utilize the services of other agencies in the community, such as an agency for vocational rehabilitation.

The veterans hospital system operates in basically the same way as the state hospital—after-care clinic system except that eligibility is limited to service-connected mental illness. Aside from the obvious limitations of any large bureaucratic system in which a great deal of professional energy is drained off into bureaucratic procedures, it is even more isolated from the community than the state hospital system.

The obvious advantage of these systems is the implied bureaucratic and financial efficiency in handling large numbers of mentally ill patients. Despite the many criticisms of the system, the fact remains that society does provide a place to go and to receive treatment, no matter how ill, destitute, or disadvantaged the patient may be. Also, despite the obvious institutionalization, possible overcrowding, inevitable regimentation, and the like, within each institution there does prevail a certain human warmth and concern which may exceed that which exists in a given patient's current living situation.

Many of the disadvantages inherent in such a system have received a great deal of attention. One that may be mentioned is the lack of individuality from one hospital to another, so that few achieve distinction in any specific area of interest or expertise. Another is the almost total isolation of the system from the rest of the community. It is a common occurrence, for instance, for a patient to have had extensive diagnostic studies, and in general, an enormously expensive and careful history and work-up by a conscientious private psychiatrist who is not even contacted when the patient enters the hospital, nor are the extensive data that he has available on the patient requested. The continuity of care is, therefore, lost and frequently permanently interrupted.

CLOSED PANEL AND UNION BASED TREATMENT SYSTEMS

These systems are predominantly union-financed and consist of panels of psychiatrists, clinics, and hospitals with referrals coming primarily from the occupational area. Often, the referring physician is the company doctor or another family physician on the union's treatment panel. An alternate plan is to provide union members with sufficient insurance so that they may seek out help in the private area. These systems tend to upgrade patient care in a progressive manner so that there is some pressure on participating psychiatrists to reach an early diagnosis, institute effective treatment, and utilize newer treatment techniques.

Union leaders and management tend to be realistic and practical in their expectations and are becoming increasingly sophisticated and vocal. Consumer special-interest groups and their pragmatic pressures on professionals can have a stimulating effect. The first union leader to achieve psychiatric coverage and mental health care for union members was Joseph DeSilva, Retail Clerks Union, Local 770, AFL–CIO in Los Angeles. The plan led to formation of the Mental Health

Development Center, considered initially to be a model clinic and the leading union plan when it was established in 1960. The Center required six million dollars in operating funds over the next 10 years to provide services for 25,000 member families.

Union and management, however, became progressively disillusioned with both the results and the costs of the Center's treatment methods, which consisted primarily of psychotherapy. Labor leaders began to apply pressure for newer treatment methods, including research in biochemical and orthomolecular approaches to the more serious disorders, and this brought on a major confrontation with the professional staff, which was accused of providing "1890 treatment at 1970 charges" (DeSilva, 1970). As a consequence, the union then sponsored a major symposium on "Biochemical Therapy in Psychiatry," and the closed panel system was dissolved. The same union is now very active in mental health education for both its members and the public. DeSilva has subsequently been appointed to the Mental Health Board of the California Department of Mental Hygiene.

Similar developments are occurring elsewhere in the country, so that in the New York area, for instance, a resolution is being introduced on the floor at the AFL–CIO convention calling for an investigation into the availability of newer treatment methods for union members, including the orthomolecular approach.

THE COMMUNITY MENTAL HEALTH CENTER

Of recent origin is the community mental health center, which has done much to reach out into the community with satellite clinics, storefront trouble-shooting operations, and the integration of hospitals with each other and with other agencies in the community. The patient may be treated by one of the "outreach" systems of the community mental health centers and may be an outpatient, inpatient, or be hospitalized part-time, so that in theory, at least, the patient's illness can be treated from early to late stages, and upon recovery can be routed to the rehabilitative unit of the mental health center. The greatest involvement of community health centers has been in the so-called underprivileged inner city and in rural communities. Its impact has not been felt to any degree as yet in suburban areas, where the traditional private-practice model predominates.

Although this system provides great bureaucratic advantages and facilitates funding, the citizens in the community are generally unaware of its existence, as they have usually gone to the nearest hospital or clinic anyway. The focus of attention becomes the tidy maps and catchment areas roughly comparable to school districts, creating the illusion that the mental health needs of the enclosed population are thereby provided for. Although alcoholism and schizophrenia are the two leading mental health problems, it is common for the local community mental health center to have no communication with existing local groups working with either illness.

For example, the largest community health center in Nassau County on Long Island does not allow Alcoholics Anonymous to use their facilities for meetings, and members of AA are unwelcome to visit patients.

In this instance the institution's attitude is persistent and expresses itself in an active resistance on the part of the health center to the mental health needs of the community. Attempts by local alcoholism groups to work with the center have been repeatedly and actively rebuffed. Thus, a community mental health center can be, in actual practice, frankly alienated from the very community which it is funded to serve.[1]

TEACHING HOSPITAL-CLINIC

Because the institution is devoted to teaching, selection of patients must meet the needs of the institution itself, so that admission is usually by referral or by staff selection. Although many of these institutions carry a great deal of prestige, in actual practice the patient is in treatment only with a resident-in-training. Admission procedures are frequently extensive and involve a great deal of screening, processing, and delay. This system is much less isolated from the medical community than many of the other systems, so that work that has been done with the patient prior to admission is usually included in the evaluation and this is made available to the treating psychiatrist subsequent to discharge. Hospital stays are usually quite lengthy. Patients with schizophrenia not infrequently remain within the institution for many months or even several years, so that the system is neither efficient nor geared for treating large numbers of patients.

In most of these institutions, the psychiatric administrative posts are filled by representatives of the psychoanalytic schools so that psychoanalytic theories become overemphasized and this tends to influence the residents in the same direction. The resident then expends a great deal of energy learning a treatment method which has a very limited application.

TAX SUPPORTED COMMUNITY PSYCHIATRIC CLINIC

This is exemplified by the traditional child guidance clinic, with emphasis on the team approach of psychiatrist, psychologist, and social worker. Over 2,000 such clinics are currently in operation in the United States, providing a substantial amount of mental health care. The majority of these clinics have similar problems of long waiting lists, geographic restrictions, and restrictions on certain diagnostic

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[1] The same conclusion was reached by a Ralph Nader group which reported in the *New York Times*, 23 July 1972, that these centers were a "vastly oversold new bureaucracy largely unresponsive to local needs . . . inaccessible or irrelevant to most of the community."

groups. Acceptance may also depend on expected duration of treatment and apparent prognosis. Most are psychotherapy oriented, and many are not interested in the really sick schizophrenic or alcoholic, nor the chronic schizophrenic. Frequently the diagnostic intake procedures are lengthy and complicated, with a great deal of professional energy going into the compilation of impressive charts and elaborate case histories, with the result that the actual cost per treatment session is higher than in private practice. In some communities local mental health boards have begun dissolving such clinics and instead are providing payment for private treatment, which is less expensive.

It is sometimes considered that the high cost of these clinics is compensated for by the fact that they provide services to the community other than just treatment of the individual patient, and there is a tendency to reduce per capita cost by increasing group therapy. Because staffing relies predominantly on social workers, psychotherapy must remain the main modality of treatment.

Specialized Disease–Specific Treatment Systems

Highly specialized treatment systems have evolved which are specific for a particular disease or problem. Examples of these are programs related specifically to drugs, alcoholism, autistic children, dyslexic children, hyperkinetic and brain injured children, suicide prevention, and schizophrenia. For instance, in the field of alcoholism there is a related system which includes the National Council on Alcoholism, with regional chapters and local alcoholism councils, clinics, halfway houses and Alcoholics Anonymous with its sister organizations, Al-Anon and Alateen. There are also specific government agencies on the local, state, and federal levels.

The first seven treatment systems are based primarily on economic, geographic, or bureaucratic criteria. The specialized treatment systems are geared to specific needs of the patient and family which arise out of a specific illness, and the utilization of their various resources is not related to geography, catchment area, insurance, or economic situations. These systems employ educated laymen, recovered patients, patient self-help groups, and family member organizations. The professionals involved tend to become "superspecialists" with high degrees of involvement on all levels of the integrated system. Referral between the various components in the system is usually informal, immediate, and highly pragmatic.

The effectiveness of such specific disease-oriented systems is demonstrated outside the field of mental health with such diseases as polio, tuberculosis, and others, in which the system effectively removed the stigma from the disease, educated the public, brought awareness of the problem to a national level, and marshalled huge arrays of forces including manpower, funds, and scientific research to bear on a

single entity. Thus, such a treatment system can, within a relatively few years, bring about a change from ignorance, shame, prejudice, and hopelessness to acceptability and ultimately successful and effective treatment.. The public is still so uninformed about schizophrenia that many physicians are loathe to discuss the diagnosis with either the patient or the family, and many euphemisms and evasive rationalizations are used to avoid the diagnosis.

The specialized type of network of service organizations grows out of community needs that are unmet by the other mental health care delivery systems. Predominant among these needs are immediacy of service, absence of red tape and lengthy processing admission procedures, the need for family members to have an active voice, absence of restrictions based on economics, geographic locale, gravity of prognosis, expected duration of treatment, suitability for psychotherapy, "psychological-mindedness," degree of insight, or suitability as a teaching case. Both patient and family want the reassurance that the service organization to which they are going for help has a specific and highly motivated degree of interest in the illness from which they are suffering. They want understanding and expertise and they also expect active research to be conducted on their illness.

Patients and families have a need to meet regularly, not only with each other, but also with the professionals for frank give-and-take discussions. A patient also wants continuity of care, so that he remains a distinct, known person wherever he may be in the treatment system. He also wants the warmth of a community feeling that comes from open and free communication between all units of the system and the community of patients being served. Patients and families also seek professional honesty; they want to know the exact nature of the illness and the exact diagnosis, and they want to have their questions answered directly. They are very desirous of active, ongoing, educational programs geared to their level of understanding, and without condescension. They want the removal of any stigma attached to the illness, and do not want even a subtle prejudice demonstrated by the people who are trying to help them.

Above all, there is an enormous need for a feeling of hope, enthusiasm, and dedication to offset the morbidity surrounding an illness as serious as schizophrenia.

DEVELOPMENT OF A SPECIALIZED INTERRELATED TREATMENT SYSTEM FOR SCHIZOPHRENIA

Developmental Concept

The assessment of the specific needs of the patient with schizophrenia and the plight of his family led to the conclusion that the ideal treatment system would consist of a clinic, a specialized laboratory, a hospital, a patient self-help group, a halfway

house, a day treatment center, and a mental health organization geared specifically to the treatment of schizophrenia.

It was considered essential that all components of this system freely relate to each other on all levels; that patient, family, and staff be involved simultaneously in all of them; that each unit be administratively and financially independent and self-sufficient; that each unit would participate in public education, conduct research, publish its findings, and participate in joint meetings. In addition, all this was to be done without the use of public funds, as none were available for the development of such a system for schizophrenia. Also, referrals between the units were to be immediate, spontaneous, without red tape or tedious processing procedures or geographic limitations. Finally, the entire system was to be correlated with the only national organization devoted to schizophrenia, the American Schizophrenia Association.

Because many schizophrenics also had concurrent drug or alcohol problems, subspecialized side systems were to be evolved for them, so that liaison was to be established with existing alcoholism and drug programs, as well as other patient self-help groups active in the community.

Components of the Complex

CLINIC: THE NORTH NASSAU MENTAL HEALTH CENTER

The North Nassau Mental Health Center[2] was the prime force behind the development of a model treatment system on Long Island. The mental health center was a large, voluntary, nonprofit clinic treating all types of psychiatric illnesses and it had a specific interest in alcoholics, schizophrenics, and drug-involved youth. The clinic was already closely involved with patient self-help groups such as Recovery, Alcoholics Anonymous, Al-Anon, and Alateen. The staff was eclectic in approach, and prior to 1966 used outpatient electroshock treatment, psychoanalysis, group therapy, individual therapy, and pharmacotherapy, followed by referral to local mental hospitals if these approaches failed. In general, treatment results were good. Results with alcoholics were considerably better than average, but there was one patient group in which results were poor—as they were elsewhere—and that was the group of patients with both alcoholism and schizophrenia.

In early 1966, via Bill Wilson, co-founder of Alcoholics Anonymous, the clinic received information pertaining to the niacin treatment of schizophrenia, especially

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[2] Address: The North Nassau Mental Health Center, 1691 Northern Boulevard, Manhasset, New York 11030.

of schizophrenic symptoms in recovered alcoholics. Investigation revealed that many members of Alcoholics Anonymous had been taking niacin for variable lengths of time and there were many favorable reports (Wilson, 1965, 1966, personal commun.). Until that time the staff was only minimally aware of the work of Hoffer and Osmond pertaining to niacin treatment, and they discovered that there was considerable literature describing successful treatment of schizophrenia utilizing niacin going back to the first double-blind study done in psychiatry, which began in 1952. Of particular significance were over 200 papers and three books describing a new approach to schizophrenia. The follow-up studies indicated a 36 percent ten-year recovery rate in the control group as compared to a 75 percent recovery rate in the treated group (Hoffer and Osmond, 1962a, 1962b, 1964, 1965, 1966).

In summary, the literature stated that niacin doubled the recovery rate, eliminated suicide in the treatment group, and had only minor, easily controlled side effects. A number of psychiatrists in the United States were already utilizing this treatment with good results, and the psychiatric staff, after consultations with some of them, began a research project using niacin and ascorbic acid, later pyridoxine, vitamin E, and hypoglycemic diets in treating the alcoholic-schizophrenic. In addition, the HOD test (Hoffer–Osmond Diagnostic; Hoffer and Osmond, 1961, 1962) greatly facilitated establishment of the diagnosis and the monitoring of the patients' responses to treatment. The marked usefulness of this has been described in "The Use of the HOD Test in a Busy Psychiatric Out-Patient Clinic" (Hawkins, 1971b; also see chapter by Kelm on the HOD Test).

The results obtained with this new treatment method were encouraging and the staff became more interested in the use of biochemical approaches, not only in schizophrenia, but in other psychiatric disorders as well. Because of this interest the clinic developed its own laboratory facilities for service to patients and for on-going clinical research. The evaluation of biochemical research in schizophrenia by Dr. Seymour Kety, the Chief of the Clinical Science Laboratory of the National Institute of Mental Health, was quite helpful (Kety, 1965, 1966), and the clinic's experience seemed to correlate with his conclusion that "a faulty transmethylation underlying schizophrenia is the most plausible and parsimonious explanation of a wide range of observations in schizophrenia and warrants further evaluation."

At a meeting of the Scientific Advisory Committee on Therapy of the American Schizophrenia Association in January 1967 favorable reports were presented by independent investigators from all over the United States who had obtained similarly promising results in their patients by the addition of megavitamins and hypoglycemia diets to the usual treatment measures. The clinic's initial research project included 100 patients; the results were reported in a paper "The Practical Application of the Results of Biochemical Research in Everyday Clinical Practice" (Hawkins, 1967) at the Brunswick Hospital Conference on Schizophrenia in January. (See Chapter 30.)

In addition to the generally good results, there was excellent acceptance of this new treatment method by the professional staff, patients, and families. Results of the treatment of the first 150 patients by this new method were published in the new *Journal of Schizophrenia* (Hawkins, 1968c), and further reports of the clinic's experience, which included treatment of alcoholics, were written by Bill Wilson (1968), co-founder of Alcoholics Anonymous.[3]

By 1968, the most effective treatment approach consisted of assessing the patient for biochemical abnormalities, and correcting those that were contributing to his illness. This approach was related closely to the concept of orthomolecular psychiatry as conceived by Professor Linus Pauling in 1968. The correlation of our approach with the new concept of orthomolecular psychiatry, and our experiences in treating 500 schizophrenic patients including a group whose illnesses were complicated by heavy involvement with psychedelic drugs, were reported to the schizophrenia foundation of New York and Connecticut (Hawkins, 1968a).

This new treatment was found to be surprisingly successful in treating drug-involved schizophrenic youth, who thus far had been reported as being generally unresponsive to traditional psychiatric approaches (Carone, 1970; Hawkins, 1969b). Neither psychotherapy, hospitalization, nor chemotherapy had been particularly successful with these patients, and without the use of the HOD test it had been extremely difficult to diagnose and assess their illness correctly.

This approach was acceptable to the drug-oriented subculture and as a result many have been brought into the clinic for treatment by members of their peer group. The clinic became the consulting psychiatric agency to the Hotline in the area and it also became the psychiatric consulting agency to the LSD Rescue Service. The specialized group therapy which evolved for the schizophrenic-psychedelic drug user was also employed by the Youth Consultation Services, some of the SA groups, patients discharged by the Brunswick Hospital, and by a considerable number of young patients who later went to The Gateposts halfway house.

By January 1969 we reported our clinical experience in treating 1,500 patients by orthomolecular psychiatry (Hawkins, 1969a). At a meeting of the Scientific Advisory Committee on Therapy in Vancouver, B.C., other psychiatrists also reported their experiences with large numbers of patients; at that meeting results in treating over 10,000 patients were compared. Our paper, "The growth and development of orthomolecular psychiatry and megavitamin therapy in New York" (Hawkins, 1970b) reported on the growing use of this treatment method.

By 1972, the clinic had treated 5,000 patients by orthomolecular psychiatry, with

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[3] The booklets *B-3 Therapy* (1968; $2) and *B-3 Supplement* (1971; $1) are obtainable from B-3, P.O. Box 125, Oyster Bay, New York 11771.

increasingly satisfactory results as experience was gained. The clinic carried an active case load of 2,000 out patients. The cost of treatment was remarkably less than the other methods had been, and was within the financial capacity of almost every patient.

Because an effective method of treating large numbers of schizophrenic and perceptually disordered patients had developed, the clinic no longer needed an outpatient shock-treatment unit, and it was closed. The Brunswick Hospital facilities were used for those patients who were already too disturbed, severely ill, or suicidal to begin therapy on an outpatient basis. Many of the patients were elected to be hospitalized for courses of shock treatments. At other times, the clinic utilized the halfway house to prevent hospitalization. The clinic had also helped in the formation of several local SA groups and the Day Treatment Center. It had increased the degree of its affiliation with the Youth Consultation Service of the Diocese of Long Island, and each unit of the growing treatment complex included representatives from all the other component units. The success of the entire system was such that the clinic was considered as the operating model by the American Schizophrenia Association for the development of similar networks of facilities throughout the United States.

In October 1971, the Clinic sponsored a "Mental Health Fair" with C. W. Post College of Long Island University. Representatives of twenty self-help organizations manned exhibit booths in the college's auditorium for an all-day public education program. This was the first time in the country that such a gathering had taken place, and it attracted widespread attention. A second public Mental Health Fair co-sponsored by the Clinic and the State University at Stonybrook took place in May 1972, with the following groups participating: Alcoholics Anonymous, Al-Anon, Alateen, Fortune Society, Gamblers Anonymous, Gam-A-Non, Hotline, Hypoglycemia Foundation, Long Island Council on Alcoholism, Long Island Schizophrenia Association, LSD Rescue—Naturalism, National Foundation for Sudden Infant Death, National Tay-Sachs and Allied Diseases, New York Association for Brain Injured Children and the Association for Children with Learning Disabilities, Parents Anonymous, Parents Without Partners, The Crisis Intervention Center, Recovery, Response, St. George Day Activity Center, and Schizophrenics Anonymous. These pioneering events expanded the usefulness of the integrated community mental health system and resulted in the planning of similar events in other communities.

By 1971, the Clinic was training fifty psychiatrists a year in orthomolecular psychiatry. During that year it also helped with the foundation of the Academy of Orthomolecular Psychiatry which had its founding meeting in London in September. Members of the Academy presented a Conference on Schizophrenia to a joint meeting of the American, Canadian, and Great Britain Schizophrenia Associations.

The Hospital: Brunswick Hospital Center

The Director of Psychiatry and Director of Psychiatric Research of the Brunswick Hospital[4] were interested in doing research on new treatment methods in schizophrenia, especially for those patients who had failed to respond to all traditional treatments. Brunswick Hospital is a large 600-bed general hospital with multiple divisions, including a 160-bed psychiatric division. It was the first hospital in the United States to use the orthomolecular approach in treating patients. Because the psychiatric hospital is part of a general hospital complex, the staff is medically oriented. All newly admitted patients are seen by an attending neurologist and an attending internist, as well as personnel from the electroencephalography, radiology, and clinical laboratory departments, so that the patient's psychiatric treatment is integrated into the overall medical setting.

The hospital agreed to accept patients on an immediate referral basis from the clinic. The treating psychiatrist from the clinic could continue to see the patient in the hospital and the Director of the clinic, who was also on the hospital's atttending staff, saw the clinic patients while they were there. At the time of discharge, the Clinic Director arranged for the patient's immediate resumption of treatment on an outpatient basis. The clinic's hospitalized patients were given the HOD test on admission and again on discharge to verify the diagnosis and monitor the effectiveness of treatment. In addition to the HOD test, these patients were also given the Organic Integrity Test (Tien, 1960, 1968; Tien and Clark, 1964).

The initial research project was begun in 1966 and covered a two-year period. Included were 140 patients who were severely ill and had failed to respond to previous outpatient treatment. Results indicated that the HOD test's administration fit easily into the admission routine and that the diagnosis was in closer agreement with the final diagnosis than was the admitting diagnosis formulated by the psychiatric staff. Verifiable improvement for 88 percent of the patients was indicated by the significant reduction of HOD scores.

While the ECT group and the control group showed an almost equally favorable change on a behavioral rating scale, the HOD scale indicated that those who had received ECT showed a greater improvement, indicating the effectiveness of ECT in reducing the extent of the perceptual disorder. Further details of this study are presented in the chapter on the orthomolecular treatment of schizophrenia (Chapter 30). The average length of hospitalization was seven weeks, during which time patients received high doses of niacin, ascorbic acid, pyridoxine, and vitamin E, in addition to the usual chemotherapy. All 140 patients were discharged from the

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[4] Address: Brunswick Hospital Center, Psychiatric Division, Louden Avenue, Amityville, New York 11710.

hospital and the study demonstrated the effectiveness of this biochemically based intensive hospital treatment approach (Chiossone et al., 1969).

The average stay in the hospital of 50 days compared very favorably with the 152-day average for schizophrenics that was reported by a nearby comparable hospital where treatment was based on a "dynamic approach with three times weekly psychoanalytically oriented psychotherapy in addition to drugs and electroconvulsive therapy when indicated" (Berger and Gralnick, 1970).

The hospital then sponsored a conference on "Newer Concepts in the Treatment of Schizophrenia," in January, 1967. Subsequent to the conference and the first inpatient research study, the hospital, together with the clinic, sponsored an aftercare research project to study the effectiveness of the continuation of megavitamins on the relapse and rehospitalization rate. The study covered a two-year period, and 160 patients were followed up subsequent to discharge from the hospital. The group of patients who did not receive megavitamins after discharge had an overall rehospitalization rate of 35 percent as compared to a rehospitalization rate of 16 percent for the patients who were continued on the megavitamins. The follow-up study thus established a definite correlation between continuation of megavitamin therapy and a 50 percent lower readmission rate than patients in the control group (Hawkins et al., 1970).

These results were surprisingly similar to those that were obtained in the original five and ten year long-term follow-up studies of Hoffer and Osmond (1962a, 1964, 1966) on the effect of nicotinic acid on the frequency and duration of rehospitalization rates. The results of this treatment method also compared quite favorably with the overall readmission rate for schizophrenics as reported by the New York State Department of Mental Hygiene. Their data showed that for the same years during which the study was conducted 55 percent of schizophrenics admitted to state hospitals were readmissions (Sidney, 1969, personal commun.).

Presently, the clinic arranges hospitalization for over 100 patients per year, many of whom come from a considerable distance just for the specialized treatment. After discharge, they return to their home state, where they continue in treatment with the referring psychiatrist.

In studying the patients who had to be rehospitalized despite megavitamin therapy following discharge, one frequent reason for readmission was the inability of the patient to make the sudden transition from the hospital to home. Even when the family did not pressure the patient to function normally, these pressures were implicit in just being returned to the community. The young schizophrenic male, for instance, felt the expectation that he should return to job or school and resume an active social life even when none of these things were as yet possible. Therefore, the hospital, the clinic, and the patients' families were aware of the need for a halfway house for the recovering patient.

The Halfway House: Gateposts

Sponsored jointly by the clinic and the Schizophrenia Association of Long Island, The Gateposts[5] was the first halfway house in the United States for young schizophrenic patients that used the total orthomolecular psychiatric treatment approach. Other halfway houses in the New York and New England area had been using megavitamins for their schizophrenics and alcoholics, but without a total orthomolecular orientation that included prescribed diet, rest, and administration of medication and megavitamins by injection when needed.

This large country house was donated by a member family of the Schizophrenic Association. The parents who donated the house continued to provide supervision with decreasing intervention as the house became a therapeutic community and additional house staff were obtained and trained. The house will accommodate approximately 20 residents and a house staff of 5. The style of work and living is organized to give patients more work and responsibility as their self-sufficiency and self-confidence return. The performance expectation of each patient is correlated with his current HOD score. Despite the many obvious obstacles and difficulties to be overcome during the first year of operation, most residents have shown remarkably good progress. Recommended length of stay is now 3 to 6 months when the aim is the establishment of self-sufficiency and the return to full functioning in the community. The halfway house activities also include an in-service training program and a close working relationship with other halfway houses.

The most difficult obstacle to overcome has been the detrimental interaction of the dependent patient and the over-protective family. The patient who has been impaired for years with this incapacitating illness has learned to become dependent, and even though the illness itself has now become quiescent the dependent pattern persists. The reverse pattern has been established by the family over the years. They have learned to become over-protective of the impaired patient, and it is difficult for them to learn to let go and allow the patient to become self-sufficient. The halfway house staff is then presented with the additional problem of trying to modify the family's behavior toward the patient. This has not always been successful; plans are developing to provide a specific program to offset this recurrent problem (see Chapter 27).

Patient Self-Help Group: Schizophrenics Anonymous

After return to the community from either the halfway house or the hospital, or while in treatment at the clinic, the education, rehabilitation, and successful treat-

[5] Address: Gateposts, c/o H. B. Pearl, President, The Gatepost Foundation, 29–46 215th St., Bayside, New York 11360.

ment of the patients are greatly augmented by their attendance at meetings of Schizophrenics Anonymous.[6] Schizophrenics Anonymous began in 1964 and is the youngest and least known of the major patient self-help organizations. It is to the schizophrenic what AA is to the alcoholic. Each group is self-supporting and stresses that schizophrenia has physical, mental, and spiritual components. The members follow the now famous 12 steps of AA, with the exception that the word "schizophrenia" replaces the word "alcoholism" and the members pay stricter attention to the physical aspects of the illness and encourage fellow members to stick to the medical regimen prescribed by their physicians.

