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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 (25).

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, which 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 psychotropic 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 benerally 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 o. 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 difference 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). Sinc 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 agoraphobia 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 which are hallucinogenic condensation products of oxidized adrenaline. Adrenaline is formed by methylation of noradrenaline and in schizophrenia the formation was thought to be excessive. These products caused perceptual 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 (HOD).

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,p659), "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."

To prevent or treat schizophrenia, it was thou necessary to reduce adrenaline formation. Since adrenaline was formed by methylation of noradrenaline, a means to diminish methylation was sought.

When nicotinic acid or nicotinamide are administered in large doses n-methyl-nicotinamide is formed and is rapidly excreted; hence, both compounds are methyl acceptors. Since they are relatively non-toxic in large doses, they were chosen as competitive inhibitors of the methylation of noradrenaline. It is worth emphasizing that they were not chosen as nutrients; indeed, in a 1957 publication advocating the use nicotinic acid in the treatment of schizophrenia, Hoffer et al. (131) speculated about the mechanism of therapeutic action of nicotinic acid. They chose as the most likely mechanism the ability of nicotinic acid to be a methyl acceptor which would reduce the formation of the endogenous hallucinogen adrenochrome. They rejected its role as a vitamin, saying, "psychosis (sic) association with pellagra does in many ways resemble the schizophrenic psychosis except that it contains qualities of toxic confusion. However, the incidence of avitaminosis among schizophrenic persons is no greater than among the general population. Doses adequate to treat any unknown deficiency are without affect on schizophrenia; it may, therefore, be concluded that this factor is unimportant." (131)

In 1968, Pauling (132) published a theoretical paper in which he suggested that some forms of mental illness might be due to deficiencies in essential nutrients occurring in susceptible irdividuals eating an ordinarily adequate diet. Man's genetic heterogeneity leads to biochemical individuality with large variations in the need for essential nutrients, especially vitamins (132). The brain might differ from other organs in its nutritional requirements so that localized cerebral deficiency could occur. Pauling named his concept "orthomolecular psychiatry" and he defined it as "the treatment of mental disease by the

provision of the optimum molecular environment for the mind, especially the optimum concentration of substances normally present in the human body." With the publication of this interesting theoretical paper, clinicians who had been practicing megavitamin therapy quickly adopted Pauling's concept and claimed that what they had been practicing from 1952 to 1968 was, indeed, orthomolecular psychiatry. This conceptual shift from the transmethylation hypothesis in which nicotinic acid was a pharmacological methyl acceptor to a nutritional hypothesis in which schizophrenia was cerebral pellagra treatable by nicotinic acid functioning as a true vitamin was accompanied by the formation of an Academy of Orthomolecular Psychiatry and a name change of their journal from the Journal of Schizophrenia to the Journal of Orthomolecular Psychiatry. With this shift in theory, many other vitamins and hormones were added to their therapeutic armamentarium. The scope of the conditions which orthomolecular psychiatrists treat has also been expanded to include autism, hyperkinesis, depression, anxiety, alcoholism, drug addiction, delinquency, etc. Their current practice is perhaps best described by Hawkins. "Clinicians practicing orthomolecular psychiatry are using a combination approach which varies from patient to patient depending upon the biochemical peculiarities of a given case and which often includes high doses of niacin or niacinamide, ascorbic acid, pyridoxine, vitamin E, thyroid, vitamin B_{12}, hypoglycemic diets, cereal free diets, daily physical exercise, lithium, the phenothiazines, and also the commonly used tranquilizers and antidepressants."(133). Electroconvulsive shock therapy is still frequently used (125). The current theory is expressed by Hoffer (134), "There is a simple message: The most important treatment for psychosis is nutritional. Other treatments which are considered THE treatment by the American Psychiatric Association are merely palliative."

The change in the theory of schizophrenic pathogenesis from excessive transmethylation to nutritional deficiency broadened the therapeutic ingredients of orthomolecular practice greatly. With the first theory, there was a pharmacological need for nicotinic acid as a methyl acceptor and no special needs for other vitamins and nutrients. With the nutritional theory there is room for the addition of many other micronutrients to the therapeutic program. In current practice, many nutrients are added in megadoses simultaneously. Nonetheless, nicotinic acid seems to be always included in the therapeutic cocktail for schizophrenia and this is because that illness continues to be looked at as cerebral pellagra. Hoffer says, "It is clear that there are no clinical grounds for separating the two diseases. A distinction is artificial". He also says, "schizophrenia is a vitamin B_3 dependent condition or an NAD deficiency disease" (135). Nonetheless, other water soluble vitamins and minerals are also used in megaquantities.

