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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.
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> 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 (1958), 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

rception" responds the best. The grown-up childhood schizophrenic with the OD score, postural stigmata of propioceptive deficit, and primarily visual per- al distortions is the least likely to benefit. The most significant visual perceptual tion in this group of patients is loss of depth. This particular distortion, even it is induced hypnotically in normal subjects, produces a schizophreniform nse with primitivization and regression, as has been shown by Aaronson in al studies (1967a, b, 1968). This type of patient appears to belong to a different iemical subcategory of the subtypes of the schizophrenias.

e megavitamins and the phenothiazines act clinically as though they had a gistic action, and for that reason patients are kept on a low daily dose of a othiazine prophylactically even after they have recovered. Sainz (1964) has onstrated that the phenothiazines elevate blood ascorbic acid levels, and there be a variety of synergistic effects such that the antipsychotic action of the pheno- ines may be augmented by the megavitamins. Demonstration of the effective- of the combination requires correction of co-existing functional hypoglycemia. any patients, in our experience, recovery was prevented by lack of adherence to ypoglycemic 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.
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> 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 re unaware of the importance of ameliorating the hypoglycemia and, therefore, r first reports on the use of nicotinamide in schizophrenic children stated that . . niacin and niacinamide were found to be relatively ineffective in childhood izophrenics and less effective in adult schizophrenics with childhood onset" awkins, 1967, 1968b). Similar negative experiences have been reported by Roukema d Emory (1970) and Greenbaum (1970b), who also demonstrated that nicotina- ide alone in the treatment of childhood schizophrenia, except for improvement in me individual cases, did not produce statistically significant results. It was Cott 969) who pointed out that recovery of childhood schizophrenics on megavitamins as 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 schizophrenic 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 (G. . Iberg, 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

rbic acid in schizophrenic patients has been shown by Cowan et al. (1970) and iously by Herjanic and Herjanic (1969) and VanderKamp (1966). Current es by Pauling and Robinson and by Herjanic are reported in Chapters 2 and 14 his volume.

igh doses of ascorbic acid may occasionally cause mild diarrhea in some viduals and it may cause false positive urine tests in diabetics who use commercial e test kits. A case is also reported in which ascorbic acid shortened the prombia time in a patient who was receiving a Warfarin (Coumadin®) anticoagulant senthal, 1971). In treating over 5,000 patients with 4 grams or more of ascorbic per day, however, we have not had a single instance of any serious side effects. /e explain to patients that vitamin B6, pyridoxine, is necessary as a precursor of tinic acid. It is an intermediary step in the biotransformation of tryptophan to tinic acid where it is required for the hydroxylation of kynurenine (derived from tophan) to 3-OH-kynurenine and for the further metabolism of 3-hydroxykynine to 3-hydroxyanthranilic acid (immediate precursor to nicotinic acid; Gibbs Walshe, 1969). Vitamin B6 deficiency interferes with the metabolism of amino s, proteins, and biogenic amines, and causes abnormalities of nervous system vity in man, where the pathological effects of deficiency are most marked on the loping brain. Abnormalities of vitamin B6 metabolism have been associated not with schizophrenia but also with a variety of other abnormalities of the central ous system, and B6 deficiency at the subcellular level may be produced by a ber of antimetabolites (Knapp, 1966; Coursin, 1969). The antagonism between min B6 and L-dopa is a recent illustration (Duvoisin et al., 1969; Cotzias and avasilion, 1971). Pyridoxine in high doses has been used by Cott (1969) in the tment of childhood schizophrenia. The role of pyridoxine in psychiatric disorders recently been summarized by Ananth, Ban, and Lehmann (1972) in their paper tled "Potentiation of Therapeutic Effects of Nicotinic Acid by Pyridoxine in onic Schizophrenics" presented at the Canadian Psychiatric Convention in ntreal, June 8, 1972. This paper states that pyridoxine potentiates the action of tinic acid, possibly by opening up the kynurenine cycle of tryptophan metabolism thereby decreasing the formation of indoles. In their study, already referred to, doxine alone had a therapeutic effect in schizophrenics as well. In more than 0 patients we have not observed a single side effect from pyridoxine administra- of 200 mg daily.

is best to write down the medication schedule and the recommendations for p and diet on a card and give it to the patient at the initial visit. It is also advisable dicate to the pharmacist that all medications be labelled to show the name and age size. Unless this is done, there will be mistakes and many call-backs as most ents are perceptually disordered and unable to remember verbal instructions.

summary, the addition of megavitamins is inexpensive and safe, and very itively 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 Cyschronia). 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 hypoglycemic 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

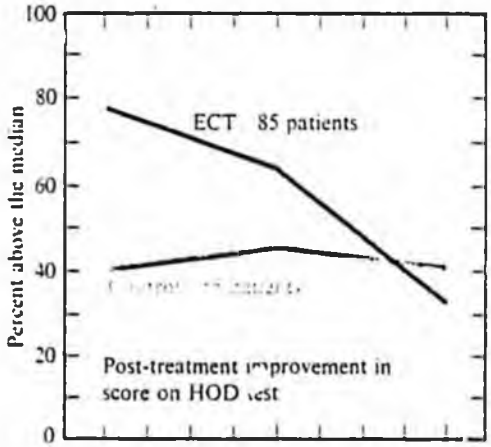


FIGURE 30-1.

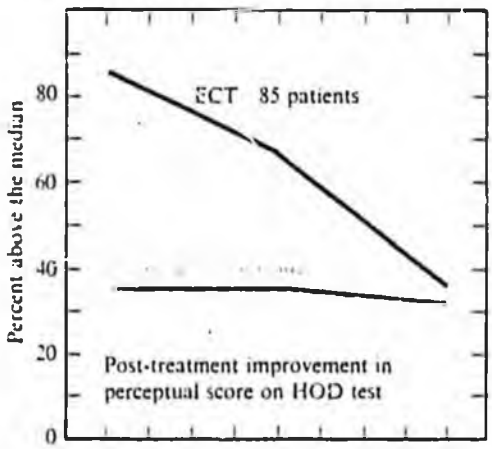


FIGURE 30-2.

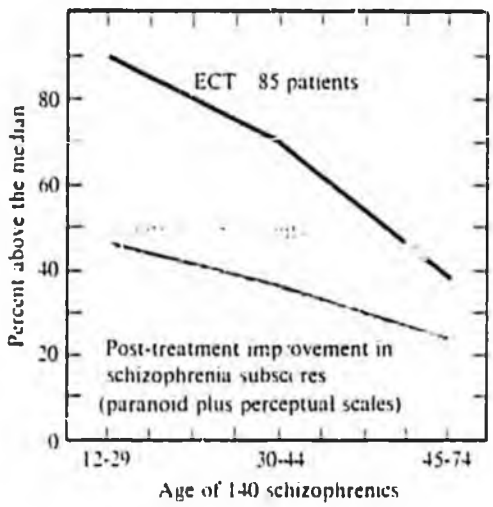


FIGURE 30-3.

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.

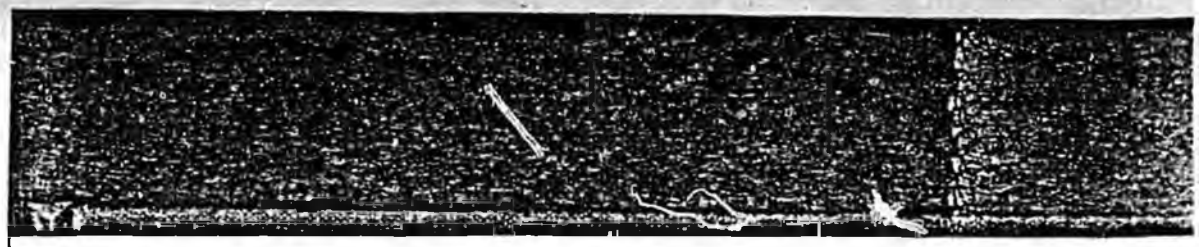
CLINIC PRACTICE

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.