In the SA group, the patient increases his knowledge of the illness. He learns the meaning and implications and names for the various symptoms he may experience. Irrationality is quickly quelled; a patient soon learns that his paranoia is just "paranoia" and nothing more and that it is only a symptom due to his altered perceptions. New members take the HOD test so that all will be aware of the degree of each other's illness and degree of progress. There is also a beginners group especially to orient new members and their families. In essence the SA groups provide an enormous amount of specialized help at no cost to the patient or society. During its first two years the SA intergroup office received over 5,000 telephone calls for help and information. It also publishes its own newsletter, *Telling It Like It Is*, which is sponsored by the Schizophrenics Anonymous groups of New York and Long Island.

There are currently 36 SA groups. Additional ones are being formed, but their formation is slowed by the necessity of each group to have available nearby a psychiatrist who is familiar with the orthomolecular approach (all the groups follow the orthomolecular medical regimen). A monthly bulletin is available from Schizophrenics Anonymous International, 200A Brent Bldg., Regina, Saskatchewan, Canada. (Refer to Appendix 1.)

Local Specific Mental Health Organization: Schizophrenia Association of Long Island

Most of the families of the members of SA felt the need for their own organization, so they met with families of patients who were in treatment at the clinic or the hospital and formed the Schizophrenia Association of Long Island.[7] Several of the founders of the local Schizophrenia Association were already members of the American Schizophrenia Association and the Schizophrenia Foundation of New York.

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[6] SA Intergroup, P. O. Box 1134, Linden Hill Station, Flushing, New York 11354.

[7] Address: Long Island Schizophrenia Association, 1691 Northern Blvd., Manhasset, N.Y., 11030.

Objectives of the organization were public education, the bringing together of professionals to develop treatment techniques, the exchange of information and education of fellow family members, publication of a newsletter, the holding of public scientific meetings and symposia on the subject of schizophrenia, the establishment of a halfway house, and the compilation of a National Directory of Halfway Houses. In addition, the organization helped start the St. George Day Activities Center coordinated with the clinic, the halfway house, St. George's Church, and Brunswick Hospital.

The Association began holding meetings at various hospitals on Long Island to interest other physicians in the community in the problem of schizophrenia and especially in biochemical approaches to the illness. During its first two years of operation, the Association achieved all of its goals. The scientific meetings were well attended, received excellent press coverage, and were held at leading hospitals (Brunswick, Meadowbrook, Nassau, Long Island Jewish) as well as the Academy of Medicine. The format of the meetings was somewhat unusual in that the first half of the meeting consisted of a scientific presentation and the last half was devoted to questions from the audience which were answered by the speakers. There developed a close interaction between the professionals and the laymen, as it was the first time the interested public had been afforded an opportunity to present direct questions and get answers about schizophrenia.

Subjects have covered all aspects of the illness, from the biochemical to the clinical handling of difficult and recalcitrant patients. The audiences became larger and the meeting halls became increasingly crowded. Typical meeting topics have been: Psychedelic Drugs—Schizophrenia and the Hippie Scene; Hypoglycemia and Psychiatry; The Patient Who Won't Take Medication; Pink Spot in Schizophrenia; Halfway Houses and Schizophrenia; Biochemical Theories of Schizophrenia. In addition there have been joint meetings with other local mental health groups, such as The National Society for Autistic Children and The Hypoglycemia Foundation.

The Schizophrenia Association and the clinic co-sponsor the halfway house, although financially the halfway house is self-sustaining. The Association also sponsored a major all-day symposium on schizophrenia which attracted over 600 professionals from the metropolitan New York area. This was also a joint venture with the clinic and an established family agency, the Youth Consultation Service of the Episcopal Diocese of Long Island.

Although independent and self-sustaining, the Long Island Schizophrenia Association, like similar local chapters throughout the United States, is an affiliate of the American Schizophrenia Association. It has its own educational literature package and its own newsletter.

Local chapters elsewhere in the country have developed complexes along similar lines. The Schizophrenia Association of Westchester County, for example, formed an SA chapter and family groups, publishes a newsletter, *Lifeline*, established the

Schizophrenia Treatment Center of Westchester, and is working toward creation of a halfway house. They have already received a commendation from the Presidents Committee on Employment of the Handicapped, Washington, D.C.

Day Activities Center

The last of the units of the treatment complex to be developed, the Day Activity Center,[8] is an independent, self-sustaining unit sponsored jointly by the Schizophrenia Association, a local church, the clinic, the halfway house, and the Youth Consultation Service. The Board of Directors include representatives from the Schizophrenics Anonymous groups and the Director of Psychiatric Research from the Brunswick Hospital complex. Located in a parish house, the center provides full-time, week-long, supervised, progressive activities on a pre-vocational and social rehabilitation level. When the patients have achieved sufficient stabilization and rehabilitation, they return to school, obtain employment, or are referred for vocational training to the Division of Vocational Rehabilitation of the State Education Department.

In addition to a full-time group worker and other counsellors, the services of volunteers are sought and utilized. The program is geared to the patient who is no longer sick, but is having vocational or social difficulty because of the residuals and aftermath of the schizophrenic illness. Many of the patients already know each other from the halfway house, the hospital, the clinic, or the SA group or the Youth Consultation Service. Similarly, the families have learned to know each other.

Family Service Agency: Youth Consultation Services

The Youth Consultation Service of the Episcopal Diocese of Long Island[9] was established in 1918 as a social work agency to treat primarily children and their families when the family problem was related to the child's welfare. Like all such agencies, they had a long waiting list and insufficient budget to meet community demands. Funds were depleted by the expense of diagnostic procedures that frequently involved long waits and resulted in rather stereotyped recommendations, such as "this child needs prolonged psychotherapy and if this is not successful, placement should be considered."

The Youth Consultation Service staff began using the facilities of the clinic

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[8] Address: St. George's Day Activity Center, Front Street, Hempstead, New York.

[9] Address: Youth Consultation Service, Episcopal Diocese of Long Island, 89–02 Sutphin Boulevard, Jamaica, New York 11435.

(North Nassau Mental Health Center) for psychiatric consultation and soon became interested in the clinic's new diagnostic and treatment approaches. They began screening their clients with the HOD Test and were surprised to find that a very sizable proportion of their difficult and most time-consuming clients had unrecognized schizophrenia. Of the unwed mothers who applied to them for help, 70 percent had HOD scores in the schizophrenic range, and 90 percent of those who were applying for help because of a second pregnancy had unrecognized schizophrenia.

After several years, their experience demonstrated that between 17 and 30 percent of people applying to a casework agency had unrecognized and previously undiagnosed schizophrenia or perceptual disorders of varying degrees of severity. They began to look back over their case load and saw that the social difficulties for which their clients were seeking help were due to impaired social ability resulting from their unrecognized illness. The utilization of the HOD as a rapid screening procedure facilitating early detection and referral for treatment had the result of enabling the agency to double its case load and eliminate its waiting list for the first time in 50 years.

The clients whose illness had been previously unrecognized began to respond to treatment in such a way that case work with them was greatly facilitated. This experience had broad implications for other case-work agencies; the importance of their experience led the agency to jointly sponsor an all-day symposium on schizophrenia with the Schizophrenia Association of Long Island and the clinic. Their paper on "Learning to Recognize Schizophrenia in a Social Work Agency" (Hulse, 1970) led to many requests by other social work agencies for presentations. The agency was able to expand its services, including the leading of family group discussions for the Schizophrenia Association and the Day Activities Center.

The clinic supplies psychiatrists to the Youth Consultation Service on a regular basis, so that immediate medical consultation is available on the agency's premises. The close working relationship between the clinic and the family agency was so mutually beneficial that it was surprising to learn that this was a rare arrangement. In a comparative study of family service agencies and mental health clinics done by the Family Service Association of America, mutual isolation was found to be the rule (Hill et al., 1971) and the study concluded with the recommendation that the establishment of close relationships between clinics and family agencies was urgent. Expansion of the agency's scope of operation has led to their development of other rapid diagnostic screening tools, such as a check-list that quickly identifies the organic, minimally brain injured, or hyperkinetic child who may also benefit from immediate medical assistance. Their future contributions are promising and demonstrate the successful application of the orthomolecular concepts in a manner which the American Schizophrenia Association would like to see implemented elsewhere in the country. Aside from the alleviation of suffering, there were major economic

benefits in that utilization of the orthomolecular approach doubled the cases that could be handled with the same budget.

National Mental Health Organization: The American Schizophrenia Association

The American Schizophrenia Association[10] was founded in 1964 and now has local chapters in most of the states. The organization is devoted to "developing a coordinated campaign to conquer schizophrenia" (Program Prospectus, American Schizophrenia Association, 1970). Its objectives are broad and comprehensive, including the following:

Education, both public and professional; research and the clinical application of research findings to the development of more effective treatment methods; the encouragement and facilitation of networks of halfway houses, clinics, hospitals, Schizophrenics Anonymous groups, and treatment centers; the development of more effective diagnostic methods and service to the profession, patients, and families, in diverse areas relating to schizophrenia.

Education of the public is achieved through documentary and training films, utilization of mass media, the publication and mailing of literature, and the sponsorship of both local and national conferences and symposia. It gives postgraduate training grants and stipends for study in the field of orthomolecular psychiatry, supplies physicians with materials, and sponsors meetings. In 1966 and 1967 it published the *Journal of Schizophrenia*, and from 1968 to 1971, the quarterly professional journal *Schizophrenia*. In 1972 it helped found the new *Journal of Orthomolecular Psychiatry*, which is published by the Academy of Orthomolecular Psychiatry. Another objective is the establishment of a national Schizophrenia Information Center with a field staff. It is also devoted to recruiting interested professionals into the work of helping schizophrenics and their families.

The organization seeks to improve the conditions of hospitalized patients, and encourages the development of hospitals and treatment facilities that are specifically designed for schizophrenics. It is also interested in the development of more effective rehabilitation techniques for patients who have recovered from the active phase of the illness. Allied with these objectives, the Association is planning a national conference on the high cost of mental illness and it is interested in finding ways to directly reduce this cost to the patient and family.

The Association publishes a quarterly *Newsletter* which is distributed free to all members and which is now in its fifth year of publication. The *Newsletter*, in the

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[10] Address: The American Schizophrenia Association, 56 West 45th Street, New York, New York 10036.

beginning, was something of a gadfly in the side of the psychiatric profession as it took up the complaints of the patient and their families who, for the first time, had a voice. They had many grievances that they wished to air, hoping that the psychiatric profession would listen and, of course, respond. They thereby managed to annoy the psychiatric establishment to a considerable degree. This annoyance was then expressed in several editorials in *Psychiatric News*, the official newspaper of the American Psychiatric Association, which let it be known that if the *Newsletter* wanted to enter into a dialogue on that level it was quite capable of responding in a similar vein. Subsequently the *Newsletter* took on a more conciliatory tone and hopefully a more constructive dialogue will ensue, as the subject involved is far too important for the indulgence of editorial resentment and rhetoric. The *Newsletter* is, in fact, primarily concerned with educational articles pertaining to schizophrenia. In addition, it includes news of national and local chapter interest and new programs and developments.

The Association is currently developing a larger national constituency. Through support and leadership it encourages the formation of new local chapters. It is endeavoring, through a major fund-raising campaign, to reach a larger segment of the population and thereby mobilize the necessary forces to achieve its goals.

The System in Operation

Patients may make contact with any of the component units or groups and many become involved successively with a combination of them at various stages of their illness and recovery. An example is as follows:

> A recovered patient who was also an active member of Alcoholics Anonymous helped a young person who was drinking heavily, had a "pill problem" (250 mg diazapam per day), and also had hallucinations, depression, and marked confusion, by referring him to a local Schizophrenics Anonymous group. At the SA group he attended the beginners' meeting, where he learned that his symptoms were probably due to biochemical abnormalities that were causing perceptual distortions. He heard that these abnormalities, if uncorrected, could result in schizophrenia and that he had a medical illness for which there was positive help. He took the HOD test and was told that his score was 90 and that this definitely indicated that he needed medical help. Other members of the group gave him encouragement and told him their case histories, and he agreed to have diagnostic tests. While at the beginners meeting the family heard of the Schizophrenia Association. They read the literature about schizophrenia and began attending meetings where they met many other families whose experiences had been almost identical with theirs. Whereas before the patient's family had been discouraged, guilt-ridden, and angry, they now became hopeful and encouraged the patient to keep his appointments at the clinic.
>
> The diagnostic studies confirmed that the patient had marked functional hypoglycemia, schizophrenia, a mixed addiction to minor tranquilizers, and alcoholism.

Immediate hospitalization was advised for detoxification and intensive treatment because of the patient's suicidal ideation. Upon discharge eight weeks later the patient's HOD score was down to 29 and he was advised to attend AA and SA meetings and keep his monthly appointments at the clinic.

While home, the patient, although much improved, was lonely and unable to function. The halfway house was discussed with him as a possible help during the first few months of convalescence. While he was at the Gateposts he continued monthly visits to the clinic, and he gradually recovered his self-respect, capacity to socialize, and self-confidence. After returning home he received computer programming training from the Division of Vocational Rehabilitation.

The example demonstrates how a flexible system can fulfil different needs at different times during a patient's recovery and can provide programs for multiple coexistent disorders (addiction to barbiturate-type tranquilizers, alcoholism, hypoglycemia, and schizophrenia).

Another typical case demonstrates the usefulness of the same flexibility in helping a young patient with schizophrenia plus severe drug involvement:

This 23-year-old man had been in treatment since the sixth grade for schizophrenia and had dropped out of school and become seriously involved in the East Village drug scene. In series and combination he took barbiturates, amphetamines, LSD, STP, hashish, marijuana, demerol, dilaudid, cough medicine, opium, kief, hog, cocaine, mescaline, psilocybin, THC, freon, amyl nitrate, morphine, heroin, dexamyl, methedrine, and carbona. His appearance was disheveled and bizarre, he was malnourished, and was injecting methedrine intravenously. By this time he had a $140 a day consumption of "speed", and had developed "needle" hepatitis. The family managed to bring him to the clinic just once for a diagnostic evaluation; at that time his HOD score was well over 100. He then disappeared back into the city and appeared a number of months later in an acute drug crisis (speed plus STP) at Bellevue Hospital, where he had been taken by the police.

He was transferred to Brunswick Hospital, and, after an extremely stormy course, he was discharged. In the interim, the patient's family had become very active in the Schizophrenic Association. Following discharge, the patient was unable to function. He was afraid to go out, and still had an intense craving for methedrine. At the clinic he attended a weekly group which was designed specifically for young schizophrenics who had become heavily involved with drugs. He became an enthusiastic member of the drug group and began helping other young people who had a drug problem or were on "bad trips" and had been referred by Hotline or LSD Rescue Service. His knowledge of the drug scene was useful in helping other young patients get off drugs.

He then went to the halfway house, where he began junior staff training. After completion of a year of satisfying hard work he went on to become a member of the Day Activities Program Staff. He has made house calls on young patients whose families had called the Schizophrenia Association for help. On these home visits they have been successful in encouraging withdrawn patients to accept help. He and other recovered patients now provide a unique kind of personal help where needed, and often they are the only ones able to reach an otherwise unapproachable ill person.

The involvement of recovered patients and their families in helping those that are still ill is an invaluable addition to any treatment system. Families who have been "through the mill" can be of enormous help in a variety of ways. Often the family has accumulated a great deal of knowledge about schizophrenia and how to handle a schizophrenic patient. This experience frequently enables them to be helpful to patients who are not members of their own family, although they often are unable to successfully use this same experience with their own family member patient because they are too subjectively involved. Collectively, the recovered patients and their families constitute a considerable asset and force which can be utilized very positively in an overall treatment system.

SUMMARY

Mixing models in psychiatry creates confusion and results in a number of deleterious consequences, including the economic, due to society's reaction to departure from the medical model. The major existing psychiatric care delivery systems have been very briefly reviewed to point up the deficiences in each system. These systems leave unfulfilled important needs of the schizophrenic patients and their families.

The orthomolecular psychiatric approach with its return to the medical model provides the basis for the development of a treatment system complex which does meet the needs of the schizophrenic patient. The successful application of the orthomolecular approach to large numbers of patients in a clinic setting is described. Growth of the treatment complex consisted of the formal affiliation of the clinic with the psychiatric division of a general hospital, formation of a specialized laboratory, development of a halfway house, establishment of a local Schizophrenia Association chapter, founding of a Day Activities Center, and increased affiliation with an established family service agency. All units of the complex operate in cooperation with the American Schizophrenia Association.

The entire complex, which may be developed without any outside funding or tax support, provides for flexible, diversified, yet specific help for both the schizophrenic and his family. The system provides great economic advantages, so that treatment is within the means of almost every family. The economic advantages of the system were demonstrated when experimental utilization of the orthomolecular approach by an established family agency resulted in elimination of the agency's waiting list and a doubling of their case load within the same budget.

Operation of the system has been illustrated by two typical case histories that demonstrated the advantages of a model system. This system follows a pattern which has proved to be very successful in combating other major diseases of mankind.

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29

The Orthomolecular Approach to the Diagnosis of Schizophrenia

DAVID HAWKINS

GENERAL ORIENTATION TO THE ORTHOMOLECULAR APPROACH

The orthomolecular medical model of mental illness provides testable hypotheses on both the laboratory and clinical levels. The term "orthomolecular" provides a clarifying concept in that it lends new significance to the interpretation of a wide range of data. Slight changes in molecular concentrations of common substances can affect the brain in such a way as to bring on major changes in behavior, mood, and perception. These phenomena can be commonly observed, easily demonstrated, experimentally induced, and therapeutically utilized.

Changing blood levels of glucose, lithium, calcium, or many other ions can bring about profound behavioral changes. The considerable difference in mood which people experience due to lowering of the blood glucose level when they are hungry, as compared to the mood experienced when the glucose level has been elevated by eating, is everyone's common experience. Incredibly minute amounts of foreign

molecules as well, such as those of lysergic acid diethylamide, profoundly alter brain function and perceptions. Combined effects may also occur, so that functional alterations which normally would not be perceived may become magnified and reach awareness because of previous sensitization. Thus, for instance, minor fluctuations in mood and perception that are due to changing blood sugar levels may be greatly magnified while under the influence of LSD (Buckley, 1969b).

Similarly, hardly noticeable changes induced by fluctuating carbon dioxide levels may bring on tetany or even convulsions in the presence of low calcium ion levels. That the functioning nervous system is exquisitely sensitive to minute fluctuations in molecular concentrations of many substances is a basic and all-important concept in the orthomolecular approach. Until the advent of structural chemistry and molecular biology, methods were not available to detect biochemical abnormalities responsible for mental illnesses whose basis had not been detectable by ordinary quantitative and qualitative biochemical methods.

Chemical transmission of information in the brain is controlled by a multiplicity of enzymes, and all known enzymes are proteins. Proteins are composed of amino acids that are arranged in chains with an almost infinite possibility of combinations. The function of an enzyme depends on its steric structure and three-dimensional conformation and, therefore, a simple chemical description, as utilized in biochemistry, provides insufficient data to account for function. The function of a molecule may also be modified by its capacity to form aggregates with similar molecules. The manner in which these aggregates are formed determines which surfaces of the molecules are exposed for interaction, and this affects the availability of secondary or weaker chemical bonds (those that are not between the molecule's individual amino acids themselves). The importance of this basic intimate relationship between information and conformation can only be understood if the relationship is examined at the molecular level (Kendrew, 1968).

On a molecular level, then, a psychobiologic disease process can be viewed as failure to transmit information or as the transmission of misinformation. This concept was formulated by Gerard (1959) in his phrase "No twisted thought without a twisted molecule." As Bateson (1971) has shown from analysis of cybernetic and communications systems, the information communicated in the biologic process is the signaling of a difference—a change of state.

Historically, the scientific approach in almost all biochemical research in schizophrenia has followed the same pattern: samples of certain chemicals have been searched for in schizophrenics as compared to control groups on the basis of their presence or absence, chemical composition, or differing levels. Now that studies in molecular biology have shown that the function of the molecule depends on its geometry, symmetry, and other three-dimensional attributes, many common assumptions will have to be re-examined.

As a possible example, Gottlieb (1971) reported that all forms of chronic schizophrenia may be associated with an abnormal molecular conformation of the alpha-2-globulin. Increased metabolic activity (in 60 percent of patients) was associated with preponderance of the alpha-helix form of this protein (in normal controls the beta-conformation predominates). This increased activity as a result of the alpha-helix form alters intracellular levels of tryptophan and affects catecholamine ratios; 40 percent of the patients had neither the alpha-helix nor the beta-conformation forms of the alpha-2-globulin. In these patients the molecule is said to have a unique shape which could be artificially reproduced in the laboratory only by exposure to a "leaked" intracellular protein which destroyed all of the alpha-helix forms. This illustrates the concept that function depends on conformation and the ratios of the various forms of protein molecules.

It is also apparent that even though a given molecule in schizophrenics as compared to normals is identical in its concentration, structural formula, and conformation, its function may be blocked by a defect at its site of interaction.

Abnormal function can also result from alteration in the rates of chemical reactions, and these rates are determined by the concentrations of the molecules. It has been demonstrated, for example, that for a given period of time, the same compound could be classified as inert, active, or even lethal, depending upon the experimental concentration. Similarly, the biological effect, if the concentration remains constant, may change, depending upon the period of exposure (Cherkin, 1968). Even the same structural genes, when the timing of their activity is altered, may produce successively different forms of polypeptide chains attributable to the changes in relative rates of synthesis (Zuckerkandl, 1968).

Recent research in molecular psychobiology includes searching for specific enzymatic defects and identification of the sites of interference. Some of these areas of research have already been covered elsewhere in this volume. A review of all the types of biochemical theories of schizophrenia is outside the scope of this chapter, but many have recently been summarized and reviewed by Beavers (1969), Nyberg (1970), and Boulton (1971).

Current biochemical theories predicate that schizophrenia is genetically determined and involves a defect in important enzyme systems (Huxley et al., 1964). Thus, for example, Stein and Wise (1971) postulate that because of a defective gene, schizophrenics have insufficiently active dopamine-beta-hydroxylase, which adversely affects functioning of the medial forebrain bundle because of the abnormal concentration of 6-hydroxydopamine. The molecular mechanism of action of 6-hydroxydopamine has been described by Sauer and Thuernen (1971).

Clinical utilization of the basic concepts of orthomolecular psychiatry has both practical and demonstrable effects in that we can selectively alter molecular concentrations of substance and then observe the objective as well as subjective reponse. In therapeutic practice, the problem is to detect those biochemical abnormalities that

are producing clinical symptoms and then find an acceptable, safe, and effective method of correction that is economically feasible.

THE CONCEPT OF SCHIZOPHRENIA AS A DISEASE

The overall style of the clinical approach to the patient, including treatment and diagnostic and evaluative procedures as described in this chapter, is based on an operational model of schizophrenia as a medical illness involving an underlying disease process. The illness itself, when unmodified by therapeutic intervention, follows familiar stages and takes recognized forms. The courses which it can take, with all too familiar outcomes, have been voluminously described over the last hundred years. Epidemiological studies have shown that the incidence, prevalence, and spontaneous cure rates have remained constant and relatively unchanged in various cultures throughout the world (Dunham, 1965). In addition, the disease process can be interrupted, ameliorated, or exacerbated by the application or removal of purely medical measures. As a consequence, both society and the law place responsibility for the treatment of this disease with the medical profession, and the diagnosis, therefore, can be legally established only by a physician.

For instance, in the *Newsletter* (1970) of the Nassau District Branch of the American Psychiatric Association, the Committee on Schizophrenia states: "The Committee accepts the basic premise that schizophrenia is a diagnosable disease whose origins are biological and whose lifetime process is based on the interaction of biological, psychological and social factors." Whether, at this particular time, the ultimate scientific medical basis for the illness can be demonstrated is irrelevant to the conclusion that, as a social fact, schizophrenia is a medical disease.

This model of schizophrenia presents a perspective considerably different from the interpersonal, psychoanalytic, social, or interfamilial models. The psychodynamic formulations of schizophrenia are so well known as to need no recapitulation but, in general, they take the form that faulty interpersonal relationships, emanating from a sick society, plus disturbed interfamilial or early infant-parent interaction, result in a variety of intrapsychic conflicts, arrested maturation, ego weakness, and ultimate regression. The result is symptom formation and behavioral impairment in emotional and social functioning.

From a purely theoretical viewpoint, the possibility of successful treatment based on the above psychodynamic model would appear to be extremely dim, as the task implied in treating even one case is herculean. Even if it were theoretically possible to achieve such a monumental task, the treatment would in practice be available to very few patients. From a public health and economic viewpoint, therefore, such formulations appear to be of little practical benefit to society. From the viewpoint of scientific clinical research, there is a scarcity of evidence that therapy based on this

model brings about any statistically recognizable amelioration of the disease—this will be discussed in greater detail later. Scientifically and medically, then, this model has not stood the therapeutic test, and the weight of scientific evidence at this time is against a purely psychodynamic etiology for schizophrenia. Family interaction studies and other formulations help to explain the particular manifestations of the illness in a given patient.

The medical model presupposes that the genetically determined biochemical defect results in interference with brain function on the molecular level in such a manner as to produce the subjective experiences and later the definable signs and symptoms of the disease. These abnormalities interfere with capacities for emotion, perception, and ultimately cognition, so that eventually the capacity to relate to other human beings is interfered with in a progressively noticeable fashion. This in turn leads to impaired functioning in every social area. The impaired interpersonal processes are therefore seen as the secondary consequences of the primary biochemical disease process. The expression of these secondary symptoms and, subsequently, the tertiary social repercussions is influenced by many factors, to be discussed later.

The fact that more schizophrenics are found at the bottom of the socio-economic ladder, in Hollingshead and Redlich's Class V (1958), for instance, is viewed as the tertiary result and not as an indication that socio-economic status is a primary cause of the illness. This view is supported by socio-cultural studies such as those of Goldberg and Morrison (1963) and Dunham (1968; Dunham et al., 1966), which showed a correlation between socio-economic class and schizophrenia that was independent of the socio-economic class of the parents. Schizophrenia is equally prevalent in families of all classes, but the impairment of schizophrenia works to the patient's disadvantage in the competitive job market (Dunham, 1971).

It is expensive and inefficient to try to treat schizophrenia by dealing primarily with the difficult social situations which the patients frequently present because of their functional impairment. That many social agencies unwittingly do just that was the discovery of the Youth Consultation Service when they began to screen all their clients with the HOD test.

When this agency began to experiment with the medical model, they discovered that they could double the effective output of their organization, because the previously unrecognized and undiagnosed illnesses of their clients were now being detected and adequately treated. As the patients clinically improved, the need for extensive social case-work services was greatly reduced (Hulse, 1970). As an analogy, they felt that they had spent years treating clients' fevers instead of obtaining definite medical treatment for their unrecognized infections.