The concept of reactive hypoglycemia and of food or environmental allergy as causative agents in many types of mental illness and behavioral disorders has also been adopted (136). Orthomolecular psychiatrists who originally rejected psychotropic drugs as unnecessary poisons imposed on the medical profession and patients by heavy industrial advertising is now accepted as sometimes useful adjunctive therapy. Characteristic of orthomolecular psychiatry is the absence of psychological or social causes for mental illness or aberrent behavior. Nor is there any admission of a useful role for psychological treatment, although halfway houses and self help groups are used.

The transmethylation hypothesis is testable and has been tested by many investigators over the past 20 years. No evidence of any excess transmethylation

has been found. If anything, there may be diminished transmethylation (137,143). There is also neither clinical nor laboratory evidence for a metabolic defect similar to that found in pellagra in any of the schizophrenias. This subject was thoroughly reviewed a decade ago in the APA Task Force Report (124) and no evidence to the contrary has appeared since that time.

The Pauling statement that there is an optimum molecular environment for the neurons in the brain is probably true, but it is not testable, because optimum, especially for any single individual, cannot be defined nor determined. It is like saying that there should be an optimum income, education, and degree of health and freedom for every citizen. There would be enormous arguments by people of different political persuasions about the meaning of the term. Pauling noted that optimum intake of phenylalanine should be very low for the patient with phenylketonuria. But, in general he tended to view optimum as very much larger than the RDA. He suggested that genetic variance in the transport of vitamins across the blood brain barrier might, in selected individuals, result in a cerebral avitaminosis despite normal blood and other tissue levels of these nutrients. He also felt that the protein apoenzymes for which vitamins or their derivatives function as coenzymes might be genetically defective so that much higher concentrations of coenzymes were necessary in order for the enzymes to function. He stated that "the so-called gene for schizophrenia may itself be a gene that leads to a localized cerebral deficiency . . one or more vital substances" (126,132).

Roger Williams (138), more than 30 years ago, had presented evidence for a degree of variability within a species which he called biochemical individuality that might account for differences in nutritional requirements. Pauling's hypothesis was an elaboration of Williams' thesis. Williams' thesis is also not arguable in principle, but the quantitative aspects

need empirical testing. We all readily accept biochemical individuality for things like height, weight, hemoglobin, intelligence, caloric needs, metabolic rate, etc., but generally speaking, such variability is seldom more than 15%. Orthomolecular theory suggests that differences in vitamin requirements might be as great as several thousand percent. Some evidence has been found in rare genetic diseases to support this. There are about 25 known genetic "vitamin-responsive in-born errors of metabolism"(139). These disorders are genetic autosomal recessives and are so rare that a total of less than 1,000 cases have been described in the world literature. All of the water soluble B vitamins except niacin and riboflavin have been implicated. Vitamin dependency illnesses are characterized by an increase in the requirement for a specific vitamin that ranges from 10 to several hundred times the RDA. This is because they have mutant apoenzymes which require high concentrations of cofactor to function. Vitamin dependency illnesses are manifest at birth or in early childhood and they are generally associated with mental retardation as well as with multiple somatic disorders ranging from convulsions to severe anemias. Patients with these illnesses show demonstrable abnormalities in circulating amino acids or other metabolites. Unless they are treated with megadoses of the appropriate vitamin early in life such patients show retardation in growth and development and usually die in childhood. Orthomolecular psychiatrists apparently believe that the large differences in nutritional needs which occur in the rare genetic vitamin dependency illnesses are common in psychiatric patients of all types. Hoffer, for example, believes that schizophrenia is a vitamin B_3 dependent condition or an NAD deficiency disease (135). Since schizophrenia fails to meet the many other criteria established for the definition of autosomal recessive genetic diseases, it becomes necessary for him to postulate that the vitamin dependency characteristic is localized to the brain.

There is another genetic variant less severe than the vitamin dependency illnesses which Blass calls "vitamin insufficiency illness" (140). This occurs in that small fraction of alcoholics who develop Wernicke-Korsakoff syndrome. Such patients are apparently able to grow normally to adulthood on ordinary daily requirements of thiamine and an average diet, but under the unusual circumstances of heavy alcohol consumption when the vitamin intake diminishes and the vitamin requirement may increase, the syndrome develops. This condition can be detected by measurement of a thiamine dependent protein apoenzyme called transketolase which in Wernicke patients requires a much higher concentration of thiamine pyrophosphate in order to function adequately. Folkers et al. (141) have reported that patients with carpal tunnel syndrome may also have a vitamin insufficiency syndrome because their erythrocyte glutamate oxaloacetate transaminase (EGOT) is unsaturated at normal dietary levels of pyridoxine. At megadoses the enzyme becomes saturated and new enzyme synthesis is induced. Of interest to psychiatry has been the report of Rimland et al. (142) who recently found that massive doses of pyridoxine could improve the symptoms of about 30% of autistic children and that in such children pyridoxine causes a drop in the urinary excretion of homovanillic acid, a major metabolite of dopamine. It is, therefore, possible that a subgroup of autistic children may have a vitamin B_6 insufficiency illness. Detection of this particular subgroup can thus far not be made clinically or biochemically. Moreover, even though some improvement occurs when these children are given pyridoxine, they are still very far from being psychologically well.