Therapeutic 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 A onymous 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-schizopnrenic 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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NUTRITION AND ORTHOMOLECULAR THERAPY

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NUTRITION AND ORTHOMOLECULAR THERAPY

Nutrition is a branch of biology which studies the requirements for foods, their composition, and the processes by which they are converted into energy and the tissue growth and repair required for health and life. Prior to about 1750, nutrition was naturalistic and ethno-pharmacological. Plant and animal foods of unknown chemical composition were eaten in diets which varied greatly from culture to culture. Centuries of trial and error had demonstrated their value or danger. Certain foods were designated by Hippocrates to have special curative properties which were useful in the treatment of many of man's illnesses. Others were poisonous or tabooed for unknown reasons. In the period from 1750 to 1900, as chemistry developed, foods were simply classified chemically as carbohydrates, proteins, fats and the non-combustible ash. Attempts to raise animals on diets containing only these quickly showed the inadequacy of this simple classification. The golden age of nutrition occurred between 1900 and 1950. When the need for micronutrients was discovered, a conceptual revolution occurred with the insight that much of man's illness resulted from the absence of significant dietary constituents. To the established infectious and toxic theories of illness were added the deficiency diseases. With the discovery of vitamins, essential amino acids and trace elements, the nature of common diseases like pellagra, beri beri, scurvy, nutritional anemia and protein malnutrition were quickly understood. The development of quantitative standards for daily requirements of these nutrients for man, animals, and plants stimulated revolutionary changes in food production and several major public health triumphs. It is difficult to recognize that less than 50 years ago there were more than 200,000 cases of pellagra annually in this country. Mortality from this illness averaged 33% and about 10% of the beds in insane asylums

the country were occupied by demented patients with this illness. In the South, where pellagra was endemic because of the staple diet of corn, fatback and molasses, from 1/3 to 1/2 of the state mental hospital population had physical symptoms of pellagra and dementia (1). Pellagra was also very common among sharecroppers and in prisons, orphanages, and other state institutions. The discovery in 1937 that vitamin B_3 (niacin) was the antipellagra vitamin and the subsequent fortification of most cereal products with this vitamin made pellagra virtually absent in this country. Clinical nutritional research was greatly accelerated in World War II because of the need to develop adequate military rations. It led to the semi-quantitative determination of human needs for most nutrients. It was so successful that World War II was the first war in which more combat troops died from war injuries than from malnutrition and infection (2). The spin-offs to civilian nutrition were large. Today, nutritional science is sufficiently advanced so that, in this country, malnutrition is uncommon and when it does occur, it is likely a function of poverty, alcoholism, or self-selected inadequate diets. This is not true in the Third World where millions of children are stillborn, retarded, or die within the first few years of life because of the unavailability of adequate calories, protein, or micronutrients (3). In the world as a whole, malnutrition today remains as large a public health problem as infectious disease with which it constantly interacts.

In the richer, industrialized world, research in nutrition has moved into more specialized areas. In medicine, there have been significant advances in the study of the nutritional needs of special populations like pregnant women, premature infants, and the elderly. Vitamin requirements have been shown to increase when some drugs are administered for treatment of tumors, convulsions,

or even contraceptive purposes (4). Great advances have been made in furnishing the nutritional requirements of postsurgical patients or those with severe burns by total parenteral feeding. Specialized nutritional needs have been found for some patients with ophthalmological or dermatological disease. Genetic illnesses, like phenylketonuria, have been found to be clinically responsive to minimizing the intake of the amino acid phenylalanine. Rare genetic autosomal recessive illnesses characterized by mental retardation and multiple somatic defects have been found. These can be prevented or cured by the daily administration of very large quantities of particular vitamins (3,5,6).

Nutritional theories of the etiology of common mental illness and behavior disorders and treatments based on these theories are very controversial. Nevertheless, new diagnostic methods have shown that several psychiatric illnesses may be complicated by nutritional deficiency and may respond to nutritional supplementation. We shall discuss these below. These are all reviewed in an excellent text, Nutritional Support of Medical Practice (7). A comprehensive review is offered in the five volumes entitled Nutrition and the Brain (8).

Many natural foods, especially those from plants, contain chemicals which are biologically active and may be either toxic or therapeutically useful. Many of these substances have been identified and isolated in pure form and now are useful products in our pharmacological armamentarium. In the industrialized world, food chemists supplement natural foods with nutrients and also with natural and synthetic additives which enhance the taste and appearance of foods and diminish spoilage, thus enhancing their useful distribution. Residues from synthetic herbicides and insecticides used to increase crop production and steroids and

antibiotics used to increase animal food production may appear in our food. Because of this, there has arisen the quasi-nutritional subspecialty of nutritional toxicology designed to protect the public from foods which might contain dangerous chemicals like mercury in fish or selenium in wheat or foods to which chemicals are purposely added during processing. There has also been increasing interest in what might be called nutritional pharmacology. Selected, specific nutrients like the amino acids tyrosine and tryptophan or the quaternery ammonium compound choline can be fed in doses greatly above their usual intake levels in order to elevate neurotransmitters in the brain. Such precursor therapy is actively under investigation and its interest to psychiatry will be discussed below. Although the substances used are natural and even essential in our daily diet in small quantities, quantities employed in precursor therapy are so much greater than are ordinarily required that we choose to call the use of the substances in these quantities "pharmacological." Moreover, their biological effects at high concentrations may be different from and unrelated to their primary action. For example, nicotinic acid and nicotinamide have identical nutritional value as vitamin B_3. In very high doses, nicotinic acid causes vasodilation and lowers blood cholesterol; nicotinamide does not. These actions of nicotinic acid at high doses are considered pharmacological (9).

There is also included under the rubric of nutrition, the study of food allergy and hypersensitivity to either specific foods or to commercial additives. Reactive hypoglycemia, generally attributed to the use of high carbohydrate diets which result in the over-production of insulin which, in turn, leads to hypoglycemia has also been studied in relation to clinical states as diverse as panic disorders, depression, and aggression leading to crime and delinquency (10,11).

Along with the slow, cautious, and steady advances in nutrition, there continues to be what we call "pseudonutrition". Nutritional fads have been promulgated in the lay press, in books, and in a few journals. These attribute many common somatic and psychiatric complaints to inadequate or toxic diets. They promise much: enhancing longevity, diminishing the risk of, or improving the treatment of cancer, heart disease, and the major mental illnesses with appropriate dietary therapies. These generally unproven treatments are especially popular among those with illnesses which are chronic and for which conventional medical or psychiatric treatment is slow, not yet fully adequate, and often, expensive. Patients with cancer and mental illness seem to be extraordinarily susceptible to seduction by these claims. Substantial efforts and quantities of time and money have been spent in scientific trials to test the claims of nutritional faddists. Despite many negative results, the claims persist. We shall, therefore, devote some time and space to a discussion of the theory which underlies the claims of the therapeutic value of orthomolecular psychiatry, additive free diets, hypoglycemic diets, and diets designed to eliminate substances to which patients claim to be hypersensitive and which they feel may cause the major mental illnesses.

Nutritional Principles

Man, as an evolutionary product of the animal kingdom, has nutritional needs similar to those of other mammals. The complex foods he eats are digested to simpler molecules which are then absorbed and resynthesized under genetic interactions to the multitude of compounds of which he is made. Maintenance of body temperature, movement, growth, repair and reproduction require energy supplied mainly by the oxidation and carbohydrate and fat. Metabolic end products like exhaled carbon dioxide or urinary nitrogen metabolites need constant replacement from dietary intake. Even the body minerals are constantly turning over metabolically and must be replaced by ingested food. For growth and development, a positive balance of calories and essential nutrients must be supplied. For adult maintenance the balance should be zero. Control of appetite and food intake involves a complex set of sensors and feedback systems in the brain and endocrine organs which are beyond the scope of this chapter.

Despite the capacity of each species to synthesize the myriad of compounds unique to it, some things must be supplied in the diet. These include water, the major anions and cations of the cellular fluids and skeleton, and trace elements like copper, manganese, cobalt, fluorine, vanadium, selenium, and zinc. Ten amino acids cannot be synthesized and must be furnished. They are needed for the synthesis of proteins and other nitrogenous compounds. Thirteen vitamins are required, four of these are fat soluble, eight are members of the vitamin B complex and vitamin C is uniquely required by man, primates, the guinea pig, an East Indian bat, and a bird. It is a remarkable testimony to the synthetic capacities of the body that the thousands of compounds of which we are made can all be synthesized from approximately two dozen organic compounds furnished in the diet.

Several features of man's nutrition deserve comment. First, as mentioned previously, he is quite rare in requiring vitamin C. The evolutionary purpose of this is not known. Second, he is an omnivore who eats a greater variety of foods than any other known species except perhaps the rat. Undoubtedly, this offers a great evolutionary advantage since it permits man to survive on the indigenous food of any region on earth. Third, he is apparently the only species whose choice of diets is determined by taste, smell, color, appearance, and even texture. He is the only animal for whom eating is both a necessity and an aesthetic experience. In contrast to most animals who eat the same food every day of their lives, man constantly seeks variety and, whenever possible, gets it. The aesthetic qualities of food have had interesting social consequences. For example, it may be argued that Columbus discovered America while looking for food additives; that is, the spices that help to preserve food and enhance its taste and color. In the industrialized United States, food companies compete vigorously to produce products which are more attractive than their competitors even though they are nutritionally equivalent. This is done with food additives. Many of the food fads are based upon presumed, but unproven, hazards created by commercial food processing. Man still attributes to foods magical properties which can hurt or help him.