Following the medical model, we try to correct or compensate for a basic medical defect, and if the treatment method is correct the secondary signs and symptoms will disappear. Normal emotionality will then progressively return, the capacity to form interpersonal relationships will re-emerge, and social functioning will improve. This

sequence would be expected to occur to the degree that the successive stages of the illness are still reversible. In many patients, therefore, full recovery should occur with no treatment other than strictly medical help. If the illness has gone on for a period of time, however, additional help will be necessary to overcome secondary disability and to make up for lost learning opportunities. The deficit caused by loss of learning opportunities will obviously be most marked if the period of illness has occurred during a crucial growth phase. These principles are generally true in all of medicine, however, and are not specific to schizophrenia.

SCHIZOPHRENIA AS A PERCEPTUAL DISORDER

The medical model presents testable hypotheses that are suited to a pragmatic approach which utilizes diagnostic tools that can objectively measure the degree of the illness and the response to treatment. This procedure voids and circumvents the evaluative artifact of dissimulation.

Behavioral modifications, brought about in the patient by milieu therapy, operant conditioning, psychotherapeutic techniques, or cultural pressures, can bring about external behavioral improvement and modify verbal productions toward the normal range. Although these changes are considered valuable by society, they do not provide an adequate means by which to determine intrinsic changes of the disease process itself.

The Hoffer–Osmond Diagnostic Test (HOD) serves as a valuable tool to circumvent these learned behaviors, and, because it measures basic perceptual alterations, it detects fluctuations of the basic disease process itself.[1]

Clinical manifestations of schizophrenia vary widely from patient to patient in such ways that in subtle cases there is often considerable uncertainty and delay in making the diagnosis. However, there is one set of determinants which is demonstrable in every case and which fluctuates with the degree of the patient's illness, and that is the perceptual disorder. This perceptual disorder can be easily clinically detected by the HOD test as well as EWI (Experiential World Inventory).[2] The perceptual disorder can also be demonstrated even in a well patient if he takes the test retroactively, so that it is possible to surmise with reasonable accuracy his degree of prior illness. Any medical measure that reduces the HOD score alleviates the illness and any measure that increases the HOD score worsens it: the effectiveness of a therapeutic procedure can be monitored directly by the change in the patient's HOD score.

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[1] The HOD Test is available in the United States from Bell Therapeutic Supplies, Inc., 396 Rockaway Avenue, Valley Stream, New York 11581.

[2] The EWI Test is available in the United States from the Mens Sana Publishing Co., P.O. Box 2966, Grand Central Station, New York, New York 10017.

Evidence, both theoretical and clinical, demonstrating the basically perceptual disorder of schizophrenia is described by Kirk in Chapter 6 of this book. The perceptual disorder can be demonstrated experimentally by a variety of methods and probably the most commonly known general method is the electroencephalographic, in which average evoked responses show perceptual abnormalities (Inderbitzen et al., 1970) and the response of the electroencephalogram to a stimulus such as a flickering light reveals an active condition of the brain (Barnes and Gerson, 1970).

Perceptual impairment in schizophrenia has also been demonstrated and described by Weckowicz (1960), Arieti (1962), Kelm (1962), Beck (1964), and Bemporad (1967) and discussed by Hoffer (1961) and Hoffer and Osmond (1962, 1967b). Meldman (1970) classifies the schizophrenias as diseases of attention and perception. Holzman (1969) correlated the perceptual dysfunction of the schizophrenic disease process with proprioceptive feedback defects. Reiss and Elstein (1971) demonstrated the existence of perceptual defect in the families of schizophrenics, and this has also been described by McConaghy (1959), Lidz (1962), Rosman (1964), and Phillips (1965). Defective perception of the body parts and physical self-image in schizophrenia has been described by Bychowski (1943), Kolb (1959), Weckowitz (1960), Burton and Adkins (1961), Fisher and Seidner (1963), Arnhoff (1964), Cleveland (1960), Cleveland et al. (1962), and others. Perceptual distortions resulting in alteration of the patient's sexual self-image have been described by Fisher and Seidner (1963) and by Gittleson and Levine (1966), and Gittleson and Dawson (1967). Weiner (1970), in a review article on perceptual dysfunction in schizophrenia, lists 90 references in the literature on the subject, and the study by Reiss and Elstein (1971) lists an additional 91 references.

Of considerable clinical significance is an appreciation of the effects of interference with even visual perception. Interference in this function alters the patient's experience of the space-time continuum. Visual sensory input must pass through a succession of data-processing stages prior to passing through the gating mechanisms leading to the subjective visual experience. Correctly operating inhibiting mechanisms are necessary in the gating process. These mechanisms are controlled by excitatory-inhibitory interaction so as to prevent input-output mismatches that would otherwise result in visual distortions (Mayzner and Tresselt, 1970).

Distortions of inner perception result in a progressive build-up of misinformation in the memory bank. Visual perception produces the central representation of space that makes the internalization of a spatial problem and its solution possible. This critical phenomenon, according to Borenstein (1970), constitutes the root from which the faculty of thinking evolves and, according to Lorenz (1965), constitutes the "indispensable basis even for our most complex thought processes." Also, because the perceptual component of each sensory system is closely correlated with a tonic component on the same level of differentiation, body tonus as a whole is simultaneously affected.

Defective visual perception can also result in depersonalization, derealization, and loss of spatial identity of object, and it leads to altered psychic states with altered perceptions of the self and body parts. This was demonstrated by Kohler (1951), who found that visually distorting prism glasses led to altered experiencing of the sense of self, body parts, stability of the world of objects, and a feeling of the "uncanny." In the experiment, subjects experienced a loss of the meaning of objects and existential confusion as to whether their existence originated from within the mind or outside of it. This experience may be described as "loss of ego boundaries." Interestingly, the subjects adjusted to the prism glasses and learned to maneuver in what was actually a distorted world but then re-experienced the same symptoms when the prisms were removed. It was not only the perceptual distortions that caused the subjective symptoms, but the process of change itself.

The perceptual distortions in schizophrenia occur independently of their subjective meaning of the patient. Affectively loaded stimuli may also create distortions depending on their psychological significance to the patient. This latter type of distortion, however, has been demonstrated to be related to personality characteristics, and is not limited to schizophrenia.

The clinical effect of perceptual dysfunction in schizophrenia is further augmented by the patient's incapacity to maintain a segmental set (Shakow, 1962) and his disorder of selective attention (McGhie, 1966). Impairment of gating mechanism leads to the clinicial picture of sensory overload and confusion. This can be seen clinically in that when the patients' HOD scores are elevated, they will withdraw from crowds and groups because the sensory input is overwhelming. Conversely, as the HOD score goes down, patients re-enter group situations. This fluctuation will also affect the patient's preference for what Walker (1970) terms "stimulus complexity."

Of considerable help in the understanding of the profound effects which altered perceptions have on the human mind are the papers by Bernard Aaronson. Using post-hypnotic suggestion in normal hypnotic subjects, the experimenters were able to reproduce all of the various signs and symptoms of schizophrenia (Aaronson, 1968, 1971). The experiments included suggestions such as "the world will appear two-dimensional," which resulted in depression and flattening of affect. Alterations of time and space were induced, resulting in elation or dysphoria, catatonia or hypomania. Similarly, it was possible to produce paranoid reactions, schizoid behavior, proprioceptic changes with alterations of posture, speech, and gait, by suggestions of altered perception of depth, size, constancy, and time rates. Similar studies have been reported by Fogel and Hoffer (1962), who used a metronome to alter the test subject's time sense and thereby produced schizophreniform states. Yaker and Franzblau (1969) have correlated altered time perception with schizophrenic speech patterns.

The early stages of schizophrenia are associated with perceptual distortions and the resulting altered subjective experiences of the self and the world. The illness may remain mild and never progress beyond this stage. Illnesses of this degree have been

aptly termed "metabolic dysperception" by Kowalson (see Chapter 19). The HOD score is elevated above normal but has not reached the degree necessary to give the overt clinical picture of schizophrenia. Patients who develop overt schizophrenia usually cannot remember the subtle initial onset of the metabolic dysperception phase and date their illness from the appearance of the more impressive severe symptoms. Families usually do the same thing, but patients who have recovered will often date the onset to a major subjective inner change years before the eruption of the overt illness.

The stage of metabolic dysperception may remain as such for years, with fluctuations of intensity, often worsened by viral infections or fatigue. A sudden worsening may occur after a crash diet, or following the use of amphetamines for weight reduction, or following childbirth, use of LSD, mescaline, or "speed." These results are evidenced by a rapid rise of the already elevated HOD score and the appearance of overt clinical schizophrenia. When these patients take the HOD test retroactively, it will be seen that their scores were in the midrange of metabolic dysperception before the schizophrenic episode. These same patients will be described as "normal" by their families prior to the overt illness. What has happened is that the patients have previously compensated for their perceptual impairments of long standing and the families have grown accustomed to their styles and do not notice subtle variations from normal. It is only when the patient fully recovers and has a normal HOD score that the families realize that a mild degree of illness was present for a long time.

By use of the retroactive HOD test, we have been able to demonstrate, for instance, that patients with so-called "LSD psychoses" actually suffered from metabolic dysperception before taking the LSD. This conclusion is based on our experience with hundreds of LSD-precipitated schizophrenias in which we have found that latent schizophrenia was previously present but unsuspected. We have, therefore, come to doubt that there is such an entity as an LSD psychosis, over and beyond the so-called "bad trip" itself. Reports of LSD psychosis in apparently normal individuals have not included tests such as the retroactive HOD or EWI that would have demonstrated the presence or absence of a pre-existent perceptual disorder. The LSD trip which preceded the illness in many cases was a "good trip" —the patient just never "came down."

LSD, in the usual 100 to 250 μg dose, produces a HOD score in the vicinity of 125, but the score returns to normal in the biochemically normal individual within 24 hours (Hoffer and Osmond, 1967a,b). When a patient with metabolic dysperception, who already has an elevated HOD score, takes LSD, the HOD score rises even higher. Often the patient will try to "cure" the now greatly increased perceptual distortions by another or even several more LSD trips. After each LSD experience, however, he becomes sicker as the HOD score goes even higher. Finally, he "freaks out" and his illness is labeled another "LSD Psychosis."

Patients who have mildly elevated HOD scores, even though they appear clinically

normal, can also be detected in a certain percentage of cases by the Malvaria Test (see chapter 8 by Irvine). Malvarians react badly to LSD and the presence of untreated Malvaria or an elevated HOD score is a contraindication to LSD therapy (Hoffer and Osmond, 1968). When patients who have taken LSD complain of "flashbacks," the HOD test reveals that they have elevated scores and recurrences are blocked by treatment which brings the score down to normal. In every single case of post-LSD reaction that we have observed, the HOD score was elevated. An LSD psychosis, then, appears to be a persistent worsening of a previously undiagnosed perceptual disorder.

Similarly, we have not seen schizophrenia caused by the use of marijuana—the converse is frequently seen, however, in that marijuana is used to help alleviate the symptoms of a developing schizophrenic process. Although there are reports in the literature implicating marijuana in the precipitation of schizophrenia, such as those of Keeler (1967) and Milman (1969), in similar cases that we have seen the HOD test has revealed that the schizophrenic process was already present. If the HOD score rises, however, pot smoking may become increasingly unpleasant, as it may intensify existing paranoia. Its use by other patients, however, allows them to continue functioning at least temporarily and delays the overt expression of the illness.

In the true amphetamine psychoses the retroactive HOD score is normal; in amphetamine-induced schizophrenia, which is more commonly seen, the retroactive HOD score is elevated.

Metabolic dysperception, then, is a very useful clinical concept and correctly typifies many patients who have "latent" or so-called "borderline schizophrenia." If the illness is detected and the perceptual disorder is treated at this stage, an overt schizophrenic illness will not occur later. This is an important concept in counselling patients to avoid those stresses known to commonly precipitate sudden elevations of the HOD score. Prophylactically, it has allowed us to prevent postpartum psychoses in our patients. Use of the concept makes it possible to counsel young drug users on an acceptable, scientific, and honest basis.

In attempting to diagnose schizophrenia in its early stages and mild forms, it is the detection of "metabolic dysperception" symptoms, their subtle manifestations, and the mild to moderately elevated HOD and EWI scores that is of crucial importance. The illness of these patients may also be detected by specialized urine tests (see chapter on Kryptopyrrole and Pink Spot). At this degree of the illness there are no gross changes of appearance or behavior and, therefore, it appears to be a grossly misleading direction of clinical thought to conceive of schizophrenia as merely abnormal behavior. Such a concept fails to take into account that behavioral changes are not observable until the illness or its symptoms are so advanced that they are no longer controllable.

Laing (1967), for instance, states that "schizophrenia is a label affixed by some

people to others in situations where an interpersonal dysjunction of a particular kind is occurring." This statement reifies a whole complex process under the concrete noun "label" (although "tuberculosis" is linguistically also a label it is far more than *just* a label). More importantly, however, it fails to include the crucial clinical observation that "interpersonal dysjunction" is the unfortunate by-product of an illness which usually began long before the dysjunction finally occurred. A tuberculous process, for example, has been going on for some time before a vertebral collapse takes place, so that tuberculosis is not just a label we affix to spinal "collapses."

Many misconceptions may have arisen because Laing and others have examined *disturbed* schizophrenics whose *disturbances* were caused by a *disturbed* family. Environmental disturbance can cause visible disturbance in schizophrenic patients, but it does not cause the schizophrenia itself: schizophrenia makes patients more vulnerable to disturbance. Similarly, the duality that typifies occidental thinking in our "mad world" may be too complex for a perceptually impaired patient to handle conceptually—he cannot handle multiple levels of abstraction.

When patients with a rising HOD score try to continue functioning in a situation that requires a high degree of efficiency and organization they will usually complain of fatigue, as the energy required under the circumstances is considerable. When failure to function finally occurs, depression or panic may lead them to seek help. This is the point at which it is of paramount importance to establish the true diagnosis and not wait for a suicide attempt or the eruption of a psychosis to establish that there is a schizophrenic process.

In summary, although there are many variables by which degrees of illness can be surmised in schizophrenia, perceptual malfunctioning, because it appears early and is easily detected, is the most valuable. It provides an objective monitoring device and correlates directly with degrees of improvement or worsening. Because perception is chemically mediated, it offers a direct measure of the effectiveness of chemical means of treatment. Other manifestations of the illness are far less reliable, as they depend on the variable clinical expressions of the illness.

CLINICAL EXPRESSION OF SCHIZOPHRENIA

The degree to which schizophrenia becomes overt is determined not only by the patient's genetic predisposition and subsequent biochemical events but also by age, rapidity of onset, the personality of the patient, and the setting in which the patient finds himself as the illness begins and progresses. The clinical characteristics of the illness in a given patient are also modified by what is said to the patient about his illness and what is done about it, so that there are certain parallels with the

psychedelic experience: the patient's set, the setting, and the persons who explain to him what is happening have an influence on what he experiences.

The disease process itself, then, is independent of the patient's personality and psychological type—the illness may occur in aggressive, extroverted, successful sales executives, or it may occur in the classical shy, inadequate, passive, introverted schizoid—but the response of these two opposite kinds of personalities to the disease process will be quite different. The degree of maturity and the number of strengths and other assets that the patient has will then determine to some degree at what point in the illness he becomes incapacitated. This is true, however, of many other illnesses and is not specific to schizophrenia.

In addition to the specifics of the disease process of schizophrenia itself, there are also present the nonspecific responses to stress that are associated with Selye's general adaption syndrome. Disturbed family patterns as well as neurotic processes within the individual patient also influence, to a considerable degree, not only the clinical picture that presents itself, but also the patient's treatability and prognosis. The appearance of the illness is further influenced by the cultural background of patient and family and by the current attitudes prevalent in society toward a poorly understood disabling illness and its manifestations.

From all the foregoing factors, it is apparent that the external appearance of the illness will vary considerably from patient to patient. Under very favorable conditions, it is possible for a patient to have a relatively severe case of schizophrenia as manifested by a markedly elevated HOD score and extensive perceptual distortions, with little suffering, minimal impairment of functioning, and only mild economic and social consequences. Under adverse conditions, on the other hand, even a mild degree of schizophrenia can result in major incapacitation, severe suffering, family disruption, and grave social and economic consequences.

It may be helpful to give illustrations of these two widely divergent clinical pictures of the illness, although it is obvious that the average case falls somewhere in between the two.

Case No. 1

Miss C. Y. was a 23-year-old teacher who was working toward a master's degree. She was a pleasant, well-liked person with many friends and an active social life.

Her sister noticed that she had recently become moody, withdrawn, and depressed. She advised her to consult a psychiatrist who had been quite helpful to a mutual friend. The sister told her that she had heard that schizophrenia could come on in this manner, and that it was a chemical problem that could easily be detected and treated. Miss C. Y. then called for a consultation to find out whether she was developing schizophrenia.

When interviewed, the patient related well and was also intelligent and sophisticated. She felt depressed and indicated that she had also become worried because she had noticed a number of changes in the way the world appeared. She had already reported these phenomena to some friends who had taken psychedelics and they apparently thought that these experiences were similar. As an example, she stated that she could see the pattern of an oriental rug hovering in the air about a foot off the carpet. The design, while suspended in midair, rippled and had an altogether pleasing effect. Although they were enjoyable, she knew that these were not normal phenomena and she wondered if perhaps they did not indicate that she was indeed developing schizophrenia, which she had heard was "sort of like tripping without having to take LSD."

The HOD test score was 117, and revealed widespread, pervasive, and severe disorganization in every perceptual modality. The patient was informed about the nature of her illness and its probable biochemical causes, and the rationale of the therapeutic regimen were explained to her. She was given literature explaining the illness and was placed on megavitamins, a hypoglycemic diet, and low dosages of phenothiazines.

The patient was then seen monthly. Her HOD score came down progressively and her symptoms spontaneously diminished. Her fiance accepted the explanation that she had "some kind of a chemical problem" for which she had to take a lot of vitamins and could not eat sugar. Seven months after she had started treatment, her HOD score had come down from 117 to 15. At that time, she felt that she had problems that she now wanted to discuss in psychotherapy.

COMMENT

This patient had many obvious assets. Her sophistication, psychedelic orientation, and early introduction to the concept that the basis of her illness was biochemical helped both the patient and her family to respond well to a biochemical explanation of her symptoms. The patient's and her family's expectations of her performance were reduced because the explanation was based on the medical model—the patient was allowed to be ill until she got better. Psychotherapy was deferred until the patient's HOD score was within the normal range. Because of the utilization of the medical model there was no resistance to taking medication. The patient performed as well as she could until her HOD score came down and she actually lost very little time from work because of the illness.

Case No. 2

A 23-year-old college student applied for treatment at the student health center. His behavior had become increasingly gauche and inappropriate so that he had met with

severe rejection from his dormitory mates and had been labeled as crazy by several people. He had sought help surreptitiously because his parents would have condemned his consulting a psychiatrist. The patient's grades had been falling and his parents had been berating him and applying increasing pressure to improve his poor performance.

At the Student Health Center, the psychiatrist's response to the patient's inquiry as to "what was the matter" with him was that it would take a great many hours of probing and, therefore, only he, the patient, could supply the answer to that question. During one of the sessions the therapist connected the patient's lack of heterosexual success with his fears of homosexuality which had emerged as his performance declined and which were reinforced by his lack of heterosexual success. The patient now developed insomnia and severe anxiety and requested medication. His requests for medication were not met but instead were explained to him as wishes for magic and dependency that he wished the therapist to fulfil. Several subsequent dreams were also interpreted as wishes to be mothered by being given medication. At this point, the patient became severely depressed and made a suicide attempt.

In the hospital the patient related poorly to the psychiatrist. The combination of shame and anger was so severe as to make him almost unapproachable. The family response to the whole situation was quite negative and they removed him from the hospital against medical advice. The father insisted, upon his return home, that he "get a job and snap out of it." At this point, the patient became so disturbed that he was finally admitted to a teaching hospital.

In this hospital he received psychotherapy three times weekly, chlorpromazine was continued, and the family was also involved in weekly family therapy. The patient was discharged 18 months later, relatively unimproved, having reached maximum hospital benefit. He was then withdrawn and apathetic. At this point, neither the patient nor his family were aware of the diagnosis. His reluctance to find a job was interpreted by the therapist as a desire to remain a cared-for infant, an avoidance of adult responsibility, and fear of competition with other males. A variety of other complicated interpretations placed the ultimate blame for these failings on his parents.

By the time the patient was finally referred for an orthomolecular treatment approach at this clinic, both he and the family were totally demoralized. His HOD score currently was only 38 and retroactively it was 58. He had severe functional hypoglycemia on laboratory testing with a drop of 50 points from the fasting blood sugar level. Despite the basically mild degree of schizophrenia his treatment was slow and it was also made difficult by his conviction that it was "all psychological." He was very resistant about diet and taking medication and he was quite difficult to manage clinically.

COMMENT

The severe disturbance of the patient, who intrinsically was only moderately ill, was obviously the result of lack of education, poor timing of psychotherapy, and bad preparation of both patient and family. Medication was withheld when it could have been extremely helpful. There was a failure to diagnose the hypoglycemia, which contributed markedly to his apathy and depression. The parents' denial was reinforced by not allowing the patient the sick role. Because he was not "legitimately" ill there was no relinquishment of expectations of performance—this further increased his shame, depression, and rage. No encouraging prognosis was given and the patient was burdened with an unbearable moral responsibility as well as alienated from his supposedly pathogenic family. The set and the setting were bad to begin with and they were worsened by subsequent experiences.

The patient did not have the benefit of either a diagnosis or an explanation of his illness. His perceptual impairment was not detected—no allowances were made for the fact that his perceptions of self, time, and space were altered. At no time did he have the feeling that he was being understood or helped. During long-term intensive psychotherapy he became progressively more demoralized so that eventually he became disabled in every area of life. In addition to the alienation from his family, it was recommended at the time of discharge from the hospital that he live away from his parents. He was obviously much too frightened by his degree of disability to attempt it and this had been unfortunately interpreted by the social worker as "resistance."

These two contrasting cases demonstrate that it is essential to differentiate those elements which are due to the schizophrenic process itself from those which are reactive on the part of the patient and family. The first patient, although a healthier personality, was medically much sicker with a far more severe degree of perceptual disorganization. The second patient, while basically only moderately ill, was far more disturbed.

DIAGNOSTIC PROCEDURES

The Interview

From the foregoing discussions, it can be seen that neither disturbed behavior, personality type, decline in performance, failure in social activity, nor the presence of a variety of psychiatric symptoms are diagnostic of schizophrenia as such. In the social area, a great many things can account for poor performance. Disturbed behavior can be either provoked or reactive. Psychiatric symptoms such as phobias,

anxiety, and depression can exist in a variety of psychiatric disorders, and schizophrenia may exist without any of the foregoing. The schizophrenic process begins long before the appearance of the classic signs of autism, inappropriate affect, discernible cognitive disorder, hallucinations, or delusions, all of which are characteristic of a relatively advanced and severe degree of the illness. The clinical signs as described by Bleuler or the clinical types as described by Kraeplin both represent, in this view, advanced stages or degrees of the illness and are secondary effects.

Earlier diagnosis is facilitated by diagnostic awareness of subtle subjective alterations in inner states and perceptual processes. These perceptual alterations may result in subtle alterations in performance in areas which are not usually clinically investigated. Sensitivity to these areas on the part of the observer facilitates early diagnosis long before the illness progresses to the more classic and blatant stages.

Mild forms of the illness are far more common than overt forms and frequently are present in patients who seek help for a variety of other presenting problems. Subtle paranoia and altered perceptions of self, for instance, commonly result in marital problems. Unpleasant feeling states may result in excessive drinking or drug usage. HOD testing of freshman college student dropouts reveals that a high percentage have metabolic dysperception. Poor performance and behavioral disturbances in school children may be due to the same disorder. This has been described by Green (1970, 1971), who has devised a perceptual dysfunction test for this treatable disease, which he terms "sub-clinical pellagra."

Many volumes have been written on interviewing techniques that are designed to elucidate a psychodynamic formulation and initiate a relationship between the patient and the therapist that will be based exclusively on a psychotherapeutic treatment. There are also interviewing procedures that are based on the formal mental status examination. In searching for a perceptual illness, however, the attention of the interviewer is directed toward the detection of perceptual alterations which may be subtle and beyond the awareness of the patient.

The waiting room appearance and behavior of the patient and family at the office may amplify diagnostic impressions which were given during the telephone interview. Because of altered perceptions of time and space, there may have been errors in travel, and times of appearance may vary considerably from the expected. Subtle inappropriateness of responses, and minor degrees of suspiciousness may be made apparent by unrealistic expectations and mode of behavior. Because of altered time perception, a few minutes wait may seem like an extremely long time to the patient, so that there may be complaints about what in reality are very brief delays. Confusion and difficulty in identifying persons may take the form of overqualification of all personnel. Spatial confusion often becomes apparent in the manner in which the patient tries to orient himself to the waiting room and details of the office lay-out. He may be unable to follow a verbal description of how to get to the rest room, so that often he has to be shown how to navigate the short distance, and may then be unable

to find his way back to the waiting room. At this time, there may be other expressions of discomfort caused by the waiting room's physical arrangements, indicative of altered space perception.

Many patients and their families are already aware of the diagnosis, or may have correctly surmised it. In cases where the diagnosis is obvious and the patient and family are quite sophisticated, diagnostic tests may have already been completed. When the situation is not so clear-cut and the patient is a relatively unknown entity, it is usually better to schedule the interview after the diagnostic testing. In our own clinic, many of the patients have had diagnostic tests done elsewhere, and they may have already taken the HOD test at an SA meeting. Frequently, after confirmation of the diagnosis, there is only diagnostic laboratory work to be done.

Where the diagnosis is known or testing has been completed, the interviewer is usually concerned primarily with interpretation of results and treatment. Surprisingly, alterations in perceptual functioning are rarely volunteered by patients even though these subjective experiences can be quite extensive. It is common experience for the patient to have had years of psychotherapy without ever mentioning these perceptual alterations. This may occur for several reasons. One is that the interviews have been focused on historical or interpersonal material or transference phenomena, so that the patient in trying to work along with the therapist has ignored this entire area. Another reason is that our language does not lend itself to descriptions of subtle alterations of psychic states. Consequently, meditative groups and the psychedelic drug culture have had either to invent new language or to borrow from Eastern religions and philosophic systems those terms which most closely approximate certain altered states.