The possibility that schizophrenia or even a significant subgroup of the schizophrenias is a vitamin dependency illness must be considered very remote. They have multiple somatic abnormalities which have not been found in schizophrenics.

They are generally mentally retarded and they have distinct biochemical abnormalities in the blood or urine which are detectable at birth or in early infancy. They respond quickly and dramatically to large doses of the single vitamin required to remedy their genetic metabolic abnormality. Schizophrenia fails to meet any of these criteria.

Is schizophrenia a vitamin insufficiency illness which resembles the Wernicke-Korsakoff syndrome? Again, it is very unlikely. A vitamin dependent specific enzyme defect has not been found, nor is there any evidence of a metabolic abnormality.

Recent Studies:

Some literature has appeared in the last several years dealing with megavitamin therapy and orthomolecular principles in autism, learning disability and mental retardation. Rimland et al. conducted a double blind crossover study of the effects of high doses of vitamin B_6 on autistic children (142). LeLord has studied the effects of high doses of vitamin B_6 and magnesium on autistic children (145) Both groups have reported positive findings. The results suggest that in a heterogeneous illness like autism there may be a subgroup that responds to this treatment. The degree of response is modest but statistically significant.

Kershner and Hawke (146) studied the efficacy of adding megavitamins to a diet low in carbohydrates high in protein with 20 learning disabled children who carried diagnoses of hyperactivity, minimal brain dysfunctions, or both. After a double blind six month period of treatment, the addition of megavitamins failed to produce any significant improvement when compared to the diet alone on a variety of intellectual, school achievement, perceptual, and behavioral measures. The efficacy of the diet alone could not be assessed because no dietary control group was employed. The parents of 18 of these children reported improvement in their children on this diet regardless of whether megavitamins or placebo were added. As the authors cautiously point out, this may reflect parent enthusiasm and/or the child's maturation rather than dietary effects.

In 1981, Harrell et al. (147) reported the results of a study in which 16 children (age range 5-15) with either Down's syndrome or unclassified mental retardation (IQ 17-70) received either placebo or a supplement containing 11 vitamins and 8 minerals for a four month period. All subjects were also placed on diets which restricted the intake of "sugary foods and soft drinks" and encouraged consumption of fruits and milk. All but one of the subjects were also given thyroid hormone because of low morning axial temperatures. At the end of four months,

the children were evaluated by 2 of 7 psychologists who did not all use the same IQ testing instruments. One of the psychologists, the principle investigator, was not blind to the conditions of the experiment. During the first four months of treatment, the five children who received supplemental vitamins increased their average IQ by 5-9.6 points and the 11 subjects on placebo showed negligible change. In a second phase of the experiment, all 16 of the subjects received vitamin supplements and the 11 subjects who had been on placebo in the first phase showed an average IQ increase of 10 points. The Harrell study has received considerable attention because of the implications of its conclusions. However, it has also received much criticism because of the weakness of its design and methodology.

Coburn et al. (157) carried out a replication study using mentally retarded young adults. This experiment was conducted entirely on a double blind basis with a uniform IQ testing procedure. None of the subjects, including those on the Harrell supplementation, showed any improvement in performance on the Stanford Binet test at 10 and 20 weeks. Admittedly, the Coburn study examined mentally retarded patients who were older than those studied by Harrell et al. Possibly, improvement in IQ may be limited to very young subjects. However, given the methodological weaknesses in the Harrell study and the absence of confirma · replication studies at this point, there is reason to skeptical. Replication studies are required for both professional responsbility and in the public interest.

Conclusion:

The history of medicine clearly shows that theory and practice are often dissociated. Regardless of the weaknesses of orthomolecular theory, the question may be asked, Does it work? The APA Task Force addressed this question by translating the hypotheses into testable questions. In doing so, they foccused only on the testing of the value of nicotinic acid in the treatment of schizophrenia. It was felt that this was justified because nicotinic acid was the cornerstone of megavitamin and, later on, orthomolecular theory and because the original publications for therapeutic efficacy used only this vitamin. The results of studies by many investigators who did double blind controlled studies are given in detail by the Task Force Report (124). The results were negative. Nicotinic acid as the sole medication for newly admitted schizophrenics was no better than an inactive placebo. As an adjuvant medication to phenothiazines it was worse and increased the duration of hospital stay and the amount of neuroleptic required. For chronic patients receiving neuroleptics, it was also worse than placebo. The Task Force was critical of the use of the Hoffer-Osmond card sorting test for perceptual difficulties which was the primary instrument for diagnosing schizophrenia and for measuring change with megavitamin therapy.