Fourth, the precise nutritional requirements for man are less well known than they are for the domesticated animals which supply his food. There are several reasons for this. Experiments can be done on food animals which cannot be done safely with man. Animals are bred to be genetically homogeneous and efficient in their conversion of food to milk, eggs, or edible animal protein. Their daily activities and energy output are much more closely regulated than are those

of man. Finally, the economics of the food industry make it essential to know the minimum food requirements of animals for maximum growth and marketability. Despite the difficulties in precisely determining the nutritional requirements of man, reasonable estimate have been made since 1941, by the Food and Nutrition Board, National Research Council of the National Academy of Sciences. These are revised every five years; the 9th edition (121) was published in 1980. It offers recommended daily allowances (RDA) for calories, protein, minerals, and vitamins for men, women, and children. The RDA are not minimal requirements. Recognizing substantial variance in man's nutritional needs because of genetic heterogeneity and living habits, they are calculated by the Board to exceed average nutritional needs by a "safe margin" allowing for individual differences in a basically healthy population. The magnitude of the safety factor is substantial. For example, the minimal requirement for folic acid is estimated to be about 50micrograms per day; the RDA is 400micrograms. The RDA has been accepted by the American Medical Association (122) and is used by the Food and Drug Administration for food labelling. It is also the basis on which the Department of Agriculture and the United States Public Health Service established national food programs and nutritional educational programs. The RDA can be found in most standard texts of medicine, pharmacology, and biochemistry (3,4,7).

In an affluent society, man's omnivorous appetite and his wish for variety makes it easy to obtain a nutritionally sound, balanced diet. RDA requirements are generally met by diets which offer a mixture of four food groups in adequate proportions. These groups are (1) Fruits, vegetables, and fruit juices; (2) Grains and grain products; (3) Meats and meat products; (4) Milk and milk products.

Such diets offer adequate nutrients as well as taste and variety. When they are consumed, vitamin or mineral supplementation is not required. Impoverished populations here or abroad who subsist largely on grain and who have no variety in their diets generally need supplementation with vitamins, minerals, and other proteins.

Under special conditions of illness, severe dieting, heavy alcohol consumption, stress, pregnancy or lactation, supplementation may be desirable with modest quantities of vitamins. Massive supplementation with megadoses of vitamins is required only in three conditions. (1) In the genetic vitamin dependency or insufficiency illnesses, (2) When there are transport difficulties for nutrients in the gut or across other cell membranes, and (3) When antivitamin antimetabolites are used as in the treatment of cancer.

Some orthomolecular psychiatrists believe that the brain may have nutritional requirements so much larger than the other body tissues that cerebral avitaminosis may exist and may account for much major mental illness.

But, malnutrition generally produces mental changes along with somatic changes like weight loss or anemia. In early or minimal nutritional deficiences mental changes may occasionally appear before readily observable physical changes ensue. But, careful examination will reveal lowered blood or tissue levels of vitamins or minerals. The mental changes associated with vitamin deficiency are nonspecific. Perusal of the literature shows that weakness, irritability, anxiety, anorexia, lassitude, depression, apathy, anergia, headache, dizziness and inability to concentrate have been reported in subjects or patients with mild deficiency of any of the water soluble

vitamins. When the deficiency is severe, memory loss, disorientation, delusions, hallucinations, and other signs of dementia may appear.

Clinical ecologists, advocates of the Feingold diet, and some orthomolecular psychiatrists believe that in some individuals, the brain may be uniquely allergic or hypersensitive to certain foods, food additives, or other environmental chemicals. Such hypersensitivity is considered by them to be related to hyperkinesis in children and a variety of illnesses including schizophrenia, depression, anxiety, drug addiction and antisocial behavior.

But, allergy or hypersensitivity when it exists involves the whole body and is manifested by physical symptoms like asthma and urticaria as well as by nonspecific mental complaints.

In the following sections we shall discuss: Consequences of protein calorie malnutrition, psychiatric manifestations of deficiencies of some of the B complex vitamins and the use of amino acids in pharmacological doses as precursors of neurotransmitters. Finally, we shall devote the remainder of the chapter to an examination of what we call "pseudonutrition" in relation to psychiatric practice.

Protein Calorie Malnutrition

Many studies conducted in impoverished socities have shown that severe, prolonged protein calorie malnutrition is especially devastating to infants and children and that the consequences are prolonged and likely irreversible. The results of such studies have been summarized in several excellent monographs derived from international conferences on this subject (12,13). The reasons for this high vulnerability is the rapid growth of the human brain in infancy and the effects of malnutrition on its growth and development. Winnick (14) has shown that, in the human, the number of brain cells increases linearly from gestation until birth and then more slowly until about 10 months of age, at which time it virtually stops. Cell size, in contrast to cell number, continues to increase for several years. Myelination occurs rapidly at birth and is still occurring at two years. The weight of the brain increases rapidly through gestation and the first two years of life, its rate of growth diminishes thereafter, but adult weight is not reached until adolescence. Studies on the brains of children who have died from malnutrition show that children dying from marasmus in the first two years of life have from 15 to 50% fewer brain cells than normal children of comparable age. Children with kwashiorkor who become malnourished after being taken off the breast in the second or third year of life have a normal number of brain cells, but the size of the cells is diminished (15). Studies of the behavior of children who survive early malnutrition show that such children have profound disturbances in the acquisition of language, motor skills, interpersonal relationships, and adaptive and motivational behavior. Memory defects have also been found (12,14). Most of these studies have been limited to children studied only a few years after recovery from malnutrition. However,

an ongoing longitudinal study by Cravioto and DeLicardi (16) should ultimately give an answer to the question of whether or not the damaging consequences of early malnutrition are truly irreversible. If they are, it would lead to a vicious cycle in which malnutrition during infancy results in a large pool of poorly functioning people who, because of their poor level of functioning, rear their children under conditions destined to produce a new generation of malnourished people (14,16). Children born in the poverty that leads to malnutrition also live in social and family environments which are themselves capable of retarding mental and behavioral development. Some ingenious experiments on rats, conducted by Francova (13) have shown that protein deficient rats, raised with their mothers and litter mates show about 20% decrement in exploratory activity. Rats on normal diets that have restricted optical and acoustical stimuli show about a 30% decrement in exploratory activity. Rats deprived of both protein and environmental stimuli show a 90% decrement. The effects of both types of deprivation simultaneously are thus more than additive; they are synergistic. The introduction of an "aunt," a nonpregnant virgin female, into the cages of protein deprived infant rats elevated their performance to that of normal rats, even though such a "mother's helper" did not lactate and was unable to offer food. She did, however, stimulate them by grooming and retrieving them. DeLicardi and Cravioto have conducted experiments which led to similar conclusions in impoverished children from an agricultural community in Central America. In this population, 83% of the children showed no clinical signs of malnutrition, 11% showed mild and moderate malnutrition, and 5% showed severe malnutrition. Yet, the families of all of the children had approximately equal incomes, land, and food. Therefore, no correlation could be established between the amount of food available to the

families of these children and the level of malnutrition. However, a significant correlation was found by psychologists who studied this cohort of children while unaware of their nutritional antecedents. They found that the degree of psychological stimulation offered at age six months to those children who later developed severe malnutrition was significantly lower than that of controls from the same population matched by age and birth weight. In children whose diets are marginal nutritionally, psychosocial deprivation predisposes them to severe malnutrition. Malnutrition, in turn, diminished activity, motivation, exploratory behavior, and those complex signals that ordinarily elicit a stimulating and gratifying response from adult parents. A vicious cycle is thus set up in which the effects of malnutrition synergize with those of environmental deprivation. The consequences may lead to irreversible emotional and mental disorders of development. The interaction between nutrition and psychosocial stimulation is not unique to rats or man. All species that have been studied show the same interaction (13).