Schizophrenic patients will often use similar language or they will respond readily to questions from an interviewer who uses such terms. As examples, the patient will either communicate in or respond to such terms as the following: "I feel spaced . . . out of it . . . speeded up . . . high . . . down." The interviewer will not elicit some of these states if terms that are more appropriate to neurotic subjective states are used. If, for instance, the patient is asked whether he feels depressed, he may answer "yes." The interviewer then writes down on the patient's chart that "the patient is depressed" when in actuality, the schizophrenic patient usually feels something quite different from what the word "depressed" means to the nonschizophrenic. It may mean that he feels confused, or blocked, or disconnected, or dead, or not with it, or out of it, or slowed down. Many patients have developed a certain hopelessness about trying to communicate these altered psychic states and will not attempt to do so. They will discuss them spontaneously with other patients in Schizophrenics Anonymous, for instance, or with members of the drug subculture, who can understand what their terms mean.

Because the patient is given the HOD or EWI test, it is not necessary to go down a whole long list of perceptual distortions. These tests will serve the same purpose

and frequently the interviewer can quickly grasp that perceptual distortions are present, from some rather common symptoms. An avoidance of groups or crowds and withdrawal are clues to perceptual distortions and an inability to sort out multiple incoming stimuli. Impaired sexual behavior may result from impaired perception of self, so that the patient does not know literally who he is and does not really experience gender. Many patients will stop driving a car or develop a fear of driving since they can no longer depend on their reflexes because of impaired experiencing of time and space and object relationships.

A general questioning about how the patient perceives time and space and the body parts, the way he feels the world, and sensory changes often immediately brings forth a description of multiple perceptual distortions. Patients are frankly pleased to be able to relate any of these changes to someone who is interested in them. These subjective experiences will not be elicited by a line of questioning that is designed to develop a psychodynamic history and, therefore, they are frequently missed in the more traditional psychiatric interview.

Although progressive failure in functioning may alert the interviewer to the presence of schizophrenia, this pattern may merely result from being ill and it is not diagnostic of schizophrenia per se. Other behavior patterns commonly associated with schizophrenia should alert the interviewer to search for the perceptual distortions which account for these characteristics. It sometimes happens that the patient's neurotic pattern and his psychodynamic correlations so impress the interviewer that the perceptual disorder is missed. This occurs most frequently where the patient has had previous psychotherapy and has a preconceived notion of what would be interesting to the therapist. Being impressed by the psychodynamics and failing to detect the more serious underlying condition happens to the most astute interviewers and, therefore, the possibility of this human error should be eliminated by giving *every patient* objective tests to determine if a schizophrenic disorder exists.

Although the following example may seem extreme, it is actually not unusual. It demonstrates the basic principle that the interview must be backed up by the use of more accurate tools.

> A family consulted a counselling agency about their son, who had developed a progressively incapacitating school phobia. The young patient was then referred for diagnostic evaluation with a well-qualified consultant who recommended, on the basis of a diagnosis of a behavior disorder, intensive psychotherapy for the patient and case work with the family. Despite case work with the family and psychotherapy (three times per week), the patient did not improve. After two-and-a-half years of unsuccessful treatment, during which time volumes of historical material had been compiled, the case was presented at a psychiatric staff conference at a leading teaching hospital. The dynamics were discussed in detail in the presence of 58 psychiatrists, and although schizophrenia was considered in the differential diagnosis, it was discarded as the patient "had never been psychotic" and continuance of treatment was recommended.

Disillusionment with progress in the case finally led to the patient's being referred for orthomolecular evaluation. The HOD test revealed that he had a score of 58. The patient was consequently placed on a medical regimen for the perceptual disorder and it was recommended that psychotherapy be discontinued until the patient's HOD was normal. Within a few months the patient's symptoms disappeared, normal functioning returned, and he did not need to resume psychotherapy.

Psychotherapy or psychoanalysis as a treatment modality has much less prestige than it once had and patients in increasing numbers are seeking solutions to their problems through a variety of alternate treatment modalities that are now available. Because of this pattern, it is increasingly important to rule out the presence of a schizophrenic process.

As is well known, the diagnosis is more likely to be missed if the patient is young, verbal, educated, attractive, and economically comfortable, or is the relative of a friend or has some other status in the estimation of the interviewer. The likelihood of the diagnosis being made also depends on the attitude of the interviewer toward schizophrenia as an illness; if the interviewer is afraid of the diagnosis or views schizophrenia as untreatable, with a poor prognosis, and so on, there is less likelihood that he will detect the illness than if he feels that it is an illness, which, like any other, can be readily diagnosed and treated.

There are two other conditions in which the diagnosis is likely to be missed: when schizophrenia is associated with either alcoholism or drug use. When the patient is alcoholic, the diagnosis of schizophrenia is often missed because the entire clinical picture is so strongly overpowered by the drinking problem and the crisis that it creates. Because schizophrenia may be present in 10 to 30 percent of alcoholics applying for treatment in a psychiatric center (Hoffer, 1968) the presence of concomitant schizophrenia must be ruled out. The young alcoholic patient who may have well-developed alcoholism in his teens or twenties frequently also has concomitant schizophrenia. The alcoholic who has tried AA for many years without success will often demonstrate by a very elevated HOD score (during periods of sobriety) that the unrecognized perceptual disorder has contributed to his clinical problem.

Schizophrenia in young people who have gotten into difficulty because of drugs is very common. In a recent study done at Bellevue Hospital, 50 percent of the young drug users were schizophrenic (Hekimian and Gershon, 1968). Without the use of the restrospective HOD Test, it is usually impossible to ascertain whether the schizophrenia preceded the drug usage or not. Characteristic of these patients is a pattern of "garbage style" drug taking in which they will inject or ingest almost any type of drug available, no matter how deleterious the consequences or risky the situation. Nonschizophrenic members of the drug subculture, the so-called "heads," usually prefer just one type of drug and except for occasional experimentation will constantly use the same type of drug—there is also a concordance between the preferred drug and the life style.

There is another pattern of drug usage which is typical of schizophrenics, however, in which the patient does stick to the same drug, and that is smoking marijuana so excessively that he is under its influence most of the time. This pattern is usually associated with a type of schizophrenia in which the predominant subjective experience is one of altered time and space, so that the patient feels as though he is living in a different dimension from others and is unable to relate to them unless he is under the influence of marijuana. This has also been described by Cott (1969), and we have been able to detect it also by using the electronic metronome. When the patient is not under the influence of marijuana he experiences alienation and dysphoria, since he feels himself to exist in a different space-time continuum from other people. With the electronic metronome, it is possible to demonstrate that the patient experiences time flowing through his mind, his body, and the world around him at different rates—he is "fractured in time" and cannot "vibrate" emotionally with others. Under the influence of marijuana, however, these three time-flows coincide. He now feels synchronized in the same time-space continuum as others around him and he can now converse and emotionally relate with them. Failure to recognize the underlying schizophrenia in these cases obviously dooms to failure attempts to treat this type of drug problem—few people can tolerate the solitary confinement of feeling totally isolated from others in this world.

Noteworthy in this connection is the effect of the beat of rock music on alleviating depressive feelings. We have noted that young patients with depressive trends tend to spend considerable time listening to rock music with the volume turned up high. With the metronome it is possible to time various musical beats, and we found that most rock music averages between 120 and 200 beats per minute. A high-intensity sensory input at this rate will alleviate depression in most patients. This depression-alleviating effect is increased if the sensory input is also simultaneously visual or tactile, as in mixed-media environments in which stroboscopes or light organs are synchronized with the beat. As a consequence, we have done some experimentation utilizing mixed media therapeutically.

These observations clarify the strong attraction that the psychedelic drug culture has for young schizophrenics. It is a world of altered perceptual styles in which individual variations from normal pass unnoticed. The language used by adherents to the drug culture to describe their inner states is understandable to the patient who has had similar experiences without taking drugs. There is a cessation of expectations of performance. Marijuana alleviates the alteration and fracture-in-time dysphoria. The mixed-media fast-tempo high-intensity beat relieves depression. Prolonged, responsible, one-to-one relationships are not required. Paranoia is accepted, as are other variations in mental functioning, which are readily attributed to drug usage. There is, therefore, a protective merging of life style where perceptual dysfunction blends with the subculture.

Interviewing young schizophrenic drug users is facilitated by focusing on delinea-

tion of their experiential world. Although generally defensive and noncommunicative, these patients will readily communicate if the interviewer is primarily interested in their altered states of consciousness and changes in their perceptual worlds. The lyrics of rock music are extremely helpful as a guide to such states, as, emanating from the psychedelic-drug subculture, they describe perceptual experiences and subjective altered states of awareness for which no words exist in psychiatric terminology. The young member of the drug culture is usually willing to reveal "where I'm at," that he is "far out," or "what's happening in my head," or "the changes that I have been going through." Familiarity with this subculture is of obvious benefit to the interviewer, as conventional interviewing techniques usually fail to elicit much meaningful information from its members.

Often these patients are extremely aware of the profound changes that result from altering body levels of certain substances. Perhaps sensitized by the psychedelic experience, they are subjectively aware of alterations produced by such a simple measure as change of diet. Because this is such a well verified, universal experience in their subculture, it is a foregone conclusion to them that "you are what you eat." Bad drug reactions, for instance, are routinely treated by raising the blood sugar level with honey and gulping a few grams of niacin. This is, in fact, a routine procedure of the LSD Rescue Service sponsored by Naturalism (Peters, 1970), which has also demonstrated the necessity of controlling sensory input under conditions of altered perceptions. As a group, members of the psychedelic subculture reject most contemporary psychiatric approaches as being naïve and lacking in awareness of basic principles that to them have already become everyday knowledge. Many of their valuable clinical observations have been too readily dismissed as being due merely to suggestion or as exotic subcultural primitive beliefs.

The majority of patients that we see with schizophrenia are not overtly psychotic. Although schizophrenia is technically classified as a psychosis, the development of irrationality indicates an advanced degree or stage of the illness. We, therefore, view schizophrenia as *a disease process which is capable of producing psychosis.* Irrationality does not usually occur unless: (1) the HOD score is markedly elevated; (2) the patient has been ill for a considerable length of time; (3) altered cognitive styles are characteristic of the patient's family; or (4) the patient has been deliberately misled about the true nature of his illness. Some schizophrenic patients show a greater effect of the illness on their thinking processes than others. For example, it is possible for two patients to have the same HOD score, but for one to show, on the subscales of the HOD test, much greater interference with thought processes than the other.

This greater interference may represent a different genetic type of illness, or it may be that certain types of personality are more vulnerable to interference with thought processes, not only by the disease process of schizophrenia, but also by other factors that interfere with brain function. For instance, only a certain percentage of people

will develop interference with thought processes at a given blood level of bromide. Although the percentage of persons whose thinking will be affected will increase as the bromide level increases, there are always some who are more vulnerable than others. This is observed in other clinical states such as interference with brain oxygenation, intoxication by a variety of substances, and decreases in blood sugar level.

Another observation of interest is that mild degrees of the thought disorder, but no other evidence of schizophrenia, may be found in the relatives of patients. This correlates with the genetic transmission of schizoid disease as described by Dr. Heston (see Chapter 2 of this book) and also with recent work by Wender et al. (1971) showing a higher than normal incidence of cognitive disorders in the relatives of schizophrenics. In the discussion of schizophrenia as a perceptual disorder, evidence was cited from a variety of sources that a thought disorder can result directly from the perceptual distortions themselves. However, we have HOD-tested a number of parents of schizophrenics and found that aside from the thought disorder there were no perceptual distortions. This presents the possibility that the thought disorder may be an associated but independent variable.

Frequently a patient will have a considerable degree of schizophrenia without having an impairment of thought process that is readily discernible during an interview. It is also observable that much irrationality tends to disappear when the patient is given a biochemical explanation of his experiences. The mere process of taking the HOD test has an educational effect and most patients feel that they have developed a good deal of insight into their experiences as a consequence of taking the test—this in itself tends to increase rationality and insight. Sophisticated patients may recognize irrational thought processes, especially those of a paranoid nature, and label them as "paranoia." This tends to occur in young patients exposed to the psychedelic drug culture, who as a group are relatively sophisticated about paranoia as such. Instead of being paranoid, psychotic, and delusional, these patients tend instead merely to complain that they are bothered by paranoid perceptual events or thoughts, with an awareness that the interference originates within their own minds and not elsewhere.

Our observations, then, are that psychosis and irrationality are not in themselves necessarily connected with schizophrenia, but that they are an effect of the disease process in certain vulnerable individuals. When brain function is progressively impaired in these vulnerable patients, they begin to display the thought patterns traditionally associated with schizophrenia as originally described by Bleuler and more recently by Arieti (1962). Regression to more primitive forms of thinking is also demonstrated by the Organic Integrity Test (Tien, 1960, 1968). Deranged thought patterns, when they are present, may correlate with the diagnostic impression of schizophrenia, but their absence does not exclude it, and the same can be said for the presence of hallucinations or delusions.

Irrationality and paranoid delusions can exist without the patient being schizo-

phrenic. Absence of a perceptual disorder clarified the diagnosis in the following unusual case.

> The patient was an intelligent 23-year-old young woman who had taken a job in a small town where she was a stranger and shared an apartment with an older roommate. The roommate, a paranoid schizophrenic, had developed a progressive paranoid delusional system. The delusional system involved the CIA and the roommate pointed out to the patient, in progressive degrees, telltale signs of intrusions into their privacy, chance remarks, phone callers that hung up, and so on.
>
> The patient, although at first skeptical, became progressively more fascinated by the details, and finally began to elaborate some of her own. In conspiratorial fashion, the plot thickened as the patient played detective and fitted additional pieces of evidence into the growing shared delusional system. Finally the patient reached the conclusion that the CIA was indeed now after her also. Because they were unable to talk her out of her paranoid beliefs, her friends finally persuaded her to consult a psychiatrist.
>
> When interviewed, the patient presented a fairly well structured paranoid delusional system. The patient, in fact, was certain that the CIA was electronically monitoring the interview. From the interview material, it was not at all clear whether the patient had developed paranoid schizophrenia and the former roommate had developed a folie-a-deux or vice versa. It seemed possible even that both of them were paranoid schizophrenics that chance had brought together.
>
> The diagnosis was clarified when the patient was given the HOD and other tests for perceptual dysfunction—her HOD test score was only 10. The folie-a-deux cleared up in a short time. She read in Lindner's *The Fifty Minute Hour* the classic case of the "Jet Propelled Couch" and then felt much better—if it could happen to a psychoanalyst it could happen to her!

When the patient is too ill to come to the office and a member of his family is interviewed instead, the family member's complaints are usually about the tertiary effects of the illness on the patient's performance or capacity to relate to others. When a patient's HOD score is high, he frequently becomes quite hostile to those who are close to him. Because his filtering mechanisms are defective, the patient is easily overwhelmed by the proximity of emotionally significant figures. Often the mere presence of the parent is intolerable to the patient, leading to his withdrawal or explosive emotionality. The family members usually then react in an emotionally disturbed way to the presence of the ill person. Recent research indicates that the adoptive parents of schizophrenic children show somewhat more emotional disturbance, primarily of a reactive nature, than do the adoptive parents of normal children (Wender et al., 1971).

Although families are seldom aware of the inner experiential, perceptually distorted world of the schizophrenic patient, they may have made helpful observations of the effects of the perceptual disorder. Most irritating to the family are the effects of the patient's altered time sense, so that they may be exasperated by the length of time it takes the patient to perform simple functions, and family battles may occur

because of the departure of the patient from the family's time schedule. The family may also report that the patient misidentifies people and places or that he has complained of the way food tastes, or has experienced paranoid thought and attitudes leading to guardedness and suspicion. Probably the most commonly reported symptom is that the patient is constantly fatigued and lacking in energy, which may cause him to sleep excessively. Families who are familiar with the perceptual hypothesis or who have read the questions on the HOD test may be considerably more observant than others, and may spontaneously report a great variety of perceptual distortions by the patient.

Diagnostic Tests

THE HOFFER–OSMOND DIAGNOSTIC TEST (HOD)

For routine use, the HOD test, which is described in Chapter 16, is the most useful tool, not only to confirm the diagnosis, but also to determine the degree of illness and to monitor the response to treatment. Beneficial measures are followed by a reduction of the HOD score and deleterious measures or an increase in the illness are followed by an increase in the HOD score. It can be administered and scored by anyone in the office. In practice, when the score is high, we usually are interested mainly in the total score. If the score is lower but still above normal, then the quality of the questions which have been answered "true" becomes of increasing significance. Thus, a chronic patient who has had considerable treatment may show a relatively low score, yet the specific questions answered as "true" may all indicate residual paranoid trends.

We administer the test, utilizing the HOD card box, and we record the "true" answers on a check list which includes all 145 questions in the test. This is useful, as the configuration of subtest scores has both diagnostic and prognostic implications. For example, a sick patient with a low HOD score, whose perceptual distortions are primarily visual, is usually a grown-up childhood schizophrenic, and his response to an overall biochemical approach is much less than that of the more usual patient who demonstrates a high HOD score with perceptual distortions distributed throughout the test's subgroups.

Some allowance has to be made in interpreting results for the effect of prior treatment. Shock treatment, for instance, brings the most rapid reduction in the HOD score. The phenothiazines will also lower the score considerably, but usually not to within the normal range. A patient can take the test retroactively; that is, he can answer the questions according to how he felt when most ill or at any specified time in the past. A typical patient who, although better, is still not well and therefore is seeking treatment, may have a HOD score of 70. Retroactively, ten months before

when he was in the hospital, his score was 135. The fact that he has been on heavy chlorpromazine medication since that time demonstrates that the effect of the phenothiazine has been to reduce his score by 65 points. The HOD score may remain at this plateau of 70 for an indefinite period with minor fluctuations until something else is added to this treatment regimen to bring it down further.

Recent exposure to psychedelic drugs will give a higher score; recent drinking by alcoholics will give a false elevation; and the score will be elevated if an organic or toxic brain syndrome is present. False negative HOD test results occur rarely: we have seen them only in some severely ill patients who utilized massive denial, but in such cases the disparity with the clinical picture is obvious, and as the patient gets better there may be a paradoxical rise in the HOD score as the patient now answers the questions more truthfully. False negatives may occur if the test is given under threatening or coercive circumstances, but these do not occur in clinical practice. Patients are surprisingly truthful when questions are directed to their experiential world and will frequently reveal what they have previously hidden in an interview.

An important reason for this phenomenon is that during an interview there is a lack of adequate language to ask the correct questions. It is rather routine, for example, to question patients about the occurrence of hallucinations, but almost never is a patient questioned about *degrees* of hallucinatory phenomena. The HOD test, however, asks such questions as "I often hear my own thoughts," "I often hear my own thoughts as clearly as though they were a voice," "I often hear my thoughts inside my head," "I often hear my thoughts outside my head," "I often hear voices talking to me," "People talk about me behind my back." Thus, in an interview, a patient may disclaim hallucinations, but the HOD test will reveal that he "hears his thoughts outside of his head." Serial retesting will reveal that with a worsening of the condition, the true answers progress from "hearing one's thoughts," to "being talked about behind one's back," and improvement will show a reversal of the progressive series to hearing thoughts outside the head, then inside the head, and finally, a disappearance of hearing one's thoughts altogether.

Administration of the HOD test to groups of patients before and after various treatments objectively demonstrates the effectiveness of the special treatment procedure. In a recent study done at the Brunswick Hospital (Chiossone et al., 1969) this technique was utilized to demonstrate the effectiveness of various treatment combinations.

A computerized score sheet and print-out[3] has been evolved which at minimal cost analyzes the patient's answer sheet, and gives not only subscore totals and percentages of response, but statistical correlations of probability which take into account the patient's age and sex. This may also be useful in testing other family members as the sub-test score for the thinking disorder may be the only elevated sub-group.

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[3] Available from Robert Peck, M.D., Computer Paramedics, 175 Jericho Turnpike, Syosset, New York 11791.

Use of the HOD boxes themselves, however, with the patient, often demonstrates spatial confusion by the very disordered manner in which the patient places the cards in the box. Nonschizophrenics file them right side up neatly in the score box—schizophrenics frequently place them end on end, backwards, and upside-down. This suggests the type of events that are likely to be happening in the patient's home where the same inability to order actions spatially results in many family frictions.

THE ORGANIC INTEGRITY TEST (OIT)

The OIT[4] is another useful, simple, inexpensive diagnostic test which is suitable for either outpatients or inpatients. In a hospital setting it can be administered to patients at the time of admission and again at the time of discharge. On this test, the lowering of the score indicates a worsening of the mental condition and an increase of the score reflects improvement. On admission to the hospital the patient's OIT is low, and after effective treatment the OIT score increases toward the normal range. The fact that the OIT does not differentiate between an organic brain syndrome and schizophrenia led Tien to the conclusion that, operationally at least, paranoid schizophrenia is an organic brain syndrome that is probably due to an endogenous toxic factor (Tien, 1960, 1968; Tien and Clark, 1969).

Our own research confirmed Tien's findings, and, in a hospital study, improvement in the HOD score was accompanied by improvement in the OIT score, with the exception of young schizophrenic patients who had taken high doses of methedrine over considerable periods of time. In these cases, after the usual treatment for schizophrenia, the HOD score improved, but the OIT score frequently remained depressed, indicating that the patient probably had residual brain damage from prolonged amphetamine usage, despite the fact that the schizophrenia was improved (Chiossone et al., 1969).

The OIT consists of ten pairs of cards which can be matched either according to form or to color. Matching the cards according to form is associated with both integrity and maturity of brain function. Color matching is associated with perceptual disorganization, brain dysfunction, and immaturity. The close correlation between the HOD and OIT scores in schizophrenia tends to confirm that the schizophrenic process is associated with changes in brain function and perceptual disorganization.

THE EXPERIENTIAL WORLD INVENTORY TEST (EWI)

This test is more lengthy and time-consuming to administer, but in a far more detailed manner delineates the altered perceptions and experiential world of the schizophrenic patient. Its use may lead to further subdivisions of patient sub-groups

[4] Available from Psychodiagnostic Test Co., Box 528, East Lansing, Michigan, 48823.

with inferences for more effective treatment of certain groups. The subject is covered in Chapter 17 on the EWI by El-Meligi and gives evidence that its more extensive application and use will lead to additional insights and benefits to patients.

OTHER SCREENING QUESTIONNAIRES FOR SCHIZOPHRENIA

Another diagnostic questionnaire for schizophrenia has been developed by Schachter (1970) and by Schachter et al. (1971) at the University of Pittsburgh School of Medicine Research Center in Child Psychiatry. Their rapidly administered and scored test has been devised to serve as a screening device and it has been correlated with the short form of the HOD test and also the MMPI. Green (see Chapter 20, Subclinical Pellagra) has also developed a questionnaire for perceptual distortions for use in children who are too young for the HOD test.

Laboratory Tests

Small, computerized laboratory equipment is now available at a cost sufficiently reasonable to make utilization of one's own laboratory facilities practical and rewarding (Gambino, 1971). For our own purposes, we have found the following equipment sufficient to do all the laboratory work necessary to adequately diagnose and treat schizophrenia:

A direct read-out digital computer, photometric colorimetric analyzer capable of doing 32 different chemical determinations.

A radiation scintillation counter.

Centrifuges.

Coleman spectrophotometer.

High power binocular microscope.

T 4 columns.

Besides a blood count and urine analysis, all patients are given thyroid function and liver function tests, histamine and uric acid level determinations and a six-hour glucose tolerance test. Additional tests may be done where indicated for trace metals (see Chapter 23 by Pfeiffer, Iliev and Goldstein) and of these, the hair test for trace metals has been found to be inexpensive and practical. Venous plasma *p*H and pCO_2 determinations are also made, as suggested by Watson (1965, 1972).

We have not found it practical to do mauve factor or "pink spot" tests, not only because of the expense, but because the majority of patients have already had prior treatment (see chapters on kryptopyrrole and pink spot). Liver function tests are always necessary as most patients have previously been on phenothiazines. If the patient has been on niacin, the nicotinic acid may react with the reagents and give a false positive SGPT reading, which disappears within 24 hours of discontinuance of

the medication. Thyroid tests will occasionally detect unsuspected hypothyroidism, which occasionally mimics schizophrenia. As thyroid medication may be used later in the treatment of the patient's schizophrenia, or to activate anti-depressants, it is necessary to be aware of the patient's thyroid status. The T_7 determination has been found to be the most reliable indicator for routine use (Hamburger, 1970).

The discovery of high or low histamine levels may influence choice of treatment and trace-metal determinations may be necessary in treatment-resistant cases. This is most easily done by using a sample of the patient's hair.

The six-hour glucose tolerance test will detect the presence of functional hypoglycemia, which is frequently of considerable medical importance. Failure to detect and treat this condition adequately may preclude recovery. This is especially so in childhood schizophrenia, where improvement is unlikely unless the hypoglycemia is recognized and treated (Cott, 1969b). Our criteria for a diagnosis of functional hypoglycemia are the same as those originally described by Salzer (1966); either a drop of 20 points or more from the fasting blood glucose or a drop during any one hour of 65 mg percent (see Chapters 21 and 22).

Although abnormal drops in blood glucose are capable of producing psychiatric symptoms in both normals and schizophrenics, the symptoms produced are greatly exaggerated in patients who are already perceptually impaired by schizophrenia. Although in normals a marked drop in blood glucose can produce fatigue, exhaustion, and depression, in a schizophrenic the response may be much greater and may even precipitate depression of a suicidal degree. Similarly, the response of irritability or tension produced in a nonschizophrenic may be expressed as excitement or even rage in a schizophrenic patient. The drop in blood glucose may also precipitate confusional states accompanied by disorientation; a patient who is driving may have to pull his car to the side of the road. It may also precipitate not only behavioral changes, but attacks of catatonia, paranoia, and overt psychosis in a patient who is at all other times rational. These responses have been described by Buckley (1969a), who demonstrated the effect of hypoglycemic episodes on the glucoreceptor mechanism of the hypothalamus which regulates the tuning of the ergotropic-trophotropic autonomic balance.

Glucose ingestion results in hypoglycemia in the following manner. Glucose activates intestinal hormones (among them, secretin and then glucagon, in sequence), which then evoke insulin release. Thus, hyperinsulinism does not occur if the gastrointestinal route is by-passed and the glucose is given intravenously (Shultz et al., 1971). Failure to recognize this mechanism explains the failure of one study to demonstrate an association between altered carbohydrate metabolism and schizophrenia (Brown et al., 1969). In that study, the authors administered the glucose intravenously in their nine subjects.

Because few psychiatrists are near a laboratory where glucose tolerance tests are being done on large numbers of schizophrenic patients, few have observed these

phenomena at first hand. The marked effect of this disorder is, therefore, not as widely appreciated as it should be.

Even normal people with functional hypoglycemia will show impairment of functioning at hypoglycemic levels. As an example, a secretary in our clinic was typing a long manuscript while she was taking the glucose tolerance test. About halfway through the manuscript, typographical errors began to appear and they then reached such frequency that later a number of pages had to be retyped. Laboratory tests showed that during that period her blood sugar had dropped to 40. This same occurrence in a patient with schizophrenia may result in total inability to function, and amnesiac periods are not infrequent, especially in patients who also have an alcoholic history.