Since the publication of the APA Task Force Report in 1973, many other professional, academic organizations have reviewed the field of orthomolecular psychiatry and have arrived at similar conclusions. The Royal Australian and New Zealand College of Psychiatrists concluded that orthomolecular medicine has "no status in the practice of medicine or psychiatry. Its clinical role is unproven and the pathology tests cannot be justified for the rational practice of internal medicine or psychiatry". The Canadian Mental Health Association collaborative study indepndently investigated some of the underlying

hypotheses supporting orthomolecular psychiatry and obtained negative results. The American Academy of Pediatrics' Committee on Nutrition, looking specifically at the published evidence on megavitamn therapy for childhood psychoses and learning disabilities, concluded that "megavitamin therapy as a treatment for learning disabilities psychoses in children including autism is not justified on the basis of documented clinical results" (144).

The reply of Hoffer and Osmond to the APA Task Force Report was published in 1976 by the Canadian Schizphrenia Foundation of which Hoffer is President (125). The authors are careful to say that it does not necessarily represent the opinion of the Directors nor all of the members of the Foundation. It is 121 pages long; more than twice as long as the Task Force Report. The interested reader should examine it carefully.

Hoffer and Osmond (125) state that the Task Force Report and the data upon which it was based were grossly unfair and biased. They have many objections: (1) Fixed doses of nicotinic acid at 3 grams/day were used; some patients require 20 to 30 grams; (2) Orthomolecular claims were for acute schizophrenics; the so-called attempts at replication employed chronic schizophrenics; (3) Megavitamin practitioners use ECT as an adjuvant when necessary; it was not used in the replication experiments, which they feel should not be called "replication"; (4) The double blind trials which counted heavily in the Task Force judgment were unnecessary and restrictive. Criticism of megavitamin therapy research which failed to do control studies is unfair becuase it is unethical for practitioners to withhold treatment which they know is effective;(5) The Task Force Report based its judgment solely on research on vitamin B_3; megavitamin therapy has evolved to a much more complex therapeutic program which now uses other vitamins, minerals, psychotropic drugs, hormones, and other procedures; (6) The NAD experiments were

were done with a preparation which was not enterically coated. Hoffer had the megavi used with specially coated tablets which resisted digestive enzymes; (7) The Task Force selected from the literature all negative reports and did not adequately weigh the confirmatory reports.

At a more political level, Hoffer and Osmond feel the report is biased because (1) Dr. Lipton, the Chairman, was an avowed opponent, (2) at least two of the other members were opponents for different reasons, (3) no orthomolecular practitioners were on the Task Force, (4) The Task Force used pejorative adjectives in describing the work of the megavitamin therapists.

Most of the work of the orthomolecular psychiatrists is printed in their Journal of Orthomolecular Psychiatry, which is published quarterly by the Academy of Orthomolecular Psychiatry and the Canadian Schizophrenia Foundation. The Journal averages about 75 pages in each issue. It is not indexed in many major citation services, such as Index Medicus, and few medical school or university libraries in this country subscribe to it.

In a one year period (4th quarter 1981 to 4th quarter 1982), half of the full length articles were essays or reviews (15) with an additional 3 editorials, 5 case reports, 14 pages of Letters to the Editor, and 8 pages of book reviews. Only 10 articles presented data, and the vast majority of these were so flawed in methodology and so confused and confusing in purpose so as to prohibit labeling them as scientific reports.

The essays and reviews cover such topics as "Principles of Bio-Ecologic Medicine", "Towards the Orthomolecular Environment" ["We have seen how the migration of our species into space may bring us into the environment that most closely approximates the optimum for human beings, the ortho-environment. . ." (156)], "Allergies and Schizophrenia", and "Stigma and Mental Illness: Theory versus Reality."

Several of the papers and Letters to the Editor make imaginative and, perhaps, correct statements. For example, we are told that Lactobacillus Casei in the

human gut serves as an antidepressant and mild euphoriant since their cell walls contain phenylethylamine" (150). The use of mercury amalgams for filling teeth may result in chronic mercury poisoning (151). Manganese and nicotinic acid supplementation prevents tardive dyskinesia in patients receiving neuroleptics (152). Nearly 100,000 schizophrenic patients have been treated in the past 20 years. There is no doubt in the mind of every physician who has used these vitamins as part of a sophisticated treatment approach that it is remarkably beneficial (153). But data are seldom given, at most there will be an anecdotal case report.

The orthomolecular psychiatry may be called a belief system or subculture. It is not cautious and self correcting as a science should be.