Vitamin Deficiency States

Vitamin Requirements

Several methods have traditionally been used to determine the vitamin requirements of human subjects. One, employed commonly with conscientious objectors during World War II was the deliberate production of nutritional deficiency followed by the measurement of the quantity of nutrient required to eliminate the signs and symptoms of the deficiency and to maintain health. This quantity was then considered the recommended dietary allowance, and was added to the K rations of our troops. Variations on this strategy use populations in which nutritional deficiency is endemic. Another approach is to measure abnormal metabolites of carbohydrate and protein known to exist in specific deficiencies in the blood and urine. For example, elevated blood lactate and pyruvate occurs in thiamine deficiency. The dose of a specific vitamin required to correct this biochemical abnormality is considered to be the daily requirement. The third approach is the direct measurement of the vitamin in the blood and urine by chemical or microbiologic means. "Normal" levels have been established. This strategy involves the use of large populations of healthy subjects of different age, sex, and race in order to obtain normative data. Recently a new approach to the measurement of vitamin requirements has been proposed. This is based on the assumption that the enzymes requiring cofactors should be fully saturated with cofactor at all times and that a vitamin deficiency exists if they are unsaturated. For example, serum or erythrocyte glutamic-oxalacetic transaminase activity is measured with and without added pyridoxalphosphate, the cofactor. If activity is greater with added cofactor, the enzyme is unsaturated and a

deficiency is said to exist. This method is somewhat controversial but it may be useful in detecting cases of vitamin deficiency and vitamin insufficiency illnesses (17).

Using such methods, a number of vitamin deficiency states relevant to psychiatry have been found; usually they are secondary to the use of pharmacological agents. They most commonly follow the long term use of antituberculosis drugs, anticonvulsants, oral contraceptives, and anti-tumor drugs (18).

The functions of the water soluble vitamins in the nervous system, the manifestations of deficiency and their therapeutic utility has recently been reviewed in great detail (8.19). The following emphasizes features unique to psychiatry:

Vitamin B_6

Vitamin B_6 has many neurobiological functions. It is the precursor of a coenzyme required for more than 50 enzymes in the body. It is so widely distributed in our food supply that it has not been found to occur in populations throughout the world. It has been produced experimentally. Mental symptoms associated with deficiency include lassitude, weakness, depression, anorexia, and confusion. Somatic symptoms include a microcytic anemia which fails to respond to iron but improves dramatically following treatment with small doses of the vitamin. Isoniazide and cycloserine form carboxyl addition compounds with pyridoxal or pyridoxal phosphate that make it unable to function as a cofactor in the approximately 50 enzymes with which it is associated. The administration of vitamin B_6 supplement along with antituberculosis medication reveals that both neurologic and psychiatric symptoms disappear when supplementary vitamin is given in appropriate quantities (20). Estrogens have been shown to compete with pyridoxal phosphate for binding sites among its numerous apoenzymes. High estrogen levels which

occur during pregnancy or the use of oral contraceptives seem to increase the requirements for vitamin B_6. In therapeutic trials on women who developed depression during pregnancy or while taking oral contraceptives, vitamin B_6 supplementation has been reported to improve mood and to correct the abnormal urinary excretion of tryptophan metabolites (21,22,23). Based on such findings some investigators recommend the inclusion of supplemental B_6 into oral contraceptive preparations (22). In Spain, manufactured oral contraceptives contain 25mg of pyridoxine and the combination is reported to produce fewer side effects (24). The RDA for vitamin B_6 for adults is 2.0mg/day. Doses 10 times this are safe and can prevent deficiencies due to drugs administered for other purposes. Although vitamin B_6 is not very toxic, doses several hundred or thousand times of the estimated daily requirement have been reported to cause convulsions and liver hypertrophy (

Vitamin B_3

Vitamin B_3 (niacin, niacinamide, nicotinic acid, nicotinamide) is combined with adenine, ribose and phosphoric acid in the body cells to form nicotinamide adenine dinucleotide (NAD). This is a cofactor for many enzymes which catalyze oxidation reduction reactions which are involved in energy release from carbohydrate, the synthesis of fatty acids, steroid metabolism, etc. Niacin in the judgment of some is not truly a vitamin because limited quantities can be synthesized from the metabolism of the essential amino acid tryptophan (26). While this is correct, historical usage, plus the fact that niacin deficiency can be produced on diets ordinarily adequate in tryptophan seem to us to warrant continued classification as a vitamin. Corn, which is deficient in both tryptophan and niacin, is the common food staple in countries where pellagra was common and where it continues to exist. Hartnup's disease is an autosomal recessive disease characterized by diminished absorption of neutral amino acids including tryptophan. Some of its

symptoms resemble pellagra and these respond to niacin (27). The recommended daily allowance of niacin is 6.6mg/1000 calories of food or about 10-20mg/day. The requirement increases during pregnancy and lactation (27).

Pellagra is characterized by a triad of symptoms - dermatitis, diarrhea, and dementia. In early deficiency, psychiatric symptoms are diffuse and include apathy, depression, anxiety and memory deficits. In severe pellagra, mania, delirium, organic dementia, bulbar palsy, and visual field deficits may be present. The EEG has excessive theta and delta activity. This returns to normal after niacin treatment. Routine manufacture of wheat flour and all cereal products supplemented with niacin has caused pellagra to virtually disappear in the U.S. Niacin deficiency in the brain, without deficiency in other tissues, has been claimed by orthomolecular psychiatrists to account for schizophrenia and other mental disturbances. This will be discussed later.

In pharmacological doses of 10-30grams/day, nicotinic acid, but not nicotinamide, lowers blood cholesterol and causes transient cutaneous vasodilation manifested by a flush (19). Nicotinamide, but not nicotinic acid, at doses of 250mg/day tranquilizes rodents and diminishes locomotor activity in gerbils (28). At similar doses, it increases REM sleep and it has been reported to be of benefit to some insomniacs (29). Nicotinamide also binds weakly to the benzodiazepine receptor (30). At ordinary dietary doses, the brain concentrations of nicotinamide are likely to be too low for biologically significant binding to this receptor, but at megadoses, this might occur. At such doses, niacinamide might have anxiolytic properties like the benzodiazepines. This has not been tested. Nicotinic acid and nicotinamide are identical as vitamins; the different properties of the two compounds occur only at pharmacological doses. Thus,

there is no evidence to relate their pharmacological properties shown at high doses to their classical vitamin action as precursors of NAD. Niacin and niacinamide are not very toxic even in megadoses, but in view of their use in orthomolecular psychiatry at doses 100-500 times higher than the average nutritional requirement, it is worth noting that reported side effects include hepatoxicity (31), hypotension, tachycardia, and hyperglycemia (32). There is a very recent report of severe sensory neuropathy from pyridoxine abuse at doses of 2-6mg/day for several months (158,159). These toxic must be balanced against any presumed therapeutic utility.

Vitamin B_{12}

Vitamin B_{12} (cyanocobalamin) is unique in three regards. It is the only vitamin containing a mineral (cobalt) as part of its chemical structure; it is not found in plants and its absorption from the gut requires a highly specialized mechanism the failure of which results in pernicious anemia. The RDA is about 3.0mg/day. 1micro daily causes remission of pernicious anemia. The vitamin is involved in transmethylation reactions, the synthesis of amino acids, purines and pyrimidines. It is vital for blood formation and the maintenance of neuronal integrity.

A number of studies have shown that 25-30% of patients with untreated pernicious anemia have either major or minor psychiatric problems (33). These include depression and apathy, irritability, confusion, and paranoid states. Neurological symptoms results from demyelination of the dorsal columns of the pyramidal tracts and result in the syndrome known as combined system disease. As many as 60% of untreated pernicious anemia patients have been found to have an abnormal EEG (33,34). Deficiencies of vitamin B_{12} may arise from strict vegetarian diets, but more often follow failure to absorb the vitamin as when there is lack of the gastric intrinsic factor or in ileitis and following bowel surgery. It may also follow chronic ingestion of alcohol or after the administration of neomycin, para-amino salicyclic acid or colchicine. There is an increased requirement for vitamin B_{12}

during pregnancy. Since folic acid is required for the absorption of B_{12}, folate deficiency may be accompanied by B_{12} deficiency (35,36).

Although a large percentage of patients with hematologic and neurologic findings of vitamin B_{12} deficiency also have psychiatric symptoms,

> in a significant number of patients the psychiatric manifestations may be the first symptoms and can antedate anemia or spinal cord disease. A recent report (37) presents two cases of organic psychosis without anemia or spinal cord symptoms that responded dramatically to the appropriate administration of intramuscular B_{12}. It is noteworthy that both patients had normal hematologic profiles. Diagnosis was made by finding low serum levels of B_{12}. With restoration of appropriate B_{12} levels, the presenting symptoms disappeared. Evans et al. (37) recommends consideration of B_{12} deficiency and serum B_{12} determination of all patients with organic psychiatric symptoms whose cause is not clearly known. Even more recently, Van Tiggelem et al. (38) have suggested that blood levels of B_{12} may not always correlate with cerebrospinal fluid levels and that the latter may be much lower.