We have conducted two studies on the incidence of hypoglycemia in adult schizophrenic patients. Of 100 patients hospitalized for schizophrenia at the Brunswick Hospital with a diagnosis of schizophrenia (confirmed by HOD scores of 50 or over), 61 percent met the criteria for relative hypoglycemia. These patients were on hypoglycemic (sugar free) diets from the time of their admission to the hospital and the tests were performed after they had been in the hospital at least seven days.

Another series consisted of 200 outpatients studied at the North Nassau Mental Health Center. All of these patients were on normal diets before the tests were performed. The diagnosis of schizophrenia was clear cut in these cases, verified by a HOD score above 50. Of these 200 patients, 64 percent demonstrated functional hypoglycemia (Hawkins et al., 1971). These figures coincide closely with those of Meiers (1967), Cott (1967, 1970), Ward (1970, personal commun.), Hoffer (1969, personal commun.), and others.

The marked effect on the mental state of patients during this test, when their blood glucose levels drop, can be readily observed in a large percentage of cases and some effect may still be observable even two or three days later. The fact that many of the symptoms persisted for several days even though the blood sugar had returned to normal suggests that some other mechanism had been triggered to account for this persistence of symptoms. This has been discussed by Tintera (1967, 1968), who related hypoglycemic episodes to the triggering of hypoadrenocortical responses and Selye's General Adaptation Syndrome (stress response). Recent animal research studies have shown that a high carbohydrate diet or increase in blood insulin alters tryptophan and serotonin levels in the brain (Fernstrom and Wurtman, 1971).

The incidence of hypoglycemia in the alcoholic-schizophrenic is even higher, and in our series approximately 90 percent had relative hypoglycemia, so that these patients can be routinely considered to be hypoglycemic until proved otherwise. In these patients, hypoglycemic attacks may trigger recurring drinking bouts and "dry drunks." These patients have learned through experience that the shaky, frightened, anxious, weak, tremulous feeling is relieved very rapidly by a drink, so that a hypoglycemic episode recreates a desire to drink.

The criterion for functional hypoglycemia from the psychiatric viewpoint differs from that used by internists generally, who look only for absolute hypoglycemia, that is, a glucose-level reading below that which is considered to be the normal range for a given laboratory. The tests results must, therefore, be interpreted personally by the psychiatrist. Also, the five-hour glucose tolerance test will miss about 3 percent of hypoglycemic reactions which occur only during the sixth hour.

It is important to recognize also that the tests are being conducted under relatively stress-free laboratory conditions. Therefore, the true incidence of hypoglycemia reactions when the patient is engaged in stressful daily life situations may be significantly higher.

We have demonstrated this phenomenon by having patients who work near the clinic's laboratory conduct business as usual in between the hourly blood samples. In several instances the reaction was so severe under these circumstances that the tests had to be discontinued. Often we verify the laboratory tests clinically by having the patient eat a high-glucose breakfast one day and a high-protein breakfast another day and have him make notes about how he feels one-half hour before he eats lunch on each day. The marked difference is often quite impressive. Many patients will also spontaneously report their own observations that under stress conditions their hypoglycemic condition worsens, but when on vacation, for instance, they may be able to go off the diet somewhat without experiencing any symptoms.

The public's increasing awareness of this disorder was reflected in the following Peanuts cartoon strip:



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SUMMARY

The orthomolecular concept as it applies to schizophrenia provides a means of understanding and interpreting a wide variety of data and clarifies the clinical management of the schizophrenic patient. The disease process is based on genetically determined biochemical defects which remain to be clarified by research in molecular biology. The disease process itself begins as an interaction between the genetic predisposition and later biochemical events and may be determined by a variety of factors which precipitate a change that is influenced by the molecular concentrations in the brain of substances normally present in the body.

Clinically, the illness begins as *altered subjective experiences associated with changes in perception*, and these may or may not in time result in the observable behavioral changes upon which a diagnosis of schizophrenia has been hitherto based. The early changes in subjective personal experience may manifest themselves in slight alterations in behavior which are not traditionally typified as schizophrenic. At this stage of the illness, the diagnosis may be made by interviewing techniques focused on detection of these subjective changes. The perceptual defect may also be detected by objective measures such as the HOD and EWI tests which parallel changes in the severity of the illness. This stage of the illness may be called metabolic dysperception; it precedes the appearance of overt clinical schizophrenia.

This medical model demonstrates that the signs and symptoms of schizophrenia are secondary to the perceptual disorders and that these in turn precede the tertiary impairments in social functioning. Evidence is presented to support the proposition that all the manifestations of schizophrenia can be produced by perceptual changes alone. The HOD score is described as being more accurate than the usual clinical criteria in evaluating the degree of the patient's illness and response to treatment. Certain parallels between the illness and the psychedelic experience are presented and special mention is made of the combinations of schizophrenia with alcoholism and with drug abuse.

In addition to tests for perceptual dysfunctioning, the use of medical laboratory tests, described as the orthomolecular approach, includes an assessment for those biochemical variables that have a direct bearing on the patient's illness. Of these, thyroid function is seen to be important and the use of the six-hour glucose tolerance test in detecting functional hypoglycemia is emphasized as of the greatest importance. Failure to detect and treat hypoglycemia adequately precludes successful treatment in a large percentage of cases.

Hypoglycemic episodes aggravate perceptual dysfunctioning in susceptible individuals and, in fact, may interfere with functioning in normals. In schizophrenic patients hypoglycemic episodes may result in severe exacerbation of symptoms even under laboratory conditions. The hypoglycemic production of symptoms is based not only on the glucose concentration but also on the rate of drop, and this is

correlated with the orthomolecular concept that mental states are dependent not only on the molecular concentrations of substrates but also on rates of change of their concentrations.

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30

Orthomolecular Psychiatry: Treatment of Schizophrenia

DAVID HAWKINS

INSTRUCTIONS TO THE PATIENT

Education of the Patient: Explanation of the Illness and Test Results

Subsequent to the completion of tests and the diagnostic interview, the patient is given an interpretation of all the test findings and the diagnosis, including a biochemical explanation of his illness. It is explained to him how the HOD test reveals faulty perception, and he is told his exact HOD score and its correlation with his symptoms. It is then explained that a medical regimen will be prescribed that is designed to correct the brain's faulty perceptual functioning. An adequate understanding of the illness frequently relieves irrationality rapidly.

Similarly, when it is explained to the patient that paranoia is a result of faulty brain chemistry and it is labeled "paranoia" he becomes less paranoid and more rational. Unless the condition is of considerable duration, so that it has become

systematized with many attendant secondary gains, paranoid symptoms usually diminish rapidly. An adequate explanation to the patient of his illness is an extremely important therapeutic procedure and sets the stage for all the treatment procedures that follow.

We use the term "metabolic dysperception" (see Chapter 19 by Kowalson and Chapter 26 by Robie) to most accurately describe the patient's condition, and we explain that metabolic dysperception, if it gets bad enough, can produce overt clinical schizophrenia. We have yet to see a patient who has rejected this explanation, if expressed correctly. Many of the patients respond very positively and will state that this is the first time a psychiatrist has ever been honest with them.

Telling the patient that he has a specific illness allows him to assume the sick role with all the attendant benefits that accrue in our society, as have been well described by Siegler and Osmond (1969). Once the patient and family understand the nature of the illness they are usually willing to accept it and do something about it. The family no longer has to utilize denial or reaction formation to handle their guilt, anger, and other emotional reactions which automatically stem from psychological formulations of the illness. Under these conditions, families readily assent to counselling in those instances where disturbed family interaction is apparently impeding the patient's progress.

General Medical Regimen

The patient is told that he will be placed on a regimen consisting of diet, megavitamins, medications, and prescribed periods of exercise, rest, and sleep. No more than 8 hours of sleep is advised as more has been shown to increase fatigue and disability (Globus, 1969). Daily physical exercise is prescribed for its physiological benefit. Anxiety in mental patients has been demonstrated to be accompanied by elevated lactate levels as a result of altered energy systems (Pitts and McClure, 1967; Beebe and Wendell, 1968; also see Chapter 21 by Beebe and Wendell). The beneficial effect of exercise has also been reported by members of Schizophrenics Anonymous; they claim that of all the forms of exercise, swimming is the most subjectively beneficial.

Patients are advised to avoid excessive fatigue and stress and they are placed on a hypoglycemic diet which consists primarily of the avoidance of sugar and sweets, reduction of starch, and elimination of caffeine. Because there is an increasing interest in functional hypoglycemia there are a number of recent books available to the patient (see Chapter 22 by Meiers). A booklet "Hypoglycemia and Me" by the Hypoglycemic Foundation[1] is excellent and provides all the information needed.

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[1] Available from Adrenal Metabolic Research Society of the Hypoglycemia Foundation, P.O. Box 48, Fleetwood, Mount Vernon, New York, N.Y. 10552.

Patient self-help groups such as Health Frontiers[2] hold regular meetings, distribute educational literature, and sponsor informative lectures by endocrinologists.

The use of adrenal cortical extract (ACE) in the alleviation of hypoglycemic episodes is occasionally necessary. Our experiences have indicated that in certain patients it can be demonstrated to have a marked benefit and in several instances, the use of the ACE injections has made it unnecessary to hospitalize patients who had precipitated relapses by going off their diets. "Physicians Guidelines to Diagnosis and Treatment of Hypoglycemia or the Hypoadrenocortical State" and "Hypoadrenocorticism" are available from the Hypoglycemia Foundation to physicians only.[3]

We also advise patients that strong aged cheeses such as Roquefort and Camembert should be avoided as these have been reported by the members of SA to aggravate their symptoms.

Patients appreciate the reasons for all of these instructions and are far more cooperative when the rationale is given. It is useful to clarify the difference between a vitamin *deficiency* disease and a vitamin *dependency* disease (Rosenberg, 1970) in which vitamins are being used in pharmacologic rather than replacement doses. To aid in their understanding of the illness, educational literature is made available and most patients and families find helpful the educational package which is available from the Schizophrenia Association of Long Island.[4] In our experience, the more the patient and family know about the illness, the better the result.

Joining Schizophrenics Anonymous is recommended when it appears the patient would benefit, and we suggest to family members that they join one of the schizophrenia associations, become acquainted with the other families, and attend the educational lectures. Many patients become interested in the hypoglycemic aspect of the illness and appreciate being referred to patient self-help groups concerned with this illness.

With the alcoholic-schizophrenic patients, treatment is first concentrated on the schizophrenia and they are referred to SA. In each of the SA groups, there are also members of Alcoholics Anonymous and, as the patient improves, these recovered alcoholics introduce the patient to AA. If the patient is not going to SA then he is referred directly to AA after his HOD score has gone down and the schizophrenic process has abated. Surprisingly, at that point the schizophrenic-alcoholic usually abruptly stops drinking without the prolonged struggle and battle typical of the nonschizophrenic alcoholic. The patient frequently attends both SA and AA groups and as the schizophrenic process dissolves, he usually drifts away from SA and continues in just AA.

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[2] Available from Health Frontiers Foundation, 149 Spindle Road, Hicksville, New York 11801.

[3] Adrenal Metabolic Research Society of the Hypoglycemia Foundation, P.O. Box 98, Fleetwood, Mt. Vernon, New York.

[4] Long Island Schizophrenia Association, 1691 Northern Blvd., Suite No. 203, Manhasset, New York 11030.

MEDICATION

Psychotropic Drugs

The academic drug researcher operates at a distinct disadvantage—he cannot employ the great variety of techniques which the clinician utilizes almost automatically in his daily practice. Also, the researcher can only handle very limited data and the number of controlled variables must of necessity include only those that are most obvious and that lend themselves to data collection and processing. The parameters of research designs are, therefore, arbitrarily quite limited, as are the results. Unfortunately, the results of such studies are often extrapolated beyond the confines of the data and the results are stated in terms which do not limit the results to the conditions of the study. Because he is unencumbered by such limitations, it is usually possible for the clinician to accomplish more with any given drug than the literature infers. The more complex the illness being treated, the more this general principle holds true, and it is especially so in schizophrenia.

Correct sequencing of medications is important in the psychopharmacology of schizophrenia. By changing the sequence it is often possible to obtain results with the same drug to which the patient was previously unresponsive. A similar observation has also been made by Kline (1969), who noted, in doing cross-over studies, that patients may react differently to the same dose of the same drug when it is later re-introduced and that this phenomenon creates a previously unrecognized problem for drug research. We have learned that this can be done deliberately—a patient can be "set up" to respond to a drug that we intend to administer at a later date. In doing this, advantage can be taken of certain readily observable principles of central nervous system activity such as the rebound phenomenon. For instance, a patient will often readily respond to an "up" drug if it is rapidly introduced during the immediate period following cessation of a "down" drug and vice-versa. Brain function, as a general rule, tends to be compensatory, and this natural tendency can be used to purposely "sensitize" a patient to the effect of the same or another drug. In attempting to induce this reaction, the action of the "sensitizing" drug should be in the opposite direction from the drug whose response we later need to effect a recovery.

Researchers who are not clinically experienced are often puzzled by the "polypharmacy" that they come across, because, from the limitations of a theoretical viewpoint, it "doesn't make sense." The clinician, however, often follows by "intuition" certain principles in drug usage which have been learned by experience. Besides sequencing, these include: utilization of mutual synergisms and antagonisms, balancing off of side effects, purposely utilizing desired side effects, extending dosage ranges by concurrent use of antagonists, calculating onsets and durations of action, predicting progressive loss of response, predicting development of tolerance or loss

of tolerance, estimating effective dosage ranges at different stages of the illness, and predicting phases of drug responses. Because of all these clinically important factors, which are not included in research designs, it is common for clinicians to obtain quite different results from those that are received from academic studies. In daily practice the clinician automatically compensates for biological individuality (Williams, 1971) and the difference between patients, which in psychiatric conditions are more marked than in other kinds of illness. In psychiatry it is common for patients to require 10 to 100 times the "average dose" of a given substance before they respond favorably.

Additional reasons for the traditional "town versus gown" difference in the results of treatment between clinicians and academic researchers are provided by understanding Joseph Wilder's "Law of Initial Value," which states that the pre-stimulus state of the organism determines the response as much as does the nature of the stimulus itself. The chemical importance of this concept has been reviewed by Lesse (1971). Because of the antipsychotic effect of the phenothiazines, all patients are placed on either a suitable phenothiazine or other antipsychotic medication if this has not been done previously. According to Hollister (1971), antipsychotic drugs "contribute the most therapeutic benefits in schizophrenia—there is little direct evidence that traditional therapies add more," and all antipsychotics produce a postsynaptic dopamine receptor blockade leading to stabilization of the membrane at the receptor site.

The site of action may also be an enzymatic protein in the presynaptic membrane adjacent to the intersynaptic cleft (Teller and Denber, 1968). They point out that the defective protein at the synaptic site is probably quite small and that the antipsychotic drugs are capable of changing protein structure even in minute doses. The change in structure then causes change in functioning of the enzymatic activity. Utilizing a "framework molecular model" (available from Prentice-Hall, Inc., Englewood Cliffs, N.J.) they demonstrated, for instance, that the "architectural" characteristic of chlorpromazine and mescaline allowed for a demonstration of their mutually antagonistic action by action at the cell's protein membrane discs.

Spontaneous disinhibition of neuronal circuits, because they are connected in series rather than parallel, can result in clinically significant symptoms even though only a few sites are involved. This may lead to production of reverberative circuits in which apparent perceptions may occur, for instance, without external stimulation. Also, in chronic schizophrenia there is a disturbance of internal inhibitory activity (Saarma, 1968), and Saarma and Vasar (1970) have demonstrated that this disturbance is positively influenced by nicotinic acid. Teller and Denber conclude that the symptoms resulting from the endogenous genetic defect in schizophrenics are similar, from the viewpoint of molecular biology, to those that are exogenously caused by the psychotomimetic drugs. Bradley and Johnston made a valuable contribution to future research in this area in their work on "The Molecular

Pharmacology of Hallucinogens" (1968). Animal research until this time had been based only on gross behavioral changes in response to the drugs being investigated. Bradley and Johnston introduced the use of operant conditioning techniques to determine more subtle behavioral changes in response to a series of possible psychotogens. By correlating these more subtle responses to a series of structural changes in the molecules being studied, they have come closer to approximating the human condition in drug research with experimental animals.

It is explained to the patient that the phenothiazines are being prescribed, not as tranquilizers, but for their effect in reducing the HOD score and for their antischizophrenic action. Intelligent patients appreciate a brief explanation of the action of the phenothiazines so that they get to know that chlorpromazine has a "down" action and is, therefore, useful when they are agitated, or upset, or have insomnia, whereas fluphenazine, especially in lower doses, has an "up" action. An explanation is given of extra-pyramidal side effects and the reason for prescribing anti-Parkinsonian medication.

Patients are told that if they get blurred vision, the anti-Parkinsonian drug dose is too high, and that if they get restless legs or cannot sit still, it is too low. An explanation is given that the phenothiazines are not properly called tranquilizers and that that term should be reserved for drugs of the meprobamate type. This removes the common prejudice against taking tranquilizers. Many patients are either fearful of tranquilizers or they have reaction formations against them and do not want to become dependent on them. Clarification of this issue is often of considerable importance because some patients will discontinue antipsychotic drugs, with dire results, for these reasons.

The dose of phenothiazines is reduced as the patient improves and his medication is shifted from one end of the phenothiazine spectrum to the other, depending on what phase of illness or recovery he is in currently. We have seen many patients whose impairment was impeded by their being kept on the wrong phenothiazine due to the mistaken notion that all phenothiazines are interchangeable. As an example:

> A 28-year-old schizophrenic man was admitted to a hospital with paranoid symptoms. He was placed on 600 mg of chlorpromazine, following which the paranoid symptoms disappeared. He then became depressed and apathetic. During the next year-and-a-half he had psychotherapy three times a week, but did not improve and so was discharged at the end of that time as having achieved maximum hospital benefit. Medication remained the same throughout the entire hospital stay and he was discharged on the same dosage.
>
> When seen at the clinic, he was still "down," apathetic, listless, and indifferent. The notes in the patient's hospital record indicated that this was thought to be due to the schizophrenic process. At the first visit, his medication was changed from 600 mg chlorpromazine to 5 mg fluphenazine three times daily. Within 24 hours the entire symptom constellation disappeared. He became alert, responsive, and energetic, and eventually recovered.

The best clinical principle is that the patient should be on the right dosage of the right phenothiazine at the right time. We tell the patient that as he recovers the dosage will be reduced, but that he will be kept on a small, perhaps "bed-time only" maintenance dose for its beneficial chemical effect even though he has long since not needed a tranquilizer. This again demonstrates to the patient that the phenothiazine is not being used as a tranquilizer, but for its biochemical effect. This explanation results in increased patient cooperativeness.

Antidepressants may be necessary in this connection. We have found that activation of the tricyclic antidepressants by thyroid medication may bring about a prompt response. This has been recently reported by Prange et al. (1969) and Earle (1970). It is important, as mentioned before, that the patient's euthyroid status be ascertained prior to placing him on this combination of medications. The patient's active symptoms should always be first brought under control with a phenothiazine before the antidepressant is introduced.

Another medication which is useful in the treatment of schizophrenia is methylphenidate hydrochloride (Ritalin®). If the depression is not too severe, 10 to 20 mg three times per day before meals will alleviate fatigue and depression, as well as any sedation effects from the phenothiazines. This medication at times has relieved depressions of suicidal degree in less than an hour and helps to tide the patient over until his basic condition improves sufficiently that the depression passes. Overreliance on this medication can lead to a diminution of effect. It can be used to potentiate the effects of the tricyclic antidepressants. This synergistic effect results in an increase of blood levels of the antidepressants through enzyme inhibition (Wharton et al., 1971). Overusage by schizophrenic patients is rare, and in our experience has occurred only in those who have a problem with multiple drug abuse.

An additional use for thyroid medication in the euthyroid schizophrenia patient is in the treatment of periodic catatonia. In this condition, between upsets, the patient's HOD score may be within the normal range, and when an attack occurs the score rises precipitously. The typical response to 3 or 4 grains of thyroid daily is exemplified by the following case:

> A 41-year-old housewife had been hospitalized *15 times* in the last seven years for recurrent acute schizophrenic episodes uncontrolled by massive doses of chlorpromazine. When seen in the office between attacks, her HOD score was only 10. The attacks were always preceded by a period of insomnia and often occurred during the pre-menstrual period. In addition to megavitamins and a hypoglycemic diet, she was placed on 4 grains of Proloid® daily at the first visit. Since then she has not had a single recurrence—she feels and functions as though she had never been ill. She returns to the clinic for follow-up visits every three months.

Although the successful use of thyroid in treating schizophrenia has been the subject of many papers in psychiatry for more than 40 years, apparently many

clinicians do not think of using it because schizophrenics are usually euthyroid. The periodic catatonic is a readily recognizable subgroup of the schizophrenias and the value of using thyroid in this condition has been reported by many researchers, including Gjessing (from 1932 on, but recently see 1964, 1967, 1969), Danziger (1958), Danziger and Kindwall (1953, 1954), Gunne and Gemzell (1956), Sourkes (1962, 1970), Lochner et al. (1963), Minde (1966), Cookson et al. (1967), Jenner (1967), Vestergaard (1969), and Hoffer (1967). Thyroid can be used in treatment of the recurrently ill schizophrenic as well as for other types of schizophrenia.

Hoffer and Osmond (1967) reviewed the literature and noted that the average dose of thyroid used was 5 grains daily. Danziger and Kindwall (1953, 1954) gave doses of 2 to 20 grains but found that few patients required more than 10 grains. All researchers have commented on the considerable resistance of the schizophrenic to thyroid hormone and in our own work we have observed the same phenomenon. Our most common dose is 3 to 5 grains daily, and many patients who were previously unresponsive to treatment will recover when this amount of thyroid is added. Many of these are patients who do not present the classic periodic pattern; one will be described later.

Megavitamins

We routinely use mega doses of four vitamins for a variety of reasons in treating schizophrenic patients, and this has resulted in increased rates of recovery. It is still not possible to predict exactly which patients will benefit by megavitamins and it remains for future researchers to give us the useful clinical indicators to identify these patients in advance. Work supported by the Canadian Mental Health Association (Ban, 1969; Ananth et al., 1969; Ban and Lehmann, 1970) is proceeding in that direction and preliminary results indicate that there is a segment of the schizophrenic population that responds to either nicotinic acid and pyridoxine or pyridoxine alone and may eventually be identifiable.

Ananth, Ban, and Lehmann report (1972) that the therapeutic effect of nicotinic acid in chronic schizophrenics is potentiated by pyridoxine. This was demonstrated in a 48-week double blind control study in which pyridoxine alone, nicotinic acid alone, or the two together were demonstrated to have a statistically significant therapeutic effect. The therapeutic effect was demonstrable even though the patients had been hospitalized for an average of 10.9 years, were not on hypoglycemic diets, and the doses of both pyridoxine (75 mg daily) and vitamin B3 (3 g a day) were considerably below the dosages we routinely prescribe.

In general, it can be said from our own experience that the higher the patient's HOD score, the greater the likelihood of response to an overall megavitamin treatment regimen. The schizophrenic patient whose illness could be called "metabolic

dysperception" responds the best. The grown-up childhood schizophrenic with the low HOD score, postural stigmata of propioceptive deficit, and primarily visual perceptual distortions is the least likely to benefit. The most significant visual perceptual distortion in this group of patients is loss of depth. This particular distortion, even when it is induced hypnotically in normal subjects, produces a schizophreniform response with primitivization and regression, as has been shown by Aaronson in several studies (1967a, b, 1968). This type of patient appears to belong to a different biochemical subcategory of the subtypes of the schizophrenias.

The megavitamins and the phenothiazines act clinically as though they had a synergistic action, and for that reason patients are kept on a low daily dose of a phenothiazine prophylactically even after they have recovered. Sainz (1964) has demonstrated that the phenothiazines elevate blood ascorbic acid levels, and there may be a variety of synergistic effects such that the antipsychotic action of the phenothiazines may be augmented by the megavitamins. Demonstration of the effectiveness of the combination requires correction of co-existing functional hypoglycemia. In many patients, in our experience, recovery was prevented by lack of adherence to the hypoglycemic diet. As an example:

> A 26-year-old unemployed schizophrenic man had been ill for several years and had been hospitalized several times, during which he had had shock treatment and all other available forms of therapy. By the time he came to the clinic, he was surly, uncooperative, paranoid, and obese. The Glucose Tolerance Test revealed definite functional hypoglycemia and he was placed on the usual regimen of megavitamins, phenothiazines, and a hypoglycemic caffeine-free diet.
>
> For the next one-and-a-half years no progress was achieved and during visits he was highly uncommunicative, despite high doses of vitamins and phenothiazines. It was then discovered from his family that he was drinking at least half a case of a cola beverage per day and on week-ends he usually drank a whole case daily. Cessation of the cola ingestion resulted in rapid, progressive improvement with noticeable changes in behavior, communicability, and relationship with the family. His inappropriateness and surly, gauche manner disappeared and he is continuing to improve.

When we first began using megavitamins in treating childhood schizophrenics we were unaware of the importance of ameliorating the hypoglycemia and, therefore, our first reports on the use of nicotinamide in schizophrenic children stated that ". . . niacin and niacinamide were found to be relatively ineffective in childhood schizophrenics and less effective in adult schizophrenics with childhood onset" (Hawkins, 1967, 1968b). Similar negative experiences have been reported by Roukema and Emory (1970) and Greenbaum (1970b), who also demonstrated that nicotinamide alone in the treatment of childhood schizophrenia, except for improvement in some individual cases, did not produce statistically significant results. It was Cott (1969) who pointed out that recovery of childhood schizophrenics on megavitamins was not possible until the hypoglycemia was corrected, and that unless this was

done it was useless to proceed. The importance of this concept cannot be overemphasized, as in this group as well as certain other patient groups no recovery at all is possible unless the hypoglycemia is corrected.[5] In this connection it might be well to emphasize again that recovery after the acute phase is over can be delayed for long periods of time if the patient is allowed to sleep beyond 8 hours a day. The apathy and lassitude which ensue from prolonged oversleep can negate attempts at rehabilitation.

Our initial combination of megavitamins usually consists of 1 gram niacinamide, 1 gram ascorbic acid, 50 mg pyridoxine, and 400 I.U. of natural vitamin E, repeated four times daily. Although occasionally an adolescent girl will develop nausea as a result of this dose of niacinamide and require a reduction of dosage, this combination is tolerated by the majority of patients without any side effects. The most frequent complaints are about the nuisance of taking the pills and, occasionally, difficulty in swallowing them.