It should be apparent that few, if any. research psychiatrists would agree with the orthomolecular definition of psychiatric disorders., their conc its pathogenesis, and the psychological instruments they use to measure its severity or its change with treatment. Given these vast differences, it is easy to understan why systematic attempts using research criteria to replicate their work invariably fail.

Orthomolecular psychiatrists say that clinical experience is enough to validate their procedures and that controlled blind studies are unethical. There may be other reasons, such as orthomolecular psychiatrists who are mainly in pr practice. Only a few hold academic or research positions.

Few psychiatric patients have unique nutritional requirements. Nutritional research in relation to psychiatry continues at a steady, if not spectacular pace. The pharmacological use of nutrients as in precursor therapy shows considerable promise. The special nutritional requirements of the early fetus and of geriatric patients are receiving constant attention and it seems very likely that these will be better understood and treated.

Who's Who in America, 42nd ed 1982-1983

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ORTHOMOLECULAR PSYCHIATRY

TREATMENT OF SCHIZOPHRENIA

EDITED BY

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Preface

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

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

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

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

and the point of view of the psychogenic school,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

I thank Dr. Gustav Albrecht for his help.

August 1972 *Linus Pauling*

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1

Orthomolecular Psychiatry

LINUS PAULING

INTRODUCTION

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

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

(*Reprinted with permission from* Science, *19 April 1968, vol. 160, pp. 265–271.*

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

The functioning of the brain is d pendent on its composition and structure; tha on the molecular environment of the mind. The presence in the brain of molecule N,N-diethyl-D-lysergamide, mescaline, or some other schizophrenogenic substa is associated with profound psychic effects (see, for example, Woolley, 1962). Cl kin has recently pointed out (1967) that in 1799 Humphry Davy described sim subjective reactions to the inhalation of nitrous oxide. The phenomenon of gene anesthesia also illustrates the dependence of the mind (consciousness, epheme memory) on its molecular environment (Pauling, 1961; Miller, 1961).

The proper functioning of the mind is known to require the presence in the brai molecules of many different substances. For example, mental disease, usu associated with physical disease, results from a low concentration in the brain of a one of the following vitamins: thiamine (B_1), nicotinic acid or nicotinamide (E pyridoxine (B_6), cyanocobalamin (B_{12}), biotin (H), ascorbic acid (C), and folic ac There is evidence that mental function and behavior are also affected by changes the concentration in the brain of any of a number of other substances that are nor ally present, such as L(+)-glutamic acid, uric acid, and γ-aminobutyric acid.[2]

OPTIMUM MOLECULAR CONCENTRATIONS

Several arguments may be advanced in support of the thesis that the optimum mol cular concentrations of substances normally present in the body may be differe from the concentrations provided by the diet and the gene-controlled synthe

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

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

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

VOLUTION AND NATURAL SELECTION

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

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

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

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

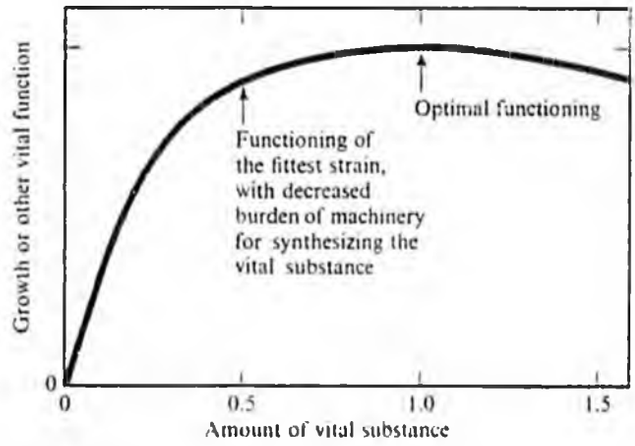

FIGURE 1-1.
Diagrammatic representation of growth rate or other vital property of an organism as function of the concentration of vital substance in the organism, showing the concentration at which the differential advantage of an increased amount of vital substance is just balanced by the differential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

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

EVIDENCE FROM MICROBIOLOGICAL GENETICS

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

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

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

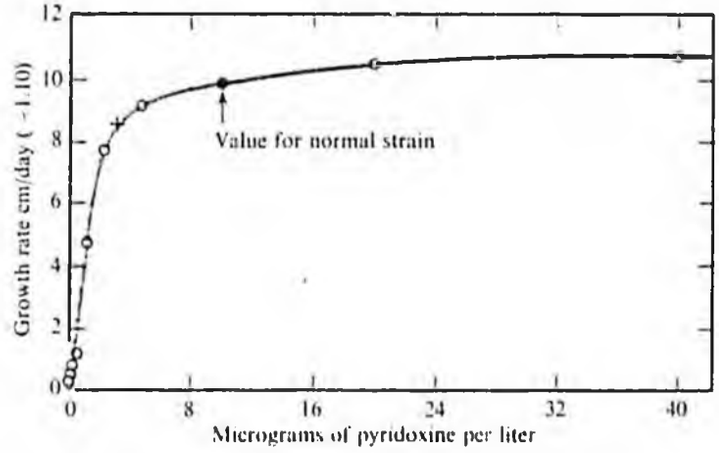

FIGURE 1-2.
The observed rate of growth of a pyridoxine-requiring *Neurospora* mutant (Beadle and Tatum, 1941), as function of the concentration of pyridoxine in the medium.