Folic Acid

Folic acid (pteroyl glutamic acid) is involved in: hydroxylation reactions required for norepinephrine and serotonin synthesis, transmethylation reactions, the synthesis of the purine bases, adenine and guanine, and the pyrimidine base thymine. Folic acid is, therefore, indispensible for the production of DNA and RNA. Transmethylation reactions are involved in myelin synthesis and in the inactivation of the neurotransmitters norepinephrine and serotonin. The RDA is less than 0.5mg/day. It doubles during pregnancy. Serum concentrations in man range from 5-30ng/ml. Folate deficiency has been produced in experimental animals. Diminished learning capacity and EEG changes have been reported in rat pups born of mothers with folate deficiency.

Folic acid, as the name implies, is present in leafy green vegetables and in meats. In man, folate deficiency occurs endemically in severely malnourished populations. It can be produced experimentally in volunteers on folate deficient diets and iatrogenically in marginally nourished people by the administration of anticonvulsants like diphenylhidantoin, oral contraceptives, or the antifolates used in the treatment of malignancy. In experimental folate deficiency, forgetfulness and insomnia appear at the same time as megaloblastic anemia and can be quickly reversed by the vitamin. In less pure deficiency states, occurring among the aged or chronically institutionalized patients, the spectrum of mental disorders includes apathy, irritability, depression, psychosis, delirium and dementia (39).

Folate deficiency can readily be determined by measurement of blood levels. When this is done, as many as 30% of psychiatric admissions have been reported to be deficient (39). Of a sample of admissions to a psychogeriatric ward, 67% have been reported to be folate deficient (40). Carney and Sheffield found that

about 25% of 432 psychiatric admissions have low blood folate levels. Folate treated patients with organic psychoses, endogenous depression and schizophrenia had shorter hospital stays and left in better clinical state than untreated patients (36).

An association between folate deficiency and gestational difficulties has been recognized for many years. Population surveys have shown that about 15% of women, especially among the poor, have marginal or deficient blood levels. Deficiency during pregnancy is associated with an increase in prematurity and teratogenicity.

In the last few years, evidence has accumulated which tends to relate folic acid deficiency during early gestation to neural tube defects and to the Fragile X syndrome of mental retardation. Both of these are polygenic illnesses in which the phenotypic expression of the genotypic defect is apparently determined by the nutritional state of the uterine environment. Smythells (42) has found that when 493 women who had already given birth to a child with neural tube defect gave birth to a second child, 23 of these had children with such a defect. In 397 similar women who were given a vitamin supplement containing folic acid prior to conception and through the first menstrual period, only 3 had such recurrences. This strikingly significant difference cannot be readily explained except by a direct prophylactic effect of vitamin supplementation very early after conception.

The Fragile X chromosome is a relatively newly discovered cause of mental retardation. The fragility of the X chromosome can be rectified <u>in vitro</u> by folic acid (43). Lejeune (44) has reported that the administration of folic acid greatly reduced symptoms of autism and psychotic complications of mental retardation in 7 out of 8 such patients.

Both of these interesting findings clearly require confirmation. If confirmed, they will represent a major advance in the understanding and treatment of two devastating illnesses of concern to neurologists, psychiatrists, and pediatricians through appropriate nutritional supplementation early in conception. A series of studies have shown that folic acid can be added to staple foods, as nicotinic acid commonly is, and that such fortification is feasible, safe, and effective (155). Until this is done, oral administration of folic acid tablets at a level of 0.5mg/day to pregnant women, especially those living in poverty, appears to be prudent (155).

A genetic vitamin dependency illness which required about 20mg of folic acid daily has been reported. These rare cases presented with homocystinuria. One such patient showed mild mental retardation with symptoms of schizophrenia which improved after folate administration and recurred 6 months after the supplementary vitamin was dicontinued (41).

Quasi-Nutrition

Precursor Therapy

Communication between neurons in the central nervous system, it is generally accepted, is overwhelmingly chemical. Neurotransmitters synthesized in presynaptic neurons are extruded into the synaptic cleft when the neuron fires. They then engage specific receptors on post synaptic neurons and initiate a series of metabolic steps which may excite, inhibit, or modulate their activity. More than 20 neurotransmitters are thought to exist; they range in composition from simple amino acids to complex polypeptides. The classical neurotransmitters, dopamine, norepinephrine, serotonin, and acetylcholine have been the most studied. The paradigm for precursor therapy is the use of L-DOPA in Parkinson's disease. The enzyme for the conversion of tyrosine to L-DOPA is lacking in the striatal neurons of the brain from patients with this disease. But, the decarboxylation of L-DOPA to dopamine can still take place. Hence, L-DOPA in pharmacological doses permits the synthesis of sufficient dopamine to be therapeutically effective for several years.

More than a decade ago, it was discovered by Wurtman and his coworkers (45) that the synthesis and release of several neurotransmitters in presynaptic neurons can be influenced by the concentration of precursors offered to them. The amino acids tryptophan and tyrosine are the precursors of serotonin and norepinephrine respectively. Choline is the precursor for the synthesis of acetylcholine. The conversion of precursors to active neurotransmitters is enzymatic. When saturating concentrations of the precursors are available, the rate at which transmitters can be synthesized is limited by the enzymatic capacity. But, concentrations of the dietary precursors in the blood is not constant and under some conditions the rate limiting enzymes may not be saturated, but can become so if

large doses of precursors are administered. Precursor therapy is relatively safe, because feedback inhibition and other neuronal control mechanisms prevent the synthesis of more transmitter than is needed by the neuron at any particular time. Consequently, few side effects are noted when subjects are given pharmacological doses of tyrosine, tryptophan (46), or choline (47,48) that is, amounts much greater the quantities usually ingested in the diet.

The finding that levels of neurotransmitters in the brain can be altered by experimentally manipulating the quantity of ingested precursor had led to considerable basic research as well as clinical research on both normal volunteers and patients in whom there is reason to believe that there may be a neurotransmitter deficiency.

Dietary precursors must be absorbed from the gut, transported in the blood, penetrate the blood brain barrier, and finally enter into appropriate neurons. These are complex processes which depend initially on the quantity of the precursor in the diet, the effectiveness of the gut in absorbing them, and the transport mechanisms within the blood. Circulating amino acids then compete with each other for active transport through the blood brain barrier into the brain (45,49). The ratio of plasma tryptophan, for example, to the sum of the concentration of other neutral amino acids like tyrosine, phenylalanine, leucine, isoleucine, and valine determines the penetrability of tryptophan into the brain, and, hence, the brain serotonin concentration. Thus, a high protein meal in which many amino acids compete for transport into the brain depresses serotonin synthesis in the rat brain (45,50). A high carbohydrate, low protein meal raises brain serotonin because it elicits the secretion of insulin which lowers the blood levels of other neutral amino acids without affecting tryptophan. Doses of tryptophan as large as 10-15grams would be

more likely to diminish transport of other amino acids into the brain than doses of 1-3grams.

Tryptophan and Tyrosine

Tryptophan, administered at a dose of 50mg/kg to healthy young men in the morning, significantly increased self reports of fatigue and inertia and reduced vigor and activity (46). It is interesting to note that in this same experiment, tyrosine at 100mg/kg had undetectable effects. It is also worth noting that tryptophan did not cause depression, anxiety, confusion, nor anger in this experiment.

Tryptophan has also been used in the treatment of insomnia with apparent favorable effects. Doses of 1 to 5 grams before bedtime have been reported to reduce sleep latency without producing distortions of physiological sleep as measured by EEG recordings (51). Doses of 10-15 grams cause EEG changes but these are less pronounced than those resulting from the use of hypnotics. The mechanism for the effectiveness of tryptophan in insomnia is presumed to be due to its effects on serotonin levels in the brain stem (52). The use of L-tryptophan for the treatment of insomnia is still experimental even though the amino acid is available for sale in health food stores. The current literature suggests that it would have substantial advantages over conventional hypnotics, but it appears not to be uniformly effective for insomniacs. Furthermore, the long term effects of doses of 5-15grams per day require further investigation.

Serotonin deficits have been implicated in some depressions and mania and clinical trials with tryptophan were conducted with mixed results (53,54). Since tryptophan is rapidly catabolized enzymatically by liver pyrollase, the idea occurred that the concomitant administration of an inhibitor could more effectively

raise brain serotonin. Nicotinic acid and nicotinamide are both pyrollase inhibitors and in a preliminary report, encouraging results were obtained with the combination of tryptophan and nicotinamide in the treatment of depression (55). These results have not been confirmed. In very recent work, it has been reported that tryptohan diminishes sensitivity to mild pain and in people over forty increases the likelihood of errors in performance tasks (56).