For a time, we hypothesized that the difficulty in swallowing, especially in adolescent girls, was hysterical in origin, but we discovered this was often due to esophageal dysfunction associated with schizophrenia as reported by Hussar and Bragg (1969, 1970). Their study on the swallowing functioning in schizophrenics using cineradiographic techniques demonstrated that almost half of the schizophrenic patients showed various degrees of swallowing abnormalities and that chlorpromazine medication had no effect on the swallowing mechanism. The conclusion of their study was that "these results contribute to an understanding of the not infrequent tragic episodes of asphyxiation on food among chronic schizophrenic patients often incorrectly ascribed to tranquilizer medication."

Both niacinamide and ascorbic acid are available in capsules, which are more easily swallowed than pills. The ascorbic acid available in crystalline form can be mixed easily with orange juice.

The maximum therapeutic dose of niacin or niacinamide is about 1 gram per day below the nausea-inducing dose. We routinely begin by using niacinamide and later switch the patient to niacin if there are specific indications to do so, such as the existence of concomitant alcoholism, elevated cholesterol, or hypoglycemia, or if the schizophrenia has been precipitated by LSD. Although the flushing side-effect of niacin can be controlled by cyproheptidine (Periactin®) 4 mg four times daily (Robie, 1967), the flush unnecessarily alarms patients even when it has been previously explained to them. Niacin also appears to be more beneficial than niacinamide in treating the alcoholic-schizophrenic, although we do not have statistical studies to prove that this is so.

Recent studies (Davis and Walsh, 1970; Lieber and DeCarli, 1970) have demonstrated metabolic pathways in alcoholics which may account for nicotinic acid's

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[5] Hypoglycemic episodes, for instance, will trigger post-LSD "flashbacks."

action in this disorder. Thus, alcohol, by way of its primary metabolite, acetaldehyde, competitively inhibits nicotinamide-adenosine-dinucleotide-linked aldehyde dehydrogenase, which interferes with the metabolic disposition of the biogenic amine dopamine, producing aberrant metabolites. Prolonged consumption of alcohol enhances the activities of the enzyme-reduced nicotinamide-adenosine-dinucleotide phosphate oxidase. In this connection, alcoholics have also been demonstrated to have a deficiency of vitamin C as exemplified by a lower level leukocyte ascorbic acid in control groups (Goldberg, 1970).

Although Saarma and Vasar (1970) report that with nicotinic acid there is an appearance of clinical improvement between the fourth and sixth week of treatment, in our experience the response to the megavitamins is generally more delayed and not discernible until the third to sixth month. A very noticeable or marked degree of improvement as compared to patients who are treated with just phenothiazines is most obvious by the end of the first year.

Improvement can be speeded up by the use of parenteral injections of the megavitamins, in which case a noticeable improvement begins within a few weeks (see Chapter 25 by Cott). Patients who have been on adequate oral doses for a considerable length of time without improvement will often suddenly respond when switched to parenteral administration. The ability of the intestinal tract to handle a given compound is not the same in all persons (Faloon, 1970). Some patients may have a defect in transport enzyme systems so that a patient may have been on a high dosage of ascorbic acid for some time and yet still show a subnormal blood ascorbic acid level. This level then suddenly increases to normal when much smaller doses of ascorbic acid (500 mg) are given by injection.

Multiple modes of action of nicotinic acid in schizophrenia have been described (see Chapter 11 by Hoffer), including the recent work of Galzigna (1969, 1970) and Galzigna and Rizzoli (1970) showing that nicotinamide reacts rapidly with the aminochromes, reducing them. In the absence of nicotinamide in the brain tissue, the aminochromes react with acetylcholine to form a stable complex which acts as an endogenous hallucinogen. They conclude that "if we consider adrenochrome reduction derivatives as non-toxic excretion products of the psychotogen aminochromes, a rationale for the clinical use of nicotinamide in mega doses as a therapy for mental illness is provided." Further work is in progress to demonstrate the nature of this interaction with ascorbic acid which is central to the authors' "short circuit" theory of the onset of mental illness.

Nicotinic acid has nonspecific properties of blocking the production of stress-induced gastric ulcers in laboratory animals and it also blocks the L-dopa-induced exacerbation of symptoms in schizophrenic Parkinsonian patients (Yaryura-Tobias, 1971). Research is currently being done to determine the effect of nicotinamide in reducing the stress responses (cold pressor test) of normal students to final examinations (Bovard, 1971, personal commun.). The contraindications for using nicotinic

acid have been described by Hoffer and Callbeck (1959), Hoffer (1962, 1969), Hoffer and Osmond (1966), Mosher (1970), and Newbold (1970), and have been reviewed in other chapters. The four main contraindications to niacin are those of peptic ulcer, hypertension, diabetes, and gout. The niacin-induced hyperglycemia may alter insulin requirements in diabetics. The histamine-release, which produces the flush, results in hyperchlorhidria in ulcer patients. The elevation of uric acid may precipitate gout attacks, and if the hypertensive patient is on a reserpine-type anti-hypertensive agent, the patient may possibly go into shock. The cholesterol-lowering effect has been demonstrated in long-term heart studies and the heart studies have discovered the same contraindications (Boyle, 1968). Here, obviously, the lowering of blood cholesterol is sought, and it is a side benefit when niacin is taken by schizophrenics.

In the review articles mentioned earlier concerning the possible side effects of nicotinic acid, several cases of possible hepatic toxicity were reported. When the effect of nicotinic acid in producing false positive liver enzyme tests is discounted, these appear to be questionable. We have not seen any cases of noninfectious jaundice which did not clear up when the phenothiazine was discontinued. In addition, we have seen several cases of intercurrent infectious hepatitis as demonstrated by liver function tests and liver biopsy. The majority of patients who develop phenothiazine jaundice were continued on the megavitamins and the jaundice cleared up with no difficulty. In a few cases, because of the isolated reports in the literature, megavitamins were discontinued along with all other medications, and the patients were subsequently replaced on nicotinamide with no recurrence of jaundice. At this time, we consider that jaundice due to nicotinic acid, although unlikely, may be a remote possibility and treatment will depend upon the judgment of the attending internist.

We explain to patients that both vitamin E and ascorbic acid are prescribed for their antioxidant effects. Ascorbic acid alone has been shown in controlled studies to benefit psychiatric patients as evidenced by improvements in their Wittenborn and MMPI scores (Milner, 1963). The effect of vitamin C in preventing the common cold has been reviewed by Pauling (1970), and this is of benefit to schizophrenic patients, who characteristically show a clinical worsening and an increase of perceptual difficulties as a response to viral infections. For those patients in whom this has been a problem, we recommend the sustained-action form of ascorbic acid in capsule granulated form, which sustains ascorbic acid blood levels during sleep (Riccitalli, 1972) and thereby eliminates recurrent colds in the majority of patients. We frequently have observed minor relapses and setbacks in recovered patients in response to upper respiratory virus infections and a possible mechanism for this observation has been described by Teller and Denber (1968) related to abnormal protein structure (such defects can occur genetically, or be caused by malnutrition, avitaminosis, infection, toxins, or immunologic reactions). The greater retention of

ascorbic acid in schizophrenic patients has been shown by Cowan et al. (1970) and previously by Herjanic and Herjanic (1969) and VanderKamp (1966). Current studies by Pauling and Robinson and by Herjanic are reported in Chapters 2 and 14 in this volume.

High doses of ascorbic acid may occasionally cause mild diarrhea in some individuals and it may cause false positive urine tests in diabetics who use commercial home test kits. A case is also reported in which ascorbic acid shortened the prothrombia time in a patient who was receiving a Warfarin (Coumadin®) anticoagulant (Rosenthal, 1971). In treating over 5,000 patients with 4 grams or more of ascorbic acid per day, however, we have not had a single instance of any serious side effects.

We explain to patients that vitamin B6, pyridoxine, is necessary as a precursor of nicotinic acid. It is an intermediary step in the biotransformation of tryptophan to nicotinic acid where it is required for the hydroxylation of kynurenine (derived from tryptophan) to 3-OH-kynurenine and for the further metabolism of 3-hydroxykynurenine to 3-hydroxyanthranilic acid (immediate precursor to nicotinic acid; Gibbs and Walshe, 1969). Vitamin B6 deficiency interferes with the metabolism of amino acids, proteins, and biogenic amines, and causes abnormalities of nervous system activity in man, where the pathological effects of deficiency are most marked on the developing brain. Abnormalities of vitamin B6 metabolism have been associated not only with schizophrenia but also with a variety of other abnormalities of the central nervous system, and B6 deficiency at the subcellular level may be produced by a number of antimetabolites (Knapp, 1966; Coursin, 1969). The antagonism between vitamin B6 and L-dopa is a recent illustration (Duvoisin et al., 1969; Cotzias and Papavasilion, 1971). Pyridoxine in high doses has been used by Cott (1969) in the treatment of childhood schizophrenia. The role of pyridoxine in psychiatric disorders has recently been summarized by Ananth, Ban, and Lehmann (1972) in their paper entitled "Potentiation of Therapeutic Effects of Nicotinic Acid by Pyridoxine in Chronic Schizophrenics" presented at the Canadian Psychiatric Convention in Montreal, June 8, 1972. This paper states that pyridoxine potentiates the action of nicotinic acid, possibly by opening up the kynurenine cycle of tryptophan metabolism and thereby decreasing the formation of indoles. In their study, already referred to, pyridoxine alone had a therapeutic effect in schizophrenics as well. In more than 5,000 patients we have not observed a single side effect from pyridoxine administration of 200 mg daily.

It is best to write down the medication schedule and the recommendations for sleep and diet on a card and give it to the patient at the initial visit. It is also advisable to indicate to the pharmacist that all medications be labelled to show the name and dosage size. Unless this is done, there will be mistakes and many call-backs as most patients are perceptually disordered and unable to remember verbal instructions.

In summary, the addition of megavitamins is inexpensive and safe, and very positively influences the long-term outcome. Side effects of a serious nature are quite

rare and easily avoided. The occurrence of even the most mild side effects is avoided by giving niacinamide instead of niacin. Precise identification of those patients most likely to respond is not yet possible but, in general, the more elevated the HOD, the more likely the response, provided however, that concomitant hypoglycemia is also corrected.

INVOLVEMENT OF THE PATIENT IN AN INTEGRATED COMMUNITY TREATMENT SYSTEM

Because of the severity of a patient's condition or situation, hospitalization may either be required or elective. The average length of hospitalization for intensive hospital treatment (which may or may not include a course of ECT) in our series of patients over the last five years is eight weeks. Ten to twelve weeks may be necessary, however, if the patient has been taking large doses of methedrine (speed). ECT rapidly reduces the HOD score, and this effect is most marked in the younger age groups, as will be discussed later.

If the schizophrenia has been exacerbated by LSD or methedrine to the degree that the patient is psychotic, then ECT, in our experience, is often necessary, as the psychosis otherwise tends to persist. It is also very effective with the depressive aspect of the patient's illness, which may be creating a suicidal risk. The response to ECT is different if the patient has been preparatorily pretreated. If, while in the hospital, the patient receives high-dosage megavitamins both orally and parenterally and is on phenothiazines and a hypoglycemic diet, the relapses following cessation of ECT formerly seen in schizophrenics seldom occur and the improvement is maintained following discharge.

Curiously, annoying side effects from medication seldom occur in a hospital setting. The patient who had side effects from practically every medication tried as an outpatient will probably have none from much higher doses of the same medication if he is hospitalized. In the hospital, patients are given 500 mg of ascorbic acid and 200 mg of niacinamide intramuscularly three times weekly in addition to the usual oral doses. Few patients fail to improve from intensive hospital treatment and even many of the severe chronic patients improve sufficiently so that they can be discharged and treated as outpatients.

Patients who appear shaky at the time of discharge or have difficult home situations or who have become disabled by the long duration of their illness benefit considerably from a convalescent period in a halfway house where they can be maintained on the same therapeutic regimen with monthly visits for changes of medication and evaluative follow-up. The use of SA, family groups, day activities programs, and

involvement with other supportive units of a treatment complex are described in Chapters 28 and 29.

Patients' self-help groups, such as Recovery, can also be of benefit to certain patients who have residual symptoms, so that, no matter what the family's financial limitations are, a great deal of supportive help and definitive group psychotherapy is available to both patient and family at no cost.

Pathological family interaction in which abnormal pressures are exerted on the patient by his family, or where there is a disturbed family situation that can impede his recovery, may require either family group therapy or parent counselling to facilitate the patient's recovery. This can be suspected as an operative factor when the patient's HOD score decreases progressively but is not accompanied by a return to normal function. The disability may then be stemming from an overprotective parent who infantilizes the patient rather than from the previously active schizophrenic process, and this pattern may require therapeutic intervention. At times this may be actively resisted by the dominant parent, who has unwittingly utilized the patient's illness for secondary gain or for other pathologic reasons.

Highly specialized group therapy may be necessary for the patient who has become heavily involved with the drug culture because unless this is done he tends to fall back into the same drug usage which precipitated his schizophrenia. In this type of group therapy, we have found that a straight chemical approach brings the best response. In this group setting, which differs markedly from the traditional analytically oriented group therapy, there is considerable discussion of drugs and their biochemical effects and especially the effects of drugs on the HOD score. The therapist needs to have knowledge of the current drug scene and the whole psychedelic subculture, especially language, life styles, and an awareness of what has recently been termed Consciousness III (Reich, 1970).

Once the patients learn that mescaline, psylocybin, LSD, STP and methedrine elevate the HOD score—with the risk of "freaking out"—they begin leaving these dangerous drugs alone. They learn that these drugs are truly psychotogens for them and that many of them have had to be hospitalized for LSD- or speed-precipitated schizophrenia psychoses. Patients inevitably discover that neither marijuana nor hashish has a residual effect on their HOD score and, therefore, for a period of time, excessive use of these two drugs may replace their former involvement with the more dangerous drugs that are likely to precipitate hospitalization and psychosis. As their HOD scores come down, the use of marijuana diminishes and they begin to function again and return to school or to work.

Prolongation of the excessive marijuana smoking may be associated with altered time perception, which should then be tested for with a timing device such as an electronic metronome (see Chapter 18 on dyschronia). Until this specific schizophrenic syndrome is alleviated, attempts to dissuade the patient from excessive pot smoking are almost always unsuccessful.

PSYCHOTHERAPY

From the model of schizophrenia which we have described, and the description of the diagnostic process, it is apparent that the patient has already been oriented to his illness and that this has been augmented by explanations of the meaning of the laboratory and perceptual test results. In addition to an explanation of the biochemical and perceptual aspects of the illness an explanation is given of how these interfere with functioning, feeling, and relating to others.

Although the illness intensifies pre-existent psychological conflicts and personality problems, it is explained to the patient that the initial phase of therapy will be devoted to medical recovery from the illness and that coexistent psychological problems will not be dealt with primarily until the HOD score is within the normal range. The explanation given for this is that impaired brain function causes so many different kinds of symptoms and effects on the personality that there would be no way of knowing, until the patient gets better, which of them are results of the patient's own personal problems and which are manifestations of an active disease process. The analogy given here is similar to a toxic brain syndrome. A more common example is that of the alcoholic who when actively drinking may develop an enormous range of pathologic symptoms and behavior and when sober may have only mild or no indications for psychotherapy.

Most patients readily concur with this treatment plan. The majority of patients will have already undergone previous psychotherapy, often of a prolonged and intensive nature with a number of therapists, so that they are seldom motivated to take part in any kind of formal psychotherapy. Many patients are actively opposed to psychotherapy as well as being bitter about such previous experiences.

The resentment of patients and families and the turmoil ensuing from previous experience with psychotherapy were responsible for much of the bitter comment about traditional methods of psychiatric treatment for schizophrenia which appeared in the early issues of the *Newsletter* of the American Schizophrenia Association. This same conflict and disillusionment has been reported by professionals themselves when a member of their family has become ill. For example, a Professor of Psychiatry reported his own disheartening experience with this dilemma (Kysar, 1968).

At the North Nassau Mental Health Center, five years of experience using the orthomolecular approach were compared with the previous five years when traditional psychiatry approaches were used. This comparison showed that dynamically based psychotherapy was of very limited benefit in schizophrenia. Although parent counselling and educational and supportive therapy were demonstratively beneficial, and often critically so, therapies based on theories of a psychodynamic etiology of the patient's schizophrenia brought questionable benefit (Hawkins, 1969). Whether psychotherapy or pharmacotherapy was more important was glaringly demonstrated

by the disastrous consequences which occurred when patients discontinued medication. Most patients relapsed upon termination of medication, but showed little response to termination of psychotherapy. One of the most common reasons for hospitalization was discontinuance of medication, yet hospitalization was never required because of a therapist's absence or termination of psychotherapy. Hospitalization was in fact more often preceded and precipitated by the patient's decision to "go for analysis." Those patients placed on the orthomolecular program who continued in psychotherapy with their previous analyst did considerably less well than those patients in whom psychotherapeutic intervention was kept to an absolute minimum.

The clinic's conclusions have been corroborated by similar findings from large-scale research studies done elsewhere as well as by the collective experience of patients and their families.

Information about the value of psychotherapy in schizophrenia can be obtained from three additional decisive areas: (1) controlled studies in the scientific literature; (2) reports from therapists in institutions who have had extensive, long-term experience with the use of psychoanalytic psychotherapy in the treatment of schizophrenia; and (3) the experiences of large numbers of patients and their families.

During recent years, there have been several large-scale authoritative studies on the value of psychotherapy in schizophrenia, the most extensive being that of May (1968, 1969), in which a comparison was made of five different treatment methods in schizophrenia. This study was so extensive and included so many collaborators that a research project of its magnitude on the value of psychotherapy will probably never be duplicated. The study was supported by the State of California Department of Mental Hygiene, U.S. Department of Health, Education and Welfare, U.S. Public Health Service, the National Institute of Mental Health, the University of California Health Services, and the research committee of the Los Angeles Psychoanalytic Society, and there was collaboration with many other authorities too numerous to mention.

In review of this work, Barnes (1971) considers the study to be the most meticulous, intensive, complex, and comprehensive research design in the field of psychiatric therapy. He notes that many will disbelieve the results but

> more for emotional reasons than on the basis of any critical analysis of the work . . . these findings are of the greatest importance both to clinical psychiatry and to mental health program administration . . . it also leads us to wonder about the efficacy of the various therapies used in out-patient work with ambulatory patients, both schizophrenics and others.

The conclusions of this immense study were that medication alone, whether combined with psychotherapy or not, was the most effective and efficient treatment for most patients. Electroconvulsive therapy was the second most effective treatment.

Individual psychotherapy and milieu therapy were found to be the least effective, most expensive, and most time consuming.

Another series of important studies on the value of psychotherapy in the treatment of schizophrenia was reported from the Department of Psychiatry, Harvard Medical School, at the Massachusetts Mental Health Center. The conclusion from these computerized studies was that psychotherapy alone, even with experienced psychotherapists, did little or nothing for chronic schizophrenic patients, even over two years time (Grinspoon et al., 1967, 1968). In another study by the same researchers (Grinspoon et al., 1969) the same conclusions were reached: medication with or without psychotherapy had the most marked benefits. These studies confirm the earlier findings of May and Tuma (1965) that psychotherapy alone does not improve the schizophrenic patient's chances for improvement. In a further study by Shader et al. (1971) the authors conclude that there was no demonstrable difference in the results whether a patient received psychotherapy by either a "Type A" or a "Type B" therapist.

The findings of these extensive studies are supplemented by the 10-year study done by the American Psychoanalytic Association, in which data supplied by 386 analysts on over 3,000 patients reported an overall rate of symptom cure for schizophrenia of 9 percent (1968).

The second area of informative data is supplied by those institutions with long-term intensive experience in the use of psychoanalytic therapy with schizophrenia. Of these, Chestnut Lodge in Rockville, Maryland, is probably the best known. Two recent books from that institution indicate the failure of this method of treatment. In *Schizophrenia and the Need-Fear Dilemma* (Burnham et al., 1969) the psychoanalytic theory of schizophrenia is deftly presented together with an explanation of the lack of positive clinical results obtained. As a matter of fact, all of their case histories end with the patient either dead or still sick with schizophrenia. In the second book, *Conflicts and Reconciliation: A Study on Human Relations in Schizophrenia* (Stierlan, 1969), a similar lack of clinical results is reported.

Gray (1970) points out in a review article that "Sigmund Freud always held that schizophrenia was not amenable to psychoanalytic cure" and that "the challengers of this statement have failed to disprove the truth of it."

The clinic has had the opportunity to provide treatment for a number of patients who had prior long-term in-patient psychoanalytic treatment. In almost every case these patients who had been unresponsive to intensive, long-term psychoanalytic therapy promptly responded to a medical regimen. After 8 weeks of medication and/or ECT in a hospital, the majority had recovered. They are now employed, or back in college, able to socialize and some married. The following case is illustrative:

> This 24-year-old man had been ill with schizophrenia for six years and for the last two years had been in the hospital for psychoanalysis during which time he received no drugs of any kind. The family was alarmed at his deteriorating condition as he had

decided to commit suicide by not eating and the institution refused to use any medications. The family experienced great difficulty in getting the patient transferred to a medically oriented hospital and finally had to threaten legal action to obtain his release. The patient was so disturbed that the hospital had to wrap him in wet sheets mummy fashion and move him by ambulance because of their refusal to use tranquilizer medication.

On admission to the Brunswick Hospital, the patient was mute, withdrawn, severely depressed, negativistic, and uncooperative. After 8 weeks of intensive hospital treatment he recovered sufficiently to be discharged. Within a few months, he was gainfully employed, and was taking college courses in the evening. He then moved away from his family, became independent, and subsequently married.

The foregoing would tend to augment the findings of Will (1970), who concludes an article on psychotherapy in schizophrenia with the statement "*few schizophrenic patients will be helped in this prolonged, expensive and largely unattainable treatment.*"

The general consensus of many schizophrenic patients also has been that the results of psychotherapy were disappointing. Not only are their experiences discussed at meetings of Schizophrenics Anonymous and the various schizophrenia associations throughout the United States, but their collective experience also was expressed resentfully in the first few volumes of the *Newsletter* of the American Schizophrenia Association, as was previously mentioned. Autobiographies by former patients or their families reflect the same attitudes. *In Search of Sanity* by Gregory Stefan (1966) and *Gone is Shadow's Child* (Foy, 1970) are typical examples.

From the foregoing survey of important sources of information, the evidence is that psychotherapy based on psychoanalytic formulations of schizophrenia is of no statistically demonstrable benefit to patients. When done by therapists who are less than expert, psychotherapy may well be deleterious. Therefore, the requests of patients and their families for the inclusion of medication in the patient's treatment is hardly irrational, nor does it constitute "uninformed lay opinion." Many families, especially those who belong to a schizophrenia association, are very well informed and have read extensively. Dr. May's book, for instance, among many others, is for sale at association meetings. (One of the families of the Long Island Schizophrenia Association recently co-sponsored a major professional symposium on Gilles de la Tourette's Syndrome—which indicates a rather high degree of sophistication.)

In the clinic's experience, most patients do not desire or require formal psychotherapy once their HOD scores have returned to normal. During the initial period of the illness, while the patient's HOD score is still elevated, the less interference the patient experiences from the psychiatrist, the better will be the result. Patients who continue in dynamically oriented psychotherapy during this phase recover much slower and to a lesser degree. This conclusion became apparent after several years of experience with patients who were in therapy elsewhere and who were allowed to continue in therapy while the clinic handled their medications. As a group, these patients recovered to such a noticeably lesser degree that the clinic finally had to

recommend that patients discontinue that type of psychotherapy until they had medically recovered from the worst of their illness. When this practice was followed, results were much better—when patients did resume therapy, it was usually for far different reasons than the ones for which they had originally sought it.

After the initial diagnostic visit, patients are usually seen weekly to adjust medications until an effective regimen has been established. This usually occurs by the end of the first month and visits during the second and third months are usually bi-weekly. The average patient is then seen monthly for the remainder of the first year. During the second year patients are usually seen every two or three months, and during the third year they are seen every three or four months.

Inasmuch as the patients go through various stages of recovery, the problems that they present during these periods of time will vary. Initially, the patient needs an explanation and interpretation of the illness followed by support and encouragement. During the first year, the main concerns are associated with symptoms, but these progressively diminish, so that by the end of the first year problems relating to returning to functioning in the various areas of life will be presented. The second year is devoted primarily to the problems of re-entry into a social life, returning to work, or returning to school, and there is a desire to become independent of the family who has supported the patient during the illness. Dependency conflicts become almost routinely manifest and at times family therapy or parental counselling may be required to handle the family's matching anxieties regarding resolution of this conflict. Adolescent-type problems then typify the second stage of recovery, which constitutes the "re-entry" phase.

During the third year, many patients will have grown and progressed beyond the level of functioning which preceded their illness. Many will state that they are "weller" than they were before they became ill, and at this time the actual onset of the illness will be dated retrospectively. This will almost always precede the previously accepted date of onset. This occurs because the patients never knew what it was to feel and function well, and now that they experience this, they will frequently give the exact time in their lives when the internal change had occurred which signalled the real beginning of the illness. Many function with perceptual impairment for years; one characteristic of this state is the subjective certainty that one has "always been this way." Patients may need practical advice as they enter areas of life in which they have never before ventured.

During the second and third years of treatment, when some patients marry and begin having children, their questions concern genetic predisposition and pertain to what percentage of their children may be expected to develop the same illness. Almost routinely, newly married recovered schizophrenics want to know if there are any ways in which they can prevent the occurrence of schizophrenia in their children or detect it early. It is important to advise the women to stay on the medical regimen during pregnancy to prevent post-partum relapses.

Some patients, especially if they became ill during early adolescence, will have developed sizeable, secondary neurotic gains—especially the fulfillment of dependency wishes—and will continue to display immature child-like behavior even though their HOD scores have returned to normal. Some will tenaciously cling to the sick role even though it is no longer appropriate and they may require both explanation of what they are now doing as well as firm encouragement in a more mature direction. Often, these problems become disguised by the patient's adoption of self-serving interpretations of the youth culture "drop-out" pattern. Group therapy techniques are often useful to overcome these delayed maturational problems.

The adolescent rebellion pattern may coexist or predominate, instead of the passive dependent style. As is well known, this may also be a reaction formation. These conflicts associated with the dependence-independence growth phase may require adroit handling, as well as considerable forbearance. Families forget that schizophrenics can demonstrate the same problems that other young people do in our culture and that the problems that they are having with the patients are not all due to schizophrenia. It is frequently necessary to reorient families to this fact, as they lose their perspective from living so intimately with the illness.

In summary, during the acute phase of the illness, when the patient's HOD score is elevated, the most effective psychotherapy is an educational approach, which is of considerable benefit to both patient and family. This is followed by supportive practical advice as the patient recovers and goes through the successive stages of recovery, during which time he may have changing symptoms, which merely indicate that he is passing through a different phase, rather than getting worse, as he may erroneously conclude. The well-known appearance of depression following disappearance of the paranoid and hallucinatory symptoms is an example, and the patient needs to be reassured that the depression symptom will also pass and respond to treatment as did the previous phase.