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

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

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

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

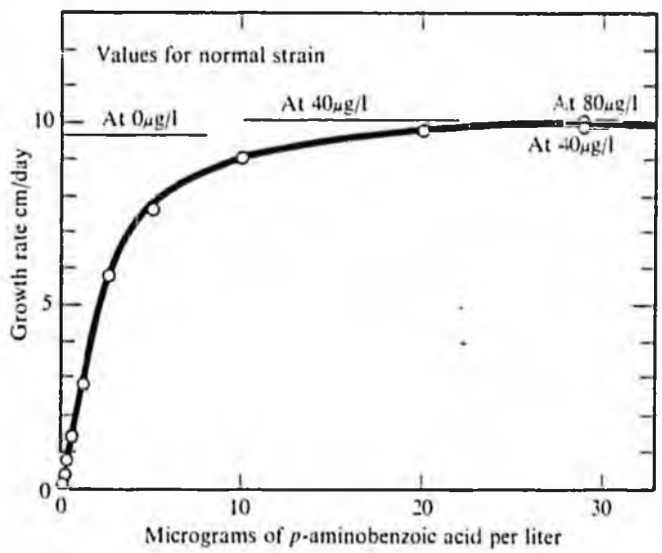

FIGURE 1-3.
The observed rate of growth of a *p*-aminobenzoic-acid-requiring *Neurospora* mutant (Tatum and Beadle, 1942), as function of concentration of the growth substance in the medium.

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

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

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

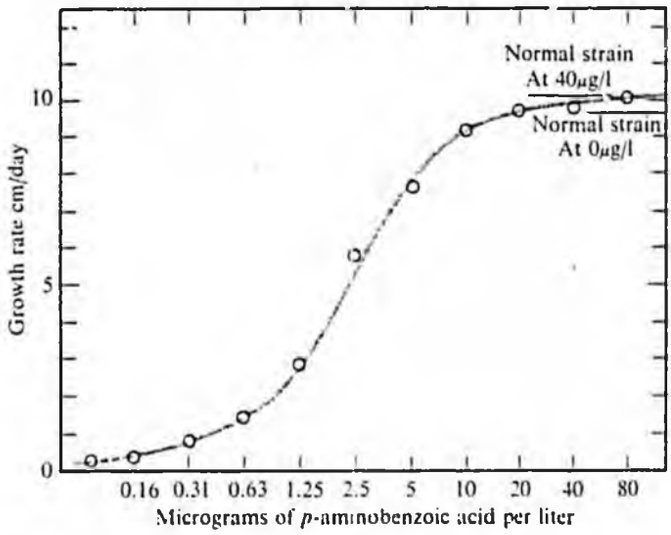

FIGURE 1-4.
Observed rate of growth of a *p*-aminobenzoic-acid-requiring *Neurospora* mutant as function of the logarithm of the concentration of *p*-aminobenzoic acid.

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

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

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

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

MOLECULAR CONCENTRATIONS AND RATE OF REACTION

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

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

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

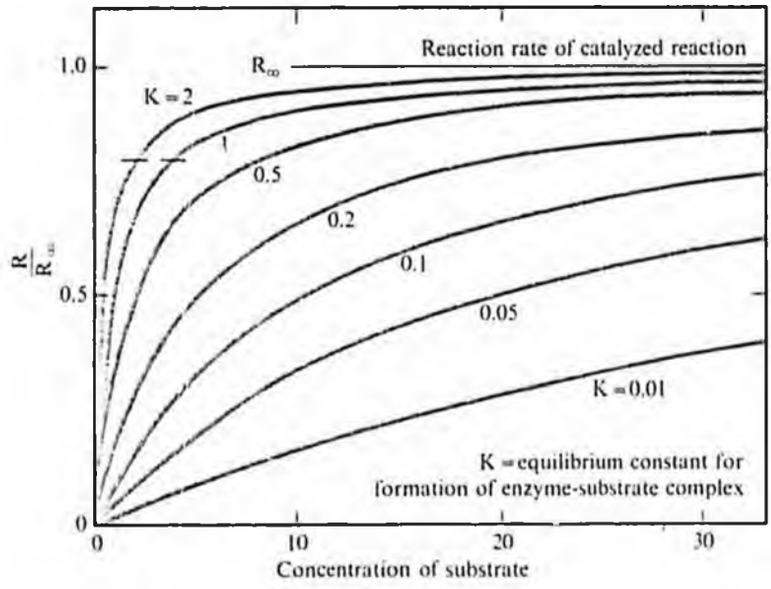

FIGURE 1-5.
Curves showing calculated reaction rate R/R_∞ of catalyzed reaction as function of the concentration of the substrate, for different values of the equilibrium constant K for formation of the enzyme-substrate complex.