The administration of tyrosine can, under certain circumstances, elevate levels of brain catecholamines (45,57). It has been reported to help some patients with depression (58) and mild Parkinson's disease (57). Continued clinical research in which tyrosine or tryptophan is used with depressed patients might help to distinguish depressions in which norepinephrine is involved from those in which the defect may be in serotonin metabolism.

Choline and Lecithin

Several studies have shown that the administration of choline or lecithin, the precursors of acetylcholine, increased cholinergic function in the brain (59). On the basis of this finding, clinical research has been conducted in which there is a possible disorder in acetylcholine metabolism. Tardive dyskinesia is one such disorder Presumably the disorder arises because of prolonged administration of neuroleptics, wh chronically block striatal dopamine receptors, cause these receptors to become supersensitive to dopamine (60). Some dopamine receptors are present on cholinergic neurons and their supersensitivity probably causes a chronic decrease in the release of acetylcholine by decreasing the firing rates of the cholinergic neurons. Davis et al. (61) reported marked clinical improvement after giving oral choline to a patient with tardive dyskinesia. Several additional studies have confirmed this (62,63). Unfortunately, large doses of choline have undesirable side effects.

including a socially unacceptable odor which results from the degradation of ingested choline to trimethylamine by intestinal bacteria. Lecithin, a phosphatidyl choline, is the most common source of our dietary choline. Lecithin is more effective than choline in raising plasma choline levels (64). Several reports suggest that it, too, is effective in diminishing symptoms of tardive dyskinesia (65,66). A review of the literature suggests that there is modest improvement in the motor function of about 1/2 of the patients who receive lecithin. Interestingly, the antipsychotic action of neuroleptics has not been reported to be diminished by the administration of either choline or lecithin.

Choline has been administered to schizophrenic subjects and failed to modify their clinical symptoms (67). Lecithin has been administered to manic patients with encouraging results (68). Disorders in acetylcholine function have been suggested in Huntington's Disease, Friedrich's Ataxia, and Tourette Syndrome. The results of therapeutic trials with choline or lecithin in those illnesses are equivocal. They have been reviewed by Growden et al. (69).

Alzheimer's disease, the most common cause of dementia among the elderly, is characterized by impaired functioning of cholinergic neurons. On autopsy, the brains of such patients show a dramatic loss of brain choline acetyltransferase (71,70,45). Memory deficits are characteristic of Alzheimer's disease and many studies have been conducted to measure the effects of acethylcholine precursors in normal people and in patients with Alzheimer's disease (48,72). These studies have not convincingly demonstrated any enhancement of memory after treatment with acetylcholine precursor.

Alternative methods for enhancing cholinergic activity include the use of choline esterase inhibitors and cholinergic agonists. Physostigmine, a reversible

short acting choline esterase inhibitor and arecoline, a short acting cholinergic agonist, improve memory when given in low doses to healthy young adults (73,74). Physostigmine, in a double blind experiment, enhanced the memory processes of patients with Alzheimer's disease for brief periods (75).

It is curious that physostigmine, which enhances cholinergic function by inhibiting the enzyme which destroys acetylcholine, should be more effective than precursors which increase the concentration of this neurotransmitter. The reason is not known, but it immediately raises the question of whether a combination of a precursor and a choline agonist or choline esterase inhibitor might be additive or synergistic. To the best of our knowledge, this has not yet been tested.

The precursor strategy with tryptophan, tyrosine, and choline has thus far yielded results which are of great research interest but have only preliminary and uncertain clinical utility. This type of research is young, and vigorous. We may hazard a guess that greater clinical effects from precursors may be achieved when they are combined with other types of psychotronic drugs. Tryptophan or tyrosine combined with tricyclics might accelerate the therapeutic process or decrease the required dose in depression. Stern and Mendels have reviewed the literature on the use of such combinations in the treatment of refractory depression (76). A recent report suggests that the combination of physostigmine and lecithin improves memory in Alzheimer's disease (75).

Pseudo-Nutrition

Food Additives and Hyperkinesis

In 1975, the late Dr. Ben F. Feingold, a pediatrician and allergist, proposed that some children have a central nervous system variant that predisposes them to sensitivity to synthetic food additives, particularly to food colors and the antioxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). He claimed that in such children hyperkinetic behavior results from the ingestion of these additives. The use of an additive free diet which he developed led to dramatic improvement or even cure in from 50-70% of hyperkinetic/learning disabled children. He stated that 75% of children who had been treated with stimulant medication could discontinue the treatment (77). The diet, he claimed, became effective in several days to several weeks and the younger the patient, the more rapid and complete his response. Total and permanent adherence to the diet is mandatory, Feingold insisted, because even a minor infringement produces a return of symptoms within about 3 hours, which may persist as long as 72 hours. Feingold based his findings on extensive clinical experience in open studies. He did not conduct controlled, double blind trials to test his hypothesis. The Feingold dietary treatment gained considerable popularity among the lay public and more than 20,000 families of hyperkinetic children were reported to adhere to the diet and to advocate its use (78). Feingold urged that labelling of additives be mandatory and the immediate clinical application of an additive free diet in school food programs to a congressional committee by stating: "it is not necessary to await the availability of basic data, it has been demonstrated that these children respond to dietary intervention" (79). Several uncontrolled clinical studies supported Feingold. Rigorous double blind studies, conducted in 7 centers and involving about 200 children have generally failed to replicate his findings (84).

Two types of controlled studies have been conducted. Harley et al. (80) offered families with hyperactive children two different diets blindly at weekly intervals. One was a conventional diet; the other was prepared solely from foods recommended by Feingold. In 36 school age boys, based on teacher and objective ratings, no significant differences in behavior occurred with the diet. With these school age children, a few parents reported a significant improvement when the additive free diet followed the controlled diet, but they were unable to detect differences when the order was reversed. In preschool age children, where only parental ratings were available, a few parents were able to consistently detect differences with the additive free diet compared to the usual diet.

Most of the double blind studies have been challenge trials; that is, children, who ate additive free diets because their parents believed that they improved on them, were blindly "challenged" by the addition of cookies or drinks which contained food color additives. About 200 children have been tested in several studies conducted throughout the U.S. (81,82,83). A summary of these experiments and the results and conclusions has been reported (84). The National Institutes of Health (88) and the American Council on Science and Health (85) have concurred. The data from these studies have recently been examined statistically by an independent group who have come to the same conclusions (86). The conclusions from these many studies are that Feingold's claims that 50-70% of children improve dramatically on an additive free diet and deteriorate rapidly after minor infractions from the diet cannot be supported in careful double blind trials. At most, 3 of the 200 children were reported by their mothers to deteriorate significantly when challenged with food colors. In these 3 children, objective tests and/or outside observers were not used. The Nutrition Foundation Report (84) concluded that there was

insufficient evidence to require a special symbol on food labels indicating the presence or absence of these food additives for the purpose of treating these behavioral disorders. There is also insufficient evidence to suggest a ban on food containing artificial food colorings in federally supported school programs.

Rimland, Vice President of the Academy of Orthomolecular Psychiatry, has challenged the methods, results, and conclusions of those who failed to confirm Feingold's results (87).

Food and Environmental Allergy and Hypersensitivity

The notion that hypersensitivity or allergy to foods or other environmental agents like gasoline fumes, soaps, or hydrocarbons results in medical or psychiatric illness is subscribed to by what Brodsky calls a "medical subculture" (89). Clinical ecologists and some orthomolecular physicians are among those who support this view. It has been popularized extensively by books and in the media (90,91,92,93). Symptoms which have been related to such sensitivity or allergy include lethargy, depression, palpitations, sleep disturbance, mood swings, poor concentration, anxiety attacks, aggressiveness, and delinquent behavior. The Feingold hypothesis (77) that hyperactivity and learning disability in children is related to the ingestion of common synthetic food additives seems to be a specific variant of the food hypersensitivity thesis which focuses on synthetic food additives and natural salicylates. Hoffer (94) has claimed that many of his schizophrenic patients who failed to respond favorably to megavitamins do respond to five days of starvation followed by diets in which single items of food to which the patients are not sensitive are carefully introduced.