After the patient's HOD score has returned to normal, specific conflicts may be handled either by supportive, individual therapy or group therapies. At this stage, recurrence of symptoms accompanied by elevation in HOD score indicates that the cause is biochemical and should be treated by a change in the medical regimen. Symptoms unaccompanied by a rise in the HOD score, on the other hand, are probably stemming from interpersonal or psychological conflicts and are, therefore, treated psychotherapeutically.

The approach to the patient during the initial phase of the illness has certain parallels with handling the psychedelic experience, in that every effort is made to influence favorably the patient's set and setting (which includes the therapeutic setting) so that the patient will be subject to benign experiences as much as possible. Following this principle will greatly increase the likelihood of recovery and the prevention of unfortunate sequellae. The importance of respecting the patient's extreme vulnerability when his defenses are inoperative is paramount. Analogies

between the schizophrenic and psychedelic experiences have been made by many authors, including Silverman (1968), Hoffer and Osmond (1967), and Laing (1967).

If the altered biochemistry of some people spontaneously sends them on a "voyage of discovery into inner space" then their experiences should be made as positive as is possible. This is also emphasized by Dabrowski (1964) in his book, *Positive Disintegration*, which demonstrates the possibility of reintegration at a higher level of functioning, as so many of our patients actually do.

In our view it is a serious misunderstanding to consider, as Laing has done, that if some people are defined as having schizophrenia the word itself is an epithet or a damaging "label." A vase can be used to hit someone over the head, but that does not mean that vases are inherently damaging or evil. *All* labels are potentially damaging—the fact that a person is labelled as American, Catholic or Protestant, black or white, rich or poor, educated or whatever, will put that person in very serious trouble in certain social circumstances. Some groups in society will negatively use any label that can be thought of. We should see to it the word schizophrenia is not used in that way against our patients, but the dilemma is not solved by pretending that the condition does not exist.

Although from a theoretical viewpoint the schizophrenic experience can be made a positive one, it should not be allowed to last indefinitely. Even a voluntary psychedelic experience is emotionally exhausting and the subject is relieved when it is over. Because the situation in which the schizophrenic experience occurs is seldom favorable for any length of time, the "voyage" of the schizophrenic illness is endlessly painful. We have never known a patient to have regrets that the experience was finally over—the plunge into another experiential world was involuntary. Even those patients who became schizophrenic following the intentional use of psychedelics did not intend to go that far—they meant to only spend a day that way—not years or maybe forever.

RESULTS AND RESPONSE TO TREATMENT

General Problems in Evaluating Treatment Results in Schizophrenia

Once it becomes known that a particular institution is using a new or helpful approach to an illness it tends to attract a distorted sample of patients. A progressively increasing percentage is made up of difficult and intractable cases. Determining the results of treatment then becomes more difficult and interpretation of statistics is less and less meaningful. Reporting of results in schizophrenia is notoriously fraught with

almost impossible obstacles, so that no matter how carefully research designs have been devised they are still subject to criticism in some area. Each professional discipline has its own criteria of what is meaningful. Control groups can also be grossly misleading, as the variables which one researcher considers essential to control are ignored by another. As Williams (1971) has shown, even identical twins are not biochemically nor even anatomically equal. Matching groups of patients with schizophrenia as to age, classical diagnosis, sex, or occupational group may actually be of minimal importance.

Of considerably more clinical significance would be the matching of groups of patients who are identical with respect to HOD score, incidence and severity of hypoglycemia, type of previous treatment, and favorability of life circumstances. Of importance also are the patient's degree of knowledge of his illness and the manner in which it has been presented to him. The use of the medical model itself, for instance, has an effect in that the patient is allowed to be ill when he is ill. The nonspecific effects of Selye's general adaptation syndrome also have to be taken into account, as the response of the patient during the alarm reaction can be quite different from the response of a patient when he is in the stage of chronic resistance or exhaustion.

We would also have to know whether the average HOD scores in the contrasting groups, even though numerically equal, were on the rise, indicating a worsening of the condition, or were falling, indicating a process of remission. We could not, for example, compare pneumonia patients based just on their temperature. A temperature of 102° might occur because the patient is in the process of going into a fulminating crisis where the temperature might eventually reach 107°, or because his temperature has been previously higher, which would indicate that he is in the process of getting well.

Evaluations of drug responses are difficult to assess, as many such studies utilize fixed dosages instead of the *optimal* dosages which take into account individual variation. Fixed-dosage-schedule studies, therefore, give only mathematical probability figures and fail to indicate the real clinical usefulness of a given medication when used in the proper dosage and in the proper sequence.

Because of the impossibility of meeting all these crucial requirements, results of any treatment method in schizophrenia are probably most usefully conveyed to clinicians by giving as detailed and accurate a description of the clinical response as is possible, so that the results could be duplicated. The average busy clinician is interested in treatment methods that are practical and produce observable results. In daily practice, he tends to be pragmatic and unimpressed by the polemics of theoreticians. Most physicians are aware that the ultimate scientific explanation of most of the treatments they use in daily practice will not be forthcoming in the near future. Practical considerations prevail when the physician is confronted by the sick patient.

Practical Factors: Acceptability, Applicability, Cost, and Safety

The orthomolecular approach circumvents most of the public's objections to psychiatric treatment. Psychiatry has generally been accused of developing treatments which are totally impractical in that they are either extremely time consuming, expensive, and drastic, they produce serious side effects, they fail to produce results, or they are so objectionably named as to cause them to be rejected and resisted. In addition, many of the treatment modalities require a high degree of motivation, sophistication, verbal ability, and insight, and the absence of factors which would result in their not being accepted for a particular treatment. Intensive psychotherapy, for instance, exemplifies many of these objections, and in addition often results in alienation of the patient from the family, which in itself is an extremely serious side effect.

"Shock" treatment, by its very name, has such dread connotations that its applicability and acceptability have been seriously curtailed. Long-term hospitalizations for psychodynamic therapies are extraordinary in cost and disappointing in results. Imprudent publicity and actions by some agencies have caused many patients to be more concerned with side effects than they are with getting well. This has reached such a degree that recently a depressed patient who wanted to commit suicide was reluctant to take antidepressants because they might cause side effects! She was not even aware of the absurdity of her position, so deeply had this fear been embedded in her mind. Another block in reaching large numbers of patients is the idea that all psychotherapy is "Freudian." Schizophrenic patients especially are not enthusiastic about the prospect of having their personal privacy invaded by interrogation, especially when it does not pertinently relate to what they are experiencing.

In our experience with the orthomolecular–medical model-approach to a wide variety of patients representing the whole socio-economic scale, this treatment method has been extremely well accepted. The involvement of patients and their families in an integrated community system allows them to compare notes, observe results, and compare experiences of different treatment methods. This has had a remarkable effect on morale and cooperation and it results in a beneficial increase in education of both patients and their families.

Because return visits are widely spaced and diminish in frequency with time, this treatment method is economically feasible and compares favorably with more traditional ones. Patients feel that their illness is being monitored by some objective means rather than by just the subjective opinion of the psychiatrist or family.

The treating psychiatrist has objective data upon which to base treatment and verify results so that this treatment method is also well accepted by the professional. In addition, the treatment method can be used in private, hospital, and clinic practice

and is suitable for treating large numbers of patients at significant savings in cost and manpower.

The safety factor is considerable, and this is important in our present society. Because psychotherapy with this treatment system is aimed primarily at educating and increasing the understanding of patient and family, disruption of the family is not a side effect of treatment. Patients are not advised to leave the family unit, because the family is not viewed as pathogenic. A recovered patient may decide to leave a family unit because he feels that the particular family structure is deleterious to his recovery, but that is an individual matter which may be handled by family therapy. In our experience with this method, in the majority of instances when the patient leaves the family unit it is because he is well enough to make it on his own. As patients recover, they develop insight into the fact that the illness caused perceptual distortions, and that many of their perceptions of family interaction were distorted and subsequently remained in that form in their memories. Recognition of this results in reconciliation with the family more frequently than disruption. The storing up of distorted memories of a family interaction has been described by others, including Rubinfine (1971), who stated that

> schizophrenics suffer impairment of consciousness from infancy onward so that percepts are registered in this altered state and memories from this state of infancy onward are impaired. These distorted perceptions become openly evident in the decompensated state and treatment requires correcting these altered percepts.

The side effects that we have observed in treating over 5,000 patients with megavitamins have been minimal and minor. We have seen no side effects from vitamin E except for loose stools in one patient. Pyridoxine has not produced side effects in any case. Vitamin C in in the routine dosage of 4 grams a day has not resulted in discernible side effects. Although loose stools are supposedly a possibility, we have not observed this. We have three patients with a history of gout on 4 grams per day and there has been no increase in uric acid level, nor attacks of gouty arthritis. There is serious doubt as to whether ascorbic acid produces any significant incidence of side effects. This was reviewed in an article on the subject in World Medical News, Vol. 12, Issue No. 8, February 26, 1971. Patients who were pregnant were continued on megavitamins with no untoward effects on either the mother or the baby.

Niacinamide in a dosage of 4 grams a day can produce nausea in a few patients, usually adolescent girls. This can be circumvented by the use of buffered niacinamide in capsule form, the addition of one tablet per day of meclazine (Bonine®), or by lowering the dosage.

The side effects of niacin have been extensively reviewed in articles by Hoffer (1969), Mosher (1970), and Boyle (1968); the contraindications remain those of duodenal ulcer, hypertension, gout, and diabetes. If niacin is not used in these conditions (although it can be with adequate medical controls) the only side effects seen are those

of the initial flush and occasional nausea. The flush can be diminished by taking the full starting dosage of 1 gram four times a day with meals and a glass of cold milk in the evening, or by premedicating the patient with cyproheptadine (Periactin®). The flush disappears in 24 to 36 hours and is hastened by raising the dosage rather than by lowering it (on a low dosage, patients will continue to flush indefinitely). Inasmuch as the flush is due to a release of histamine from the mast cells, the histamine is sufficiently "washed out" after a day so that insufficient histamine is released by subsequent doses to cause further flushing. Nausea can be controlled by the same measure as with niacinamide. An inositol salt of nicotinic acid, available in Canada as Linodil®, also effectively circumvents nausea. Young patients, especially those with red hair and fair complexions are least tolerant of niacin and may develop a recurrent itchy rash requiring its discontinuance. The niacin flush may also produce heartburn or other gastrointestinal symptoms in a minority of cases, also requiring its discontinuance. Niacin may also give false positive liver enzyme tests and should be discontinued two days prior to the testing procedure. It will also cause hyperglycemic changes in the glucose tolerance curve, and accordingly should not be given for 48 hours before that test.

We have seen patients who have taken 20 to 40 grams of niacin daily for prolonged periods with no adverse effect. In general, as both Hoffer and Mosher conclude, and our experience corroborates, niacin appears to be relatively harmless as long as due caution is taken in avoiding its use in the presence of the aforementioned contraindications.

Administratively, the orthomolecular approach provides several sizable advantages. The cost, waiting time, and professional manpower for psychodiagnostic testing are greatly reduced. Psychiatrists can handle large numbers of patients without any special equipment, although having one's own biochemical laboratory is a distinct advantage. Continuity of treatment is not interrupted when there is a change of doctors, which is a frequent circumstance in clinics and hospitals and one that poses difficulties if the therapy is based primarily on psychotherapy. The treatment method results in enormous economic advantages in that seeing a patient once a month costs about one-twelfth as much as seeing patients three times weekly for long-term therapy.

Joining Schizophrenics Anonymous and taking part in the activities of the schizophrenia associations further reduces costs in that they supply specific group therapy at no cost to the patient. When the cost of treatment in the average case is prorated over a three-year period the annual cost of treatment itself will amount to only a few hundred dollars, which compares very favorably with any other available treatment system. Even in those cases where hospitalization is necessary the comparative cost is still relatively low because the average duration of hospitalization with this treatment method is only 8 weeks, and rehospitalization is seldom necessary except in a very chronic and severe case where the patient has been ill since childhood.

Because this treatment method utilizes objective monitoring of the patient's response, it facilitates reporting of improvement by treatment agencies, and this may become of progressive importance. In New York City, for instance, all mental health agencies contracting with the City's Funding Agency must now demonstrate tangible outcome of treatment to justify funding. With this treatment system, response to treatment in individuals or groups can be demonstrated even before the patient's behavior begins to reflect that improvement. The following case is an illustrative example:

> A 34-year-old housewife developed schizophrenia postpartum. She had been hospitalized and then treated unsuccessfully for two years. When the patient applied for treatment at the clinic she was depressed and relatively immobilized, with a HOD score of 110. On a treatment regimen of megavitamins, hypoglycemic diet, phenothiazines, antidepressants, and supportive therapy, she clinically remained essentially the same, with neither symptomatic nor behavioral improvement.
>
> Serial HOD testing showed, however, that the score was coming down progressively. It was not until the fourteenth month of treatment, when the HOD score got down to 30, that her symptoms finally disappeared and she resumed total functioning. Two months prior to her behavioral recovery the question of hospitalization had arisen. Because of the trend of the HOD scores, however, hospitalization was not advised, as it appeared to be only a matter of time before the HOD score would finally reach the level where recovery would occur.

In this case, several important things were demonstrated. First, an unnecessary hospitalization was avoided, but had it occurred her recovery two months later would have been falsely attributed to it. Second, a behavior rating scale or multiple interviewing techniques would have erroneously concluded at the end of the first year of treatment that she was no better, when in fact the basic disease process was considerably improved. The obverse is also true, in that, for instance, many patients have worked the very day they committed suicide, and the HOD score could have picked up the increasing severity of their illness despite behavioral status quo. The pressures in our society toward normal behavior are so enormous that relatively normal behavior may still occur in the face of *serious* degrees of illness.

Evaluation of Effectiveness

In view of the previously described difficulties in evaluating treatment results in schizophrenia, a variety of ways of demonstrating the effectiveness of this treatment approach can be described in terms that are appropriate for different settings.

OFFICE PRACTICE

The only absolute control which meets all of the essential criteria is the utilization of the patient as his own control. This also eliminates the problem of placebo or transference responses. In this regard, it is useful for the physician to select from his own practice patients with whom he has become familiar, whose failure to recover despite all previous treatments had been personally observed, and about whom he has collected a great deal of subtle and usually unreported data. A change in the patient's response then becomes readily apparent even though transmission of this observation to others may only sound anecdotal and be difficult to demonstrate convincingly. The following two cases are illustrative:

Case No. 1: This 33-year-old housewife and mother of three young children had been overtly and severely psychotic with schizophrenia for five years. The family had unlimited means and provided her with the best of professional help. She had been in a number of hospitals and was treated by many highly qualified psychiatrists. She had had all the psychotropic drugs in massive doses and in multiple combinations, as well as several courses of electroshock therapy. Despite all this, her condition became progressively worse. She was openly delusional, suicidal, out of contact, and irrational.

Because of the hopelessness and severity of her condition, a prefrontal lobotomy was finally advised and it was scheduled to be performed. At this point, the family asked if she could be given a trial of megavitamin therapy before resorting to the drastic surgical procedure. The reply was "Lobotomy, yes—niacin, no!" The family then had the patient transferred, against medical advice, out of the hospital and had her admitted to the Brunswick Hospital. The patient was not at all happy about the transfer; she did not like the new hospital, did not believe any treatment would help, and did not like the new doctor—she did, however, agree to take the prescribed medications.

On a combination of megavitamins, thyroid, hypoglycemic diet, and a small dose of tranquilizers, she recovered in 10 weeks. She was discharged from the hospital 4 years ago and during the intervening time has returned to full normalcy, including taking care of her children, running her household, and becoming active in the PTA and other social activities. In addition, she is working at a part-time job. She is seen for after-care visits at the clinic every four months. She looks well, feels well, and has no symptoms. During February 1971, she was interviewed by a correspondent on CBS News on nationwide television and she gave no sign of ever having been ill.

Case No. 2: A 24-year-old unmarried, unemployed young woman with a diagnosis of borderline paranoid schizophrenia had spent 10 years in weekly psychotherapy during which time she had three different therapists. Despite everything, she remained "half well" in that her borderline paranoia prevented her from holding a job, keeping a boyfriend, or making close friends. She stayed home and bemoaned her fate that she would always be disabled and would never be able to get married. She felt herself to be a social fifth wheel and an embarrassment to her family, who belonged to a subculture in which for a young woman of her age to be unmarried was a social disgrace. All of the psychodynamic possibilities had been repeatedly explored, but her condition remained static. In addition to different phenothiazines, a variety of medications had

been tried. She usually had unpleasant side effects and her attitude toward medications was suspicious.

At this point, the therapist put her on a sugar-free diet with no explanation, except that it might help her to take off weight. She was also placed on the megavitamin regimen with the explanation that vitamins might give her more energy. Because she suffered from apathy, listlessness, and hypochondriasis, she agreed. Within a few months she began to demonstrate a different emotional tone and lost the hostile, paranoid edge in her interactions with others, so that for the first time in her life she made a friend. Soon after, also for the first time, she was able to keep a boyfriend (prior to this time she had gone out with many young men but she was so hypercritical that seldom did they call her for a second date).

She now was able for the first time to hold a job and get along with her superiors. In the past she had always become paranoid and had either been fired or quit in a huff. She subsequently married, now has two children, and functions normally as a housewife. All medications were prophylactically temporarily increased after the birth of each child to prevent a postpartum episode.

To the clinician then, the efficacy of a new treatment method is most convincingly evidenced by a clinical response in patients who have failed to recover by all previously tried methods.

HOSPITAL PRACTICE

Changes in the collective HOD scores of groups of patients demonstrate the effectiveness of a given procedure. A research project done at the Brunswick Hospital demonstrated the usefulness of this method in determining the effect of ECT in the treatment of schizophrenia (Chiossone et al., 1969). In this study, all patients were given both the HOD and OIT tests on admission and again on discharge. The same patients were also evaluated on a clinical rating scale and although there was no statistically significant difference between the two groups at the time of their discharge as far as their degree of recovery, suitability for discharge, and scores on the rating scale, the HOD scores demonstrated that there had been a marked difference in response to treatment.

All patients were treated with phenothiazines, megavitamins, accessory symptomatic medications, group therapy, and all the other usual adjunctive measures, with the exception that 85 patients received ECT and 55 served as controls. When the results were tabulated and graphed, the very significant effect of ECT was observable. This was most marked in the younger age groups (Fig. 30-1).

Figure 30-2 shows the effect of ECT as compared to the control group by graphing only improvement in the percentage of scores above the median on the perceptual subscale of the HOD test.

Figure 30-3 graphs the same results, except that the improved scores have been obtained by totalling the paranoid and perceptual subscales. The purpose of comparing these subscales with the total scores is to eliminate the effect of improvement

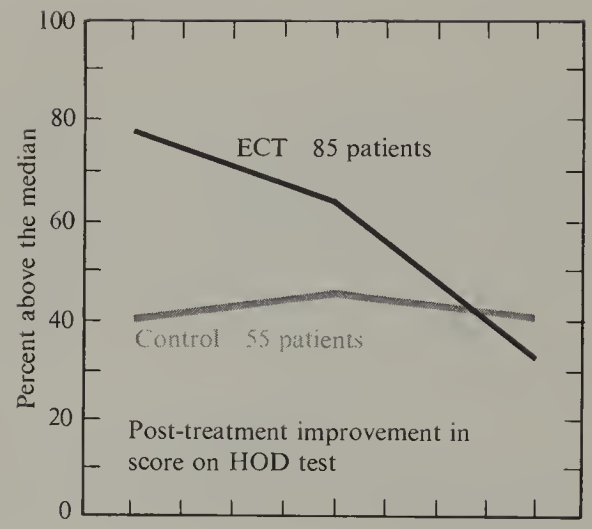


FIGURE 30-1.

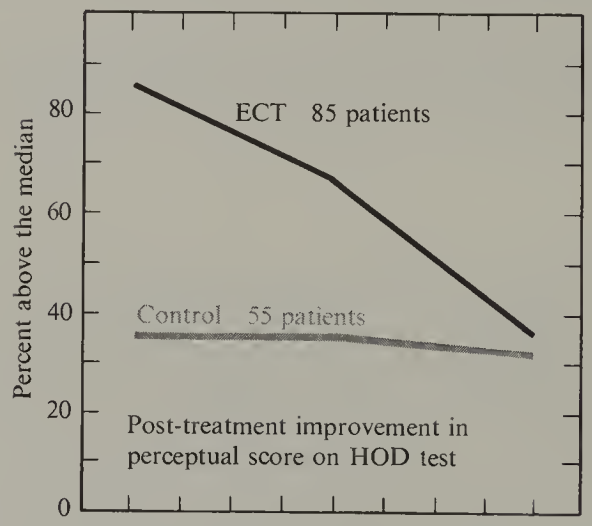


FIGURE 30-2.

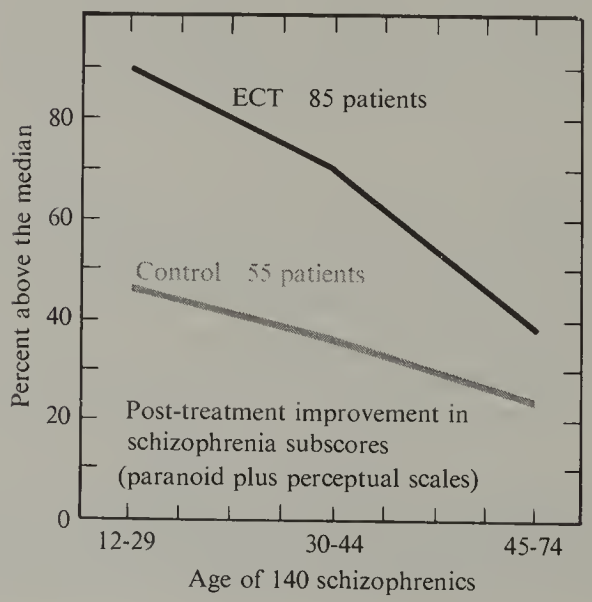


FIGURE 30-3.

in the patient's depressive susbcales, as depression in and of itself is not intrinsic to the schizophrenic process and is often only reactive. By eliminating the depressive subscale, comparison of the two groups demonstrates the substantial benefit of ECT in the young schizophrenic and it demonstrates that this is not due to the alleviation of any accompanying depression, but rather to an alleviation of the schizophrenic process itself.

Without the use of the HOD test, this marked difference could not have been demonstrated as rating scales based on behavior showed no difference between the two groups. This study again supports the view that schizophrenia is both an inner experience and a perceptual disorder and not just abnormal behavior, arbitrarily labeled as schizophrenia.

In reporting the above data, a method was selected to by-pass rater bias and to demonstrate that behavioral rating scales would have been grossly misleading. Also, it was assumed for purposes of this study that the patients were in a worsening condition with a rising HOD score at the time of their admission to the hospital. In addition, all patients were on the same diet and all patients were seriously ill. This type of reporting of data is suitable for evaluation of the effectiveness of a treatment which has a rapid response. During a short-term hospital stay it would be impossible to evaluate the effects of other treatment measures such as the use of thyroid or megavitamins, which usually take a few months or even six months to a year to demonstrate results.

A follow-up study was conducted at the Brunswick Hospital during a two-year period to determine the effects of the continuance of megavitamins on the recovery rate (Hawkins et al., 1970). So that results of the study would be comparable to other follow-up studies reported in the literature, it was arbitrarily decided to use the rehospitalization rate as evidence of response, as that is the most frequently cited criterion. The pros and cons of utilization of rehospitalization rates have been well discussed over the years and will not be cited here except to say that in a practical way it represents the resultant of many factors, including social survival. The study included 140 patients who had been hospitalized because of severe schizophrenia, during which time the patients were hospitalized for an average length of 8 weeks. While in the hospital, all patients received phenothiazines, megavitamins, and adjunctive therapy. The diagnoses were confirmed by HOD testing and no cases were included in which there was doubt about the diagnosis. At the time of discharge from the hospital, megavitamins were discontinued in 85 patients. The remaining patients were subdivided into subgroups taking the megavitamins for periods of three months or for one year. Tabulation of the rates of rehospitalization (to any hospital) over the two-year period of study revealed that among the control group, in whom megavitamins were discontinued, 35 percent were rehospitalized. Of patients who continued on the megavitamins for three to six months, 25 percent were rehospitalized. The rehospitalization rate for the patients who stayed on megavitamins for one year

or more was 16 percent (9 of 57 patients). The χ^2 score value for this comparison is in excess of the 5.99 required for a significance at the 0.05 level, indicating a definite correlation between the continuation of the megavitamin therapy and a 50 percent lower readmission rate than for the patients in the control group.

CLINIC PRACTICE

In a clinic setting it is possible to follow large numbers of patients for a considerable length of time and also to observe subgroups in which schizophrenia is associated (for example, with alcoholism, drug abuse or homosexuality). In evaluating a new treatment method, several of the most common sources of evaluative error need to be eliminated—rater bias, placebo reaction, and positive transference "cures."

Placebo effect can be eliminated by studying patients who have had many trials over the years on multiple drugs without success and also by waiting for a year to pass before evaluating results. Rater bias can be bypassed by objective testing, such as the HOD test. Other objective data can also be used, such as achievement of sobriety by the alcoholic, discontinuance of drug abuse, cessation of homosexual activity, return to college, or whatever criteria are appropriate to the sample being studied.

Positive transference reactions can be eliminated by a variety of techniques which are also applicable to private practice. Using patients as their own controls is obviously the best. Looking for a difference in recovery rates between patients who have a positive transference and those who have a negative transference is another commonsense approach. In actual practice, treating large numbers of patients who are chronically ill and who have had a number of therapists and many different drugs eliminates most doubts, as it is obvious that if they were prone to placebo or transference cures they would not still be ill. There is really no answer to the question of spontaneous remissions except that in the comparison of large groups of patients over many years it can be assumed that the spontaneous remission rates in both groups will have equalized.

One criterion for the effectiveness of a medical regimen is the response of the patient when it is discontinued. Another way of ascertaining the specificity of a treatment modality is to determine the type of case or disease entity where it does not work. In schizophrenia, which is most likely a group of different biochemical illnesses, evaluation of drug studies requires clinical interpretation. As an example, if the effectiveness of a given antibiotic in treating pneumonia is reported in percentages, it can well be that of all pneumonias treated by a given drug, only 10 percent might respond. This might be taken to mean that the antibiotic is only 10 percent effective, and therefore hardly warrants marketing. The clinical fact may be, however, that the 10 percent represents a particular type of pneumonia for which the particular antibiotic is close to 100 percent effective and is in fact specific for that type of pneumonia but not for others. It would appear that in the psychiatric

literature similar conditions prevail. The importance of some of these factors was pointed out by Fritz Freyhan in his presidential address to the American Psychopathological Association. The influence of the double-blind study on the actual practice of clinical psychiatry has been curiously nil. Not a single treatment used in psychiatry was discovered by the use of the double-blind method, with one single exception—the first double-blind study done in psychiatry (actually it was a triple-blind study), devised by Hoffer and Osmond to study the effect of niacin in schizophrenia, and the results of this meticulous, long-term study were generally ignored for some years (see Chapter 10 by Osmond on the history of the niacin treatment).