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

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

may be considered a normal rate, 90 or 95 percent of the maximum ra
sponds to saturation of the enzyme. As described above, the gain
associated with the manufacture of a larger amount of the substrat
sponding advantage to the organism, might be balanced by the disa
organism associated with the upkeep of the larger amount of machin
manufacture the increased amount of substrate. An increase in rate
could also be achieved by an increase in the amount of the enzyme syn
organism. Here, again, the advantage to the organism resulting fro
may be overcome by the disadvantage associated with the increase in
machinery required for the increased synthesis. During the process of
has presumably been selection of genes determining the concentrati
zymes catalyzing successive reactions such as to achieve an approx
optimum reaction rate with the smallest amount of disadvantage to t

The rate of an enzyme-catalyzed reaction is approximately propo
concentration of the reactant, until concentrations that largely satura
are reached. The saturating concentration is larger for a defective en
creased combining power for the substrate than for the normal enzyn
defective enzyme the catalyzed reaction could be made to take place
normal rate by an increase in the substrate concentration, as indicated
The short horizontal lines intersecting the curves indicate what may
"normal" reaction rate, 80 percent of the maximum. For $K = 2$ the "n
achieved at substrate concentration $[S] = 2$. At this substrate conc
reaction rate is only 29 percent of the maximum and 35 percent of "r
mutated enzyme with $K = 0.2$; it could be raised to the "normal" valu
increase in the substrate concentration, to $[S] = 20$. Similarly, the sti
advantage of low reaction rate for a mutated enzyme with K only 0.01 c
come by a 200-fold increase in substrate concentration, to $[S] = 400$.
ism of action of gene mutation is only one of several that lead to disa
manifestations that could be overcome by an increase, perhaps a great in
concentration of a vital substance in the body. These considerations ol
gest a rationale for megavitamin therapy.

MOLECULAR CONCENTRATIONS AND MENTAL DISEASE

The functioning of the brain and nervous tissue is more sensitively depe
rate of chemical reactions than the functioning of other organs and tiss
that mental disease is for the most part caused by abnormal reaction rat
mined by genetic constitution and diet, and by abnormal molecular conce
essential substances. The operation of chance in the selection for the chi

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

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

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

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

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

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

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

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

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

LOCALIZED CEREBRAL DEFICIENCY DISEASES

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

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

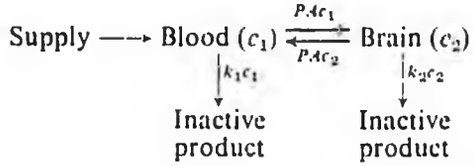
[8] A recent survey of the role of glutamic acid in cognitive behaviors has been published by Vogel et al. (1966). Many references to earlier work are given in this paper.

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

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

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

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



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

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

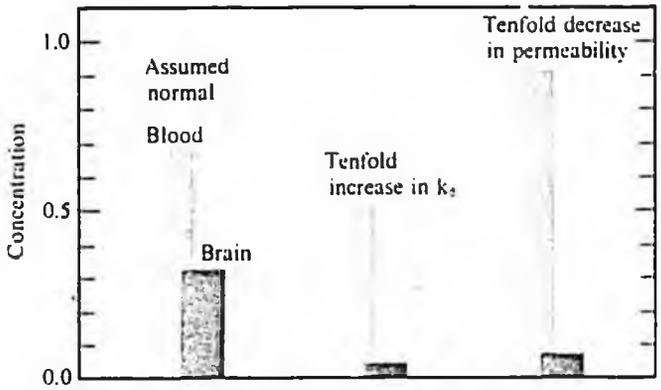


FIGURE 1-6.
Values of the concentration of a vital substance in the blood and in the cerebrospinal fluid for three different assumed sets of values of blood-brain barrier permeability and rate of destruction in the cerebrospinal fluid.