Pierson et al. recently sought objective evidence for the role of food hypersensitivity in 23 patients who attributed a wide variety of their physical and psychological symptoms to food allergies (95). These patients were seen independently for initial diagnosis by a psychiatrist who withheld his findings from the other investigating physicians. The allergists assessed the patients by medical and dietary history, a physical examination, and skin tests for common inhalant and food antigens. The patients were then put on exclusion diets consisting of uncommon foods to which they had no alleged hypersensitivity. All the patients improved. Single foods which the patients had themselves incriminated were then

added openly. Many patients became ill with their initial complaints. Blind tests were then performed using the same foods, freeze dried, and in opaque capsules. The investigators found that only four of the 23 patients had true food hypersensitivity. None of these four had significant psychiatric symptoms and all of them had physical symptoms characteristic of atopy, i.e., allergic rhinitis, urticaria, asthma or atopic eczema which appeared even when the offending foods were given blindly. The 19 in whom food hypersensitivity could not be confirmed in the blind trials had physical and psychological symptoms not characteristic of the atopic syndrome; 18 of these 19 patients had been diagnosed by the intake psychiatrist as having significant psychiatric illness; 10 of these were considered neurotically depressed, the remainder had other neuroses and personality disorders but none were psychotic. The authors conclude that psychogenic reactions to food are very common and that some form of double blind testing is the only certain means by which the diagnosis of food hypersensitivity can be established. They note that "since the dangers of unwise dietary restriction are real, patients should not be encouraged to restrict their diet without specialist, dietetic advice and without objective confirmation of food hypersensitivity."

There have been claims that food allergies are responsible for delinquency and criminal behavior (96,97,98). Statements are made that food allergies are common in delinquents but prevalance rates are not given. The only reported double blind studies of behavioral change in relation to food allergy have used sublingual testing, a method whose validity is considered doubtful (99).

Clinical ecologists go farther. Patients are initially tested for dietary sensitivity and are placed on elimination diets. If these are not helpful, they are placed in a "chemical free" environment in a hospital. If they improve in

that environment, they are then treated by prescribed avoidance of environments which include the common substances like perfume, smoke, etc. to which they claimed sensitive. Such avoidance inevitably leads to major changes in their lives including a move to a "clean climate". Patients may also receive injections of the indicted substances in order to desensitize themselves. According to Brodsky (89) they spend much of their time on diets, tests for sensitivity, reading about allergies, participating in a support group of similar patients, and tending to worker's compensation claims.

Schizophrenia and Gluten

In 1966, Dohan suggested that peptides derived from cereal grain glutens may play an important role in the pathogenesis of schizophrenia in genetically predisposed people. This proposal was based on the observations of considerably higher than chance occurance of celiac disease in schizophrenics as well as schizophrenia among adults with celiac disease. In addition, both schizophrenia and celiac disease have been reported to be three times more prevalent in Ireland than in England and Wales. Dohan also found a strong correlation between a change in rates of admission of female patients with schizophrenia to psychiatric institutions and a change in wheat consumption during World War II among five

countries (USA, Canada, Finland, Sweden, and Norway) variously affected by the war. Following these observations, he and his colleagues studied the effects of milk free and cereal free diet on schizophrenic patients. 47 schizophrenic patients randomly assigned to a cereal free diet showed a significant increase in rate of release from hospitals compared to 55 patients on a high cereal diet. No differenc was found when wheat gluten was added to the cereal free diet in a subsequent double blind study (100).

Singh and Kay (101) found that schizophrenic patients who received neuroleptics and a cereal free, milk free diet showed a significant decline when challenged with wheat gluten in a double blind manner. They suggested that clinical improvement on a gluten free diet and subsequent deterioration on gluten challenge may be related to a gluten mediated decrease in neuroleptic absorption. In support of this, Fried et al. (102) found that wheat gluten given to mice 20 minutes before a 1mg/kg dose of haloperidol reduced the amount of neuroleptic absorbed into the blood stream. Recently, however, Osborne et al. (103) found that 5 chronic schizophrenic patients did not improve on a gluten free diet; furthermore, the gluten free diet had no effect on blood levels of butaperazine, which had been administered in constant doses throughout the study. The study, however, selected patients who had failed to respond to traditional neuroleptic therapy and who thus might represent an atypical subpopulation. Also, as the authors note, their patients were on the special diet for 36 weeks. Dohan and Grassberger (104) stressed that chronic patients may require months or years of gluten free diets before significant results are achieved.

Potkin et al. (105) studied 8 chronic schizophrenic patients who were maintained on a diet free of gluten, cereal grains and milk and who were challenged

in a double blind manner with dietary wheat gluten and placebo. They found no deterioration in clinical status (as measured by the BPRS) on gluten challenge; however, Singh and Kay (106) have pointed out that with an N of 8, the authors' chances of detecting a true small or medium effect of gluten would be only 7% and 15%, respectively.

Hallert (107) who has studied many celiacs in Sweden where it has a relatively high prevalence rate found no schizophrenia in adult celiacs, but did find significant depression. He suggests that celiac disease is not an appropriate model. Dohan recently (108) reviewed the evidence supporting the model and suggests approaches for further study.

Recently, Zioudrous et al. (109) reported that gluten peptides have naloxone-reversible endorphin activity at brain opiate receptor sites. This finding might explain a link between gluten free diets and clinical response in a subpopulation of schizophrenics. However, such a relationship has yet to be consistently demonstrated and the important observations of Dohan's group and Singh and Kay merit further exploration.

"Reactive, Relative, or Postprandial Hypoglycemia"

In animals and man, food intake is intermittent and yet the blood sugar levels, except for transient rises after eating, remains relatively constant. Such homeostasis requires the synchronized participation of the liver, muscles, pancreas, other endocrine organs and the central nervous system. Most body tissues can tolerate fluctuations in blood sugar but the brain, which is unable to store glucose or glycogen in significant quantities and which uses glucose as its primary fuel, requires a constant supply. In the resting state, the brain accounts for 80% of the glucose consumed by the body.

Glucose homeostasis is remarkably effective. In a normal population, fasting levels of plasma glucose range from 50-115mg/dc. Such levels occur 5-6 hours after feeding and do not change significantly overnight. In well nourished individuals, blood glucose levels change very little after several days of fasting. Many physical illnesses like diabetes or islet cell tumors of the pancreas can either elevate or lower the fasting blood sugar (110,111).

Reactive, relative, or postprandial hypoglycemia is an abnormal degree of depression of the extracellular glucose concentration reflected in the plasma, without a well defined cause. When plasma levels fall below 50mg/dc or blood levels below 40mg/dc, symptoms and signs of adrenergic hyperactivity or nervous system depression or a combination of the two usually appear. Hypoglycemic activation of the adrenergic system causes tremulousness, anxiety, hunger, sweating, palpitations, and tachycardia. Central nervous system hypoglycemia causes perturbations of cortical and subcortical functions with symptoms of fatigue, headache, weakness, diplopia, confusion, amnesia, incoordination, seizures and coma. There is substantial variation in the cluster of symptoms of hypoglycemia from patient to patient.

Several of the symptoms of hypoglycemia resemble those with which anxious, depressed, and hypochrondiacal patients present. Consequently, some patients may diagnose themselves as having hypoglycemia. The tendency to do this is augmented by popular books in the lay press which have featured hypoglycemia as a global cause for a welter of illnesses and antisocial behavior like "nervous breakdown", alcoholism, juvenile delinquency, drug dependence, inadequate sexual performance, and overt aggression in prisoners (112,113,114).

Some orthomolecular physicians and clinical ecologists are among the physician groups who attribute much mental illness and antisocial behavior to hypoglycemia and who treat this condition with low carbohydrate, high protein diets. Psychotropic drugs are frequently added but this is not usually acknowledged. While the majority of endocrinologists, psychiatrists, and criminologists have not accepted nutritional theories and dietary treatments of neurotic and antisocial behavior, these theories have, nonetheless, had an impact on prisons, probation departments, and school systems. The Los Angeles County Probation Department, for example, banned the consumption of chocolates, other sweets, and refined sugar products from juvenile facilities and is attempting to reduce consumption of processed and additive-containing foods in prisons (115). There have also been malpractice suits in which patients have claimed that their physicians missed the diagnosis of reactive hypoglycemia and, therefore, mistreated them.

The concept that postprandial or reactive hypoglycemia is common in the population has not been generally accepted by the medical profession. The American Diabetes Association (116), in collaboration with other societies, has published statements to downplay the prominence of the misattribution of hypoglycemia as a cause of multiple illness. Yager and Young (117) have referred to the epidemic

proportions of the incorrect diagnosis of hypoglycemia as a cause for multiple psychiatric and somatic complaints. Too often the diagnosis is made without a glucose tolerance curve at all. Diagnosis by questionnaires which attempt to relate symptoms to eating habits is inadequate. Many patients who have affective, somatization or anxiety disorders report a relationship of symptoms to food intake which is not borne out in a glucose tolerance test (110,118,119).