In reporting data, then, the clinical researcher is confronted by a communications problem (Heston, 1970). We have found that the most useful style of reporting results to other clinicians is in terms of definite observations that include enough data about the circumstances to allow the results to be duplicated. To report the total clinical experience of treating 5,000 schizophrenic patients with a new treatment method involving a new conceptual framework over a five-year period presents sizeable difficulties. Because the setting itself influences treatment results, some general description of the situation in which a clinical experience takes place will be described.

The clinic itself is situated in a very informal setting, above a set of stores, and is innocuous and unforbidding in appearance. Each office is decorated differently so that a schizophrenic patient is unlikely to feel depersonalized or lost. The informality extends to the waiting room which lends itself to conversation and is friendly rather than institutional in style and atmosphere. It is not the kind of place where a patient is likely to feel like a number. Each patient and family becomes aware that specific arrangements are being made for them individually. Over the years, many of the families and clinic staff have had meetings under a variety of circumstances and have developed a certain community feeling and mutual concern. To some degree, the well-being of each patient then subsequently becomes part of the total community concern, so that if a given patient is not doing well there is an immediate feedback. This is a unique situation and although it exerts considerable pressure on the staff, it also results in a certain enthusiasm and a heightened therapeutic intention. There is an expectation that every patient is going to improve sooner or later, therefore any self-fulfilling prophecies that occur are likely to do so to the patient's benefit.

The patient most likely to respond to this overall treatment regimen has an elevated HOD score and a discernible perceptual dysfunction. These represent the majority of patients and most of these patients will have improved or recovered by the end of a year. The patients who fail to improve are, as stated previously, usually those in whom the onset was in early childhood, and they are further characterized by low HOD scores, primarily visual distortions, and the stilted postural attitudes indicative of an underlying proprioceptive disorder of long duration. This latter group constitutes the

minority of patients, and of them only about half will improve.[5] Also, they do not show the complete recovery which frequently occurs in the more favorable group. Even so, the improvement may be in areas which are extremely important to patient and family, so that limited improvement may still be of considerable importance. The following case is an example:

> A 30-year-old chronic schizophrenic patient was brought to the clinic after having had 15 years of continuous prior treatment, including six hospitalizations where she had a full course of insulin shock treatment plus a total of 125 electroshock treatments. The family indicated that this was to be the last trial of treatment before they would reluctantly have to accept permanent state hospital placement for the patient. The family reported that she was incontinent, refused to wear her false teeth, constantly rocked, and was uncommunicative. She therefore presented a considerable nursing problem for her parents.
>
> The patient was placed on an overall treatment regimen of hypoglycemic diet, megavitamins, phenothiazines, and thyroid. She responded very slowly, but by the end of two years her appearance was markedly improved, she used make-up, wore her teeth, spoke politely, had stopped rocking, and had long since been continent. The family was able to take her on social family visits, and could travel in public with her.
>
> This patient was far from recovered, however, in that her affect was flat, her behavior was still moderately inappropriate, and her overall style was awkward and somewhat stilted, but her family was extremely pleased. The treatment also had been based on bi-monthly and then tri-monthly visits, which were within the family's financial capacity.

The megavitamin approach is effective in other conditions associated with an elevated HOD score, such as alcoholism or post-psychedelic drug reactions. It is the most effective treatment for post-LSD "flashbacks" of the type reported by Horowitz (1969) and far more efficient than psychotherapy (Hoffer, 1972). It also is of benefit to some hyperkinetic children and also to some with learning disorders (Rossi, 1967; Green, 1970, 1971). There are many adolescent patients who present a clinical picture of pseudo-psychopathic behavior due to an underlying, unrecognized schizophrenia disorder, and in these patients the behavior improves on the overall megavitamin regimen.

We have not observed any benefit from megavitamins on convulsive disorders but the hypoglycemic diet has helped several. Megavitamins are also ineffective in manic-depressive or other psychoses. They are also ineffective in the psychoneuroses. (Many "neurotic" patients, however, are greatly helped by the hypoglycemic diet—especially depressed, anxious, phobic, fatigued, irritable, or hypochondriacal patients. In many of these, the diet eliminated the need for psychotherapy.) We have

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[5] These results were confirmed by a research study conducted by the Institute for Child Behavior Research in which it was reported that 50 percent of the children responded to megavitamins (Rimland, 1970, 1972, and Chapter 24 of this book).

treated six patients with prior lobotomies and none of them responded to the treatment although their diagnosis was definitely that of schizophrenia.

The homosexual schizophrenic patient responds quite favorably, and by the end of the first year of treatment the majority report the disappearance of the supposed homosexuality. In these cases, no discussion of the homosexual pattern was entered into during the entire year and the recoveries from these patterns were reported spontaneously. It would seem that the perceptual disorganization impairs the self-image, including sexual identity. This was accompanied in these patients by regression and the development of pseudo-homosexuality, as has been described by Ovesey (1954, 1955a, 1955b). This was most likely to occur with male schizophrenics. Several female schizophrenic patients who were also alcoholic continued a homosexual life style despite abatement of the schizophrenic process.

Postpartum psychotic episodes were completely eliminated in our schizophrenic patients with this treatment method. By prophylactically increasing doses of medications immediately following delivery, this complication was prevented, which was in marked contrast to clinical experience of years past. On the other hand, several patients who had previously recovered and then stopped all medication became pregnant and did have postpartum relapses.

Thereapeutic results do not depend on a positive transference. Its presence, however, is helpful, not so much to the eventual outcome as to the ease of clinical management of the case. We have treated a number of patients via family members and also by mail with results equal to those for patients seen in the clinic. The following case is an example:

> A 44-year-old man with chronic paranoid schizophrenia of 10-years duration had been given up as hopeless after many years of treatment. The family kept him home in an upstairs room where his condition was disturbed and dishevelled. He screamed obscenities at his hallucinatory enemies, refused to change clothes, refused to take any medication, and exhibited no interest in external events. The family came to the clinic, learned of the megavitamin treatment and worked out a combination of vitamins titrated with bicarbonate of soda and flavored with chicory, which was then placed surreptitiously in all of his beverages.
>
> After a few months he began to respond and improve, and at that point a small dose of thioridazine in liquid form was added to his formula. By the end of the year he had become a clothes dandy, carried on a normal conversation, was no longer hallucinating, was calm, read a daily paper, watched television, and answered the telephone. Two years later he continues to do well and is planning to live on his own, which has created apprehension with the family, as they are still reluctant to inform him of their secret treatment. When they finally tried to persuade him to take megavitamins he said he didn't think he needed them as he had been doing pretty well on his own for the last few years!

Getting patients to take the medication and stay on it is seldom a problem, especially after they have had an opportunity to experience subjective improvement.

A few patients who have recovered will feel so well that they will experiment with discontinuance of the therapeutic regimen and promptly relapse. One reason this occurs is that in altered states of consciousness there is difficulty in remembering what one has learned in another state of consciousness. This has also been demonstrated experimentally in animals and is a common clinical observation. This phenomenon does not appear to be attributable to the mechanism of denial, although that, too, may at times play a role. Recovery from relapses unfortunately is usually slower and more difficult than was the original recovery. This is more true in children than adults, however, and has been reported also by Cott (1969).

As patients recover, certain questions tend to recur. Many of these relate to the ability to concentrate and the question of when to return to college or work. Initially, when the patient's HOD score is high, his ability to concentrate is markedly impaired, and we usually ask patients if they are able to follow a story on television. When the HOD score is close to 100 this is usually not possible, but as the patients recover they will report that they are now able to follow the story, so this is a favorable indicator. It is usually some months and, in many cases, close to the end of the first year of treatment, before concentration returns to the point that the patient is able to remember what he has read, and we advise him not to return to college until this capacity has returned. We recommend that the patient take 6 credits the first semester and if that goes well, that he take 12 credits the following semester and then 15 credits thereafter. Allowing patients to return to school prematurely invites failure and discouragement.

Return to work, on the other hand, is quite different and this may occur almost immediately or as soon as the patient feels "up to it." It is a common observation then that the patient is capable of returning to work sometimes the very day following discharge from the hospital and yet he is unable to take evening college courses for a whole year.

As has been pointed out previously, we avoid invading the patient's personal privacy when his HOD score is elevated and interpersonal contact is painful. This saves a great deal of reparative work later which would otherwise become necessary to undo the deleterious effects of such intrusions. Where the patient has already had this unfortunate prior experience, some reparative therapy to the patient's damaged self-esteem may become necessary as he recovers. A patient's resentment over having had this experience forced upon him in the past can be amazingly severe.

Lastly, it is on the administrative level that the effect of the orthomolecular treatment approach first becomes most strikingly apparent. There is an almost immediate disappearance of waiting lists. There is a marked reduction of diagnostic testing costs and time. There is a progressive increase in the case load within the same budget and manpower limitations, and there is an overall improvement in treatment results which is expressed in a very positive feedback. The level of functioning in group therapy with schizophrenic patients increases noticeably to a higher level and the

percentage of patients who are capable of such interaction also increases greatly. The preoccupation is no longer with "keeping the patient out of the hospital" but rises to the level of counselling him about the advisability of seeking a better job at this time, or on the timing of an impending marriage.

Another response noticeable to administration is that sizeable numbers of patients who were on welfare at the time they began treatment will be off welfare by the end of a year, since their social disablement stemmed from a previously undiagnosed perceptual disorder.

GROUP AND HALFWAY HOUSE EXPERIENCE

All of the Schizophrenics Anonymous groups that did not use the orthomolecular-megavitamin approach soon failed and all the groups that were successful had taken the orthomolecular approach. In Alcoholics Anonymous, many members were unable to stay sober until they were placed on a sugar-free diet with megavitamins. In 1972, an estimated 20,000 to 25,000 alcoholics were taking megavitamins.

This approach is an integral part of the therapeutic regimen in many alcoholic rest homes. Of these, the most comprehensive and intensive therapeutic regimen is the one in use at Guest House, Lake Orion, Michigan, for alcoholic priests. In their experience, high-dosage megavitamins and hypoglycemic diets are critically essential in the recovery of a sizeable percentage of their alcoholics. It is notable that they achieve an overall recovery rate of 80 percent (Ripley, 1969, personal commun.).

A more elaborate study by Smith (1971) included 4,243 alcoholics. Of these, a group of 507 patients had been carefully followed for five years. All were long-time-treatment failures, and 400 of the 507 cases had been sober for two years and more, which is quite remarkable considering the severity of their condition. A formal cross-over double-blind study of two sanitarium groups will be completed in 1972. A full report of 3,673 patients will also be forthcoming. In this study, it can already be reported that niacin was superior in effectiveness to niacinamide.

Similar positive results were reported by Hawkins (1967) in the first group of clinic patients treated with this method. In that group there were 53 alcoholic-schizophrenic patients. By the end of a year, 41 patients were active in AA and 36 had achieved sobriety.

When the HOD test was given to residents at a halfway house for soft drug users (Kinsman Hall, New York), almost two-thirds were found to have abnormally elevated scores and they were unresponsive to the intensive therapy until placed on megavitamins (Palmer, 1970; Hepper, 1970, personal commun.). The experience of this halfway house could be expected from the work already done on the use of the HOD test with psychedelic-drug users by the LSD Rescue Service which is in operation in major cities throughout the United States (Peters, 1971, personal commun.).

The LSD Rescue Service has for years relied primarily on giving megavitamin doses and on attempting to raise blood sugar level to counteract adverse psychedelic drug reactions. It is notable that they have discovered that high doses of thiamine hydrochloride have been found to be beneficial in reducing the craving and return to the use of methedrine (speed).

The use of niacin and niacinamide in ameliorating LSD reactions is well known among the more knowledgeable members of the drug subculture and has been reported widely in the underground newspapers. *The Hippy's Handbook* (Bronsteen, 1967) details this use under "Rx for a Bad Trip" and also has this to say about psychiatry, "Without one single exception, every hippy interviewed had, at one point, gone to a therapist—in every single case the experience was negative . . . modern psychiatry is out of touch with young people. . . ." The "Practical Advice" section of Abbie Hoffman's *Revolution for the Hell of It* (1968) includes similar advice to avoid the psychiatric establishment and to use niacin or niacinamide for "freak-outs." The use of megavitamins for the "drug wipeout" is described in the Do It Now Foundation's *Conscientious Guide to Drug Abuse* (Pawlick, 1971).

The evidence then for the effectiveness of the combination of megavitamins and hypoglycemic diets in correcting perceptual disorders, whether they are associated with outright schizophrenia, alcoholism, or drug use, is derived from widespread experience in a variety of patient population groups and settings.

We can compare the results of this treatment with statistics as given by authorities in the field of schizophrenia. For instance, the Chief of the Center for Studies of Schizophrenia for the National Institute of Mental Health, Dr. Lorin Mosher, indicates that only 30 percent of the patients who develop schizophrenia are able to return to work, and according to Caffey et al. (1970) only 15 percent of patients who had been hospitalized for any appreciable length of time ever function in a completely normal way thereafter. Statistics from the New York State Department of Mental Hygiene indicate that 55 percent of patients hospitalized for schizophrenia are readmissions and in this percentage are many patients with multiple rehospitalizations. As compared to these overall large-scale statistical guidelines, it would appear beyond any doubt that the orthomolecular psychiatric approach offers substantial and valid hope to patients and family. As the number of patients increases, the development of an integrated community system for the treatment of schizophrenia evolves to meet the growing needs of the patient population. The strength of the system, however, relies entirely on demonstrable results.

SUMMARY

Following the diagnostic process, the patient is given the results of the tests and the diagnosis, along with an explanation of his illness based on the orthomolecular

medical model and the significance of his perceptual disorder. The patient is then placed on a medical regimen consisting of a hypoglycemic diet, prescribed rest and exercise, phenothiazines, and other ancillary medications and megavitamins. The importance of detecting and treating functional, relative, or absolute hypoglycemia is stressed.

While the HOD score is elevated, psychotherapeutic intervention is kept to an absolute minimum. Those problems that still remain after the HOD score has returned to normal may be dealt with by psychotherapy if the patient is so motivated. Recovery is facilitated by the use of ancillary measures such as SA, group therapy, family therapy, AA, halfway houses, or specialized drug groups. Case histories and vignettes are used to explain and illustrate many of these principles. Evidence is reviewed to corroborate the experience that psychodynamically oriented psychotherapy does not influence the basic disease process itself to any statistically demonstrable degree.

The patient group most responsive to the orthomolecular approach is identified by an elevated HOD score, which demonstrates perceptual dysfunction. The majority of these patients recover by the end of the first year, re-enter life's activities during the second year, and in the third year are able to function on a higher level than they were before they became ill. We have not seen this response with any other treatment method.

The general problems inherent in evaluating the results of treatment in schizophrenia have been briefly surveyed and an attempt made to report a huge mass of data in terms which are useful to the clinician.

The orthomolecular approach is very practical. There is a high degree of acceptability and it is suitable for a wide range of applications in a variety of settings such as private practice, hospital, clinic, halfway house, and a diversity of groups. Because patient visits are widely spaced, there is a great saving in cost, not only to the patient, but also to the institution. With proper safeguards, there is an ample safety factor. Medical contraindications to the use of certain vitamins in high dosage are enumerated and toxicity is reviewed. The positive safety and cost factors are augmented by the establishment of a specialized laboratory.

We have described the effectiveness of this overall treatment approach with several thousand patients over a five-year period. Its evaluation in private practice has been with an emphasis upon using the patient himself as the ideal control, and we have also discussed how this overall system is used in hospital practice. We included the results of a study utilizing group improvements in HOD scores to demonstrate the effectiveness of ECT. This study demonstrated the defect of behavioral rating scales and the marked effectiveness of ECT in amelioration of the schizophrenic process especially in the younger patient. The results of a two-year follow-up study to evaluate the effect of continuance of megavitamins on the relapse rate have been reported. Using the rehospitalization rate as the criteria of effectiveness, the control group had twice the relapse rate of the megavitamin group.

The patients most likely to respond to this treatment have elevated HOD scores associated with schizophrenia, or schizophrenia plus homosexuality, psychedelic drug abuse, or alchoholism. Although each requires different handling, the overall results are promising and the degree of positive response in the majority of cases was responsible for the development of an integrated community system for the treatment of schizophrenia. The system is related to a variety of other treatment settings where a large body of positive results with this approach have been reported over the years.

The overall results from such a wide range of clinical experience correlates with both theoretical formulations and laboratory research to establish a broad foundation for the concept of orthomolecular psychiatry.

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APPENDIX

The History and Work of *Schizophrenics Anonymous*

JOSEPH R.
DONALD F.

In 1963 Gregory Stephan (a *nom de plume*), a schizophrenic recently released from a veterans hospital in Ann Arbor, Michigan, attended a meeting of Alcoholics Anonymous to see if he would be able to relate to other people. As Stephan listened to the members discuss their problems, he was surprised to learn that two other nonalcoholics were attending, and while talking with them after the meeting, he discovered that they too were schizophrenic. If schizophrenics were benefiting from AA meetings, Stephan thought they could derive even greater strength and stability from belonging to a group whose members shared their own illness, schizophrenia. Thus, Stephan decided to try to establish a group similar to AA, in which schizophrenics would be able to share their common problems and strengths.

It is important, before continuing the story, to point out that after Stephan was released from the VA hospital he sought and found biochemical help from two doctors who had spent years working on the chemical origins of schizophrenia. He became convinced that schizophrenia was not an environmental illness and decided to make the megavitamin regimen an integral part of the therapeutic process to be used

by the new group. Thus, Schizophrenics Anonymous can boast that it was the first "self-help" group to champion the belief that schizophrenia is biochemical in origin.

Stephan's plan was to bring him much frustration. He was attempting something controversial and found that many doors were closed to him. He talked with the chaplain of the VA hospital where he had formerly been a patient and attempted to get help for his new organization, but the chaplain could do little, for the psychiatrists with this institution were opposed to the belief that schizophrenia was caused by a biochemical imbalance.

He did not give up, however, and soon afterwards he met with Dr. Abram Hoffer and Dr. Humphry Osmond in New York. Here the question was brought up by Stephan as to the advisability of starting a self-help group for schizophrenics. The two doctors were very enthusiastic and arranged for a meeting with Bill W., co-founder of AA. Bill also thought the idea was worth trying and he, Hoffer, and Osmond encouraged Stephan to follow through with his plan. It was decided that Stephan would start the first group, bringing together other people who were afflicted with the same disease. Hoffer told him to look upon what he was doing as an experiment that could very well pay large dividends.

Stephan travelled to Flint, Michigan where he intended to set up his pilot project. He helped to found the group, and he also became affiliated with another organization that believed schizophrenia to be caused by a biochemical imbalance. He did not feel that he could lead both groups, and he got in touch with a friend who was schizophrenic, and talked him into becoming the active chairman of the new self-help meeting. Most of the twelve persons who became interested members were going to psychoanalysts who were opposed to the theory of a biochemical origin of schizophrenia. The patients enjoyed and benefited from the meetings, but their doctors were extremely hostile, and this led to the group's demise.

This first attempt to form a group composed solely of schizophrenics suffered defeat, but defeat for the idea would not be accepted. Dr. Hoffer decided to organize a group in his own home town of Saskatoon. He wrote to eight alcoholic schizophrenics, four of whom were AA members. They met with Dr. Hoffer on October 15, 1964, and he explained his plan to them. They unanimously agreed to form the group. After the first meeting Dr. Hoffer informed them that he would no longer be in attendance, that this was to be a self-help organization and they were on their own. It was this small group in Saskatoon that successfully founded Schizophrenics Anonymous.

SA is a fellowship of men and women who seek a common goal: recovery from the disease known as schizophrenia. SA members accept the belief that schizophrenia is basically a biochemical disease that must be treated with those vitamins, other nutrients, and chemicals that will give the individual the opportunity to live as normal a life as possible. The psychological aberrations are seen as being caused by faulty body machinery.

What is the purpose of anonymity in the program? Unfortunately, to the general

public schizophrenia is still considered to be a shameful disease. Therefore, many SA members would not be as candid about themselves if their full identities were known. Also, it is the desire of the organization to prevent some individual members from capitalizing on the name of the organization for publicity or pecuniary advantages.

Since the founding of SA new discoveries about schizophrenia have been made through research. It is now realized that besides the vitamins, other methods of treatment can be used to alleviate schizophrenia. Thus, Schizophrenics Anonymous is now supporting the treatment modality for schizophrenia that has been given the name "orthomolecular psychiatry" by Linus Pauling.

Most SA groups administer the Hoffer–Osmond Diagnostic (HOD) test, which is a compilation of cards from which the individual must decide whether the statements are true or false regarding himself. The cards give an accurate indication of whether or not the individual is schizophrenic. The questions should be answered honestly, since this is the best way to decide the degree of the illness and the particular areas in which the main problems exist. The test is simple to administer and easy to score, which makes it possible for a member of an SA group to score it quickly and accurately.

An SA chapter, to operate successfully, must be composed of several important ingredients. The first of these is a devoted membership, whose interest is not only to get themselves well, but to help others as much as possible, within their own capabilities. A chapter cannot function adequately without solid leadership. The people composing the leadership of SA must have a fairly comprehensive knowledge of the chemistry of schizophrenia and devote much time to encouraging others to practice the steps and to follow the physician's instructions in the treatment of the disease. Each group has a chairman (who may be called the president) and it is his job to make sure the meetings start on time and are run properly. There is also a corresponding secretary in most SA chapters, who plays a very important role. It is his responsibility to make sure all incoming mail is answered, and to handle any communications with the mass media. SA is a self-supporting group, and therefore needs an efficient treasurer. He must make sure that collections are taken up at the meetings and that all financial obligations are met. It is also usually his job to be certain that the vitamins are available to the membership at each meeting. The key ingredient, though, in all chapters, is the awareness by each member of the importance of a well-balanced life. If this does not exist, recovery becomes a much more formidable task.

A person with schizophrenia is ill physically, emotionally, and spiritually. The physical part of the disease should be treated by a doctor who is knowledgeable in orthomolecular psychiatry. The task of restoring the schizophrenic to mental and spiritual health can be done to a large extent by SA. Basically, SA uses the twelve steps and twelve traditions compiled by Bill W. for AA. The only major difference in our use of the steps and traditions is the deletion of the word "alcoholism," which is replaced by "schizophrenia." It is believed that if a person follows these guidelines

his chances for recovery will be greatly enhanced. The twelve steps have become the way for many members of SA to lead a happy and productive life. We also borrow sayings from AA such as "Let go and let God" and "Take things one step at a time." The latter is fundamental to recovery. The schizophrenic too often becomes overwrought because he worries about the future instead of concentrating on the present. In SA it is believed that we should live in the present, for the past is beyond our control and we have no idea what the future will bring.

In SA, as in AA, there are two kinds of meetings. The most common is the closed one, where schizophrenics are able to express those things which are troubling them, and they often get solutions to their problems from other members of the group. It is seldom that a schizophrenic has a problem that some member of his chapter has not already solved. A doctor can look up a symptom in a textbook, but he is often not sure how to treat it. A person who has coped with a particular situation successfully may very well be of more help to the patient than the doctor. This is one of the tenets on which SA is founded. Usually, the problems a person is having will be discussed in the closed meeting, and they often relate to the particular step being covered. Even if they do not, the patient is encouraged to talk about those things that are bothering him.

Once a month, most groups hold an open meeting at which a doctor who practices orthomolecular psychiatry or a recovered schizophrenic is invited to speak. It is at this time that relatives, friends, and the general public can benefit from the SA meeting. Those in attendance can receive great inspiration and hope from these speakers.

Besides the meetings, members of SA become involved as a group in other activities. Perhaps once a month, they get together for a social activity such as bowling or a party. They are also in frequent communication during the week, sometimes for social reasons, and at other times to help those who are not feeling well. Setbacks seldom occur, but when they do the person who is ill can depend on his fellow members to do everything in their power to assist him through his difficulties.

The schizophrenic tends to be extremely egocentric and, unlike the alcoholic, he is usually asocial. When he first comes into SA the schizophrenic is usually very wary of those around him. His desire is to be left alone and not to become involved. The first week he hears about the successful results that have been derived from orthomolecular psychiatry and listens with some attention. From the second week on he joins the closed meetings and begins to relate to those problems being discussed. By the third or fourth week the new member begins to see hope and realizes that his problems are not unique. Other members have been in his situation and have recovered. He now begins to talk at meetings and to communicate with his fellow schizophrenics, who are often the only people with whom he feels comfortable. After a slightly longer period of time in SA, he comes to the conclusion that if he can communicate with the members of the group he should have no trouble associating with

people who are not in the organization. At this point he has made a great psychological adjustment and he is ready to re-enter society as a productive individual. However, we hope he will stay with Schizophrenics Anonymous and become part of its leadership. There is little doubt that he can still gain much from SA, and more important, SA can gain much from him and his experiences.

The spiritual recovery of the schizophrenic is fascinating to watch. When he first comes to SA, he sees God, if he believes in Him at all, as a sadist who is putting him through all kinds of tortures and who should be feared as the supreme vengeful being. At this point the schizophrenic is concerned primarily with himself, secondarily with others, and lastly with God. As recovery takes place he becomes much less concerned with himself, more concerned with others, and, if he now believes in God, he sees Him as beneficent and all-loving. Thus, the spiritual aspect usually shows a complete reversal as the member responds to therapy.

In Schizophrenics Anonymous, we have found the step which states complete surrender to be the most important. If the individual insists on fighting the disease himself, without the help of SA or a competent physician, his chances for recovery are minimal. Determination, while a good quality, will not aid him in correcting a biochemical imbalance. If the imbalance remains, no matter how hard he tries, the illness will not subside.

The members of SA have discovered that the best way to treat this illness is with orthomolecular psychiatry, and they have found that psychoanalysis, during the early phases of treatment, is usually harmful. It tends to enhance the egocentrism which is one of the signs of the illness, and instead of relieving symptoms it adds to their intensity or number. When the patient has recovered, therapy may be helpful, but during the crisis period, it should be definitely avoided, in the opinion of SA members.

Schizophrenics Anonymous has experienced great growth in the few years of its existence. Starting out with eight members in Saskatoon, it now has approximately thirty chapters in the United States and Canada. This not only shows that schizophrenics are united to help each other, but also that the concept of orthomolecular psychiatry is becoming widely accepted. SA has prospered during its brief existence, and its future looks even brighter, for the news of its success is quickly spreading throughout North America.

Additional information about SA may be obtained by writing to Schizophrenics Anonymous International, Box 913, Saskatoon, Saskatchewan, Canada.

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