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

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

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

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

customary in psychotherapy but less customary in conventional chemotherapy. the course of time it should be possible to develop a method of diagnosis (measu ment of concentrations of vital substances) that could be used as the basis for det mining the optimum molecular concentrations of vital substances for the individu patient and for indicating the appropriate therapeutic measures to be taken. My c workers and I are carrying on some experimental studies suggested by the foregoi considerations, and hope to be able before long to communicate some of our resul

SUMMARY

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

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30

Orthomolecular Psychiatry: Treatment of Schizophrenia

DAVID HAWKINS

INSTRUCTIONS TO THE PATIENT

Education of the Patient: Explanation of the Illness and Test Results

Subsequent to the completion of tests and the diagnostic interview, the patient is given an interpretation of all the test findings and the diagnosis, including a biochemical explanation of his illness. It is explained to him how the HOD test reveals faulty perception, and he is told his exact HOD score and its correlation with his symptoms. It is then explained that a medical regimen will be prescribed that is designed to correct the brain's faulty perceptual functioning. An adequate understanding of the illness frequently relieves irrationality rapidly.

Similarly, when it is explained to the patient that paranoia is a result of faulty brain chemistry and it is labeled "paranoia" he becomes less paranoid and more rational. Unless the condition is of considerable duration, so that it has become

systematized with many attendant secondary gains, paranoid symptoms usually diminish rapidly. An adequate explanation to the patient of his illness is an extremely important therapeutic procedure and sets the stage for all the treatment procedures that follow.

We use the term "metabolic dysperception" (see Chapter 19 by Kowalson and Chapter 26 by Robie) to most accurately describe the patient's condition, and we explain that metabolic dysperception, if it gets bad enough, can produce overt clinical schizophrenia. We have yet to see a patient who has rejected this explanation, if expressed correctly. Many of the patients respond very positively and will state that this is the first time a psychiatrist has ever been honest with them.

Telling the patient that he has a specific illness allows him to assume the sick role with all the attendant benefits that accrue in our society, as have been well described by Siegler and Osmond (1969). Once the patient and family understand the nature of the illness they are usually willing to accept it and do something about it. The family no longer has to utilize denial or reaction formation to handle their guilt, anger, and other emotional reactions which automatically stem from psychological formulations of the illness. Under these conditions, families readily assent to counselling in those instances where disturbed family interaction is apparently impeding the patient's progress.

General Medical Regimen

The patient is told that he will be placed on a regimen consisting of diet, megavitamins, medications, and prescribed periods of exercise, rest, and sleep. No more than 8 hours of sleep is advised as more has been shown to increase fatigue and disability (Globus, 1969). Daily physical exercise is prescribed for its physiological benefit. Anxiety in mental patients has been demonstrated to be accompanied by elevated lactate levels as a result of altered energy systems (Pitts and McClure, 1967; Beebe and Wendell, 1968; also see Chapter 21 by Beebe and Wendell). The beneficial effect of exercise has also been reported by members of Schizophrenics Anonymous; they claim that of all the forms of exercise, swimming is the most subjectively beneficial.

Patients are advised to avoid excessive fatigue and stress and they are placed on a hypoglycemic diet which consists primarily of the avoidance of sugar and sweets, reduction of starch, and elimination of caffeine. Because there is an increasing interest in functional hypoglycemia there are a number of recent books available to the patient (see Chapter 22 by Meiers). A booklet "Hypoglycemia and Me" by the Hypoglycemic Foundation[1] is excellent and provides all the information needed.

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[1] Available from Adrenal Metabolic Research Society of the Hypoglycemia Foundation, P.O. Box 48, Fleetwood, Mount Vernon, New York, N.Y. 10552.

Patient self-help groups such as Health Frontiers[2] hold regular meetings, distribute educational literature, and sponsor informative lectures by endocrinologists.

The use of adrenal cortical extract (ACE) in the alleviation of hypoglycemic episodes is occasionally necessary. Our experiences have indicated that in certain patients it can be demonstrated to have a marked benefit and in several instances, the use of the ACE injections has made it unnecessary to hospitalize patients who had precipitated relapses by going off their diets. "Physicians Guidelines to Diagnosis and Treatment of Hypoglycemia or the Hypoadrenocortical State" and "Hypoadrenocorticism" are available from the Hypoglycemia Foundation to physicians only.[3]

We also advise patients that strong aged cheeses such as Roquefort and Camembert should be avoided as these have been reported by the members of SA to aggravate their symptoms.

Patients appreciate the reasons for all of these instructions and are far more cooperative when the rationale is given. It is useful to clarify the difference between a vitamin *deficiency* disease and a vitamin *dependency* disease (Rosenberg, 1970) in which vitamins are being used in pharmacologic rather than replacement doses. To aid in their understanding of the illness, educational literature is made available and most patients and families find helpful the educational package which is available from the Schizophrenia Association of Long Island.[4] In our experience, the more the patient and family know about the illness, the better the result.

Joining