The reasons for the conflict between those who emphasize hypoglycemia as a major contributor to multiple psychiatric illnesses and those who discount it lie largely in the rigor with which a 5 hour glucose tolerance test is conducted and in how it is interpreted. In this test, the patient should be prepared by eating a diet containing about 250gm of carbohydrate daily for three days. He is then fasted overnight, and is given 50-100gms of sugar orally in solution. Alterations in plasma or blood glucose are monitored at half hour intervals for the ensuing five hours, while subjective symptoms are recorded. The typical normal glucose tolerance curve shows a rise of 60-70mg/dc in the first 30-60 minutes; this is the period when glucose enters the circulation from the gastrointestinal tract. In normal persons, increasing glucose concentration, abetted by cholinergic signals, stimulate insulin secretion. The increased circulating insulin in conjunction with declining glucagon production results in decreasing hepatic glucose output and a fall of blood glucose to levels approximating or slightly lower than the fasting state over the next four hours. By the fifth hour, there is usually recovery to base levels. At its peak, blood glucose levels in normal subjects seldom exceeds 160mg/dc. Higher levels suggest diabetes. At the nadir, glucose levels below 50mg/dc should raise the suspicion of reactive hypoglycemia. For a definitive diagnosis to be made, the low blood sugar values should coincide in time with the symptoms of adrenergic activation and central nervous system hypoglycemia referred to above. The diagnosis

should not be made on the basis of a low blood sugar without clinical symptoms or on symptoms alone without a low blood sugar. Many patients report symptoms and signs of anxiety with blood sugar levels above 70; others may have the blood sugar fall to levels of below 40 without manifest symptoms or signs of hypoglycemia (118). Since the glucose tolerance test may vary from day to day in any patient, borderline tests should be repeated. Orthomolecular psychiatrists interpret the results of glucose tolerance tests differently from endocrinologists. An example of orthomolecular interpretation is shown in the work of Meiers who claims that 70% of schizophrenics have relative hypoglycemia (123).

The notion that hypoglycemia is related to panic attacks, reported by patients, has recently been tested by Gorman et al. (11). These investigators measured the blood sugar in ten patients who met DSM III criteria for panic disorder or agorophobia at the moment when panic was experienced by the patient during an infusion of 0.5molar sodium lactate under single blind conditions. They found that, on the average, such patients had a fasting blood sugar of 98mg/dc and at the moment of panic it was 94mg/dc. None of these patients had serum glucose levels even close to hypoglycemic levels. These findings demonstrate that hypoglycemia is not a necessary condition for panic attacks, but do not, of course, prove that hypoglycemia may not cause panic attacks. To determine the latter, it may be necessary to experimentally lower blood sugar in such patients by an insulin tolerance test and then determine whether it triggers panic and whether the blood sugar levels correlate well with the onset of panic. It is also now possible for patients who suspect that they have hypoglycemia related to panic, or to any other clinical symptoms to screen themselves at home by collecting capillary blood on impregnated filter paper. They can measure the blood sugar levels themselves or send it to a laboratory for analysis (120). In either type of experiment, a close correlation between clinical symptoms and blood sugar

values must be found in order to designate hypoglycemia as a proximate cause of the symptoms. It seems likely that such research will be conducted in the near future.

In summary, there is little evidence from carefully conducted research to support the concept that reactive hypoglycemia is a common condition and that it is causally related to psychiatric or behavioral disorders. Nonetheless, some professionals and patients are convinced a priori that emotional illness and inappropriate behavior is caused by postprandial or relative hypoglycemia which follows a high dietary intake of carbohydrates. Individuals who choose to believe this may alter their diets to diminish intake of simple sugars and to increase protein and complex carbohydrates with little danger or expense. But, the translation of hypoglycemic mythology into dietary regulation on a mass scale in schools or prisons is not justified.

Orthomolecular Psychiatry

> "Psychiatry seems unusually vulnerable to almost any fad which happens to drift into its amoeboid maw."
> (Osmond, 1982)

The theory, practice, and clinical value of megavitamin therapy and orthomolecular psychiatry has been the subject of debate for almost twenty years. An American Psychiatric Association Task Force reviewed the evidence thoroughly in 1973 and was very critical (124). Orthomolecular psychiatrists responded (125), calling the Task Force Report biased, unfair, and full of errors. Pauling (126) was also critical. His criticisms were answered by Klein (127) and Wyatt (128). A book Orthomolecular Psychiatry: Treatment of Schizophrenia which details their theory and practice was published in 1973 (129). A detailed update of the APA Task Force critique which included a review of the role of the water soluble vitamins in the nervous system was published in 1979 (130). The present chapter summarizes some older reviews of this subject and adds material published since that time.

Orthomolecular Theory

The term "megavitamin therapy" was coined in the early 1950s to describe a treatment for acute schizophrenia that employed doses of vitamin B_3 (nicotinic acid or nicotinamide) in the dose range of 3-30 grams daily. The theoretical basis for this treatment was initially pharmacological, not nutritional. The originators of megavitamin therapy attributed the pathogenesis of schizophrenia to the endogenous formation of adrenochrome and adrenolutein whichare hallucinogenic condensation products of oxidized adrenaline. Adrenaline is formed by methylation of noradrenaline and in schizophrenia the formation was thought to be excessive. hese products caused pe ceptual distortions which were the primary causes of schizophrenia. The perceptual defects could be detected and quantified by a psychological card sorting test called Hoffer-Osmond Diagnostic Test (

They see schizophrenia as primarily a perceptual disorder. For example, Hawkins, co-editor of the book Orthomolecular Psychiatry (129,p627) says, "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 changes upon which a diagnosis or schizophrenia has hitherto been based .... At this stage of the illness, the diagnosis may be made by interviewing techniques focused on detection of these subjective changes. The perceptual changes may also be detected by objective measures such as the HOD and EWI tests which parallel changes in the severity of the illness. The stage of the illness may be called metabolic disperception. It precedes the appearance of overt clinical schizophrenia -- the signs and symptoms of schizophrenia are secondary to the perceptual disorders and these in turn precede the tertiary impairments in social functioning." Hawkins then presents evidence to support the proposition that all of the manifestations of schizophrenia can be produced by perceptual changes alone. The HOD score is described by him as being more accurate than the usual clinical criteria in evaluating the degree of the patient's illness and response to treatment. He say (129,p617), "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 of the state of the illness. We, therefore, view schizophrenia as a disease process which is capable of producing psychosis." He continues (129,p602 "The HOD 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. Underlying this work is 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 function of the central nervous system which is responsible for maintaining perceptual abilities."

Kelm (129,p327-342) defines metabolic disperception as "people who suffer from varying degrees of abnormal perception, with corresponding changes in thought, mood

and behavior who respond favorably to megavitamin B_3 and allied therapy if treated before irreversible damage has developed." Subclinical pellagra is defined as "a deficiency syndrome characterized by the presence of perceptual changes affecting any or all of the five senses associated with neurasthenia. The HOD and related tests can measure the degree of perceptual abnormality and changes in thought and mood."

Hawkins (129,p620) continues, "For routine use, the HOD test. . . .is the most useful test, 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. It can be administered and scored by anyone in the office. Shock treatment brings the most rapid reduction in the HOD score, the phenothiazines will also lower the score considerably, but usually not to within normal range. The patient can take the test retroactively; that is, he can answer the question according to how he felt when most ill or at any specified time in the past."

Hoffer remains committed to nicotinic acid deficiency as the primary cause of of schizophrenia, which he sees as cerebral pellagra. He says (129,p250), "If all the vitamin B_3 were removed from our food, everyone would become psychotic within 1 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."

"Schizophrenia and pellagra are not identical since they require different quanitities of vitamin B_3. Most symptoms of pellagra are alleviated by doses of vitamin B_3 below 1 gram/day, but a small proportion may need many times as much. Most schizophrenia respond to 3 to 6 grams, but a small proportion may require more than 20 grams per day" (129,p251).

But, Hoffer also believes in the use of ECT in the treatment of schizophrenics who do not respond to megavitamins. Commenting on the failure of others to confirm megavitamin therapy, he says (129,p206), "Several experiments are underway, but they are testing only 1 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. The patients who recover are maintained on the program in order to keep them well. Patients who do not recover within 3 months are then given a series of ECT in addition to the chemotherapy. They may require a second or 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% within one year and improvement in the other 10%."

He also says (129,p559), "All patients were treated with phenothiazines, megavitamins, accessory symptomatic medication, group therapy and all the other usual adjunctive measures. The exception was 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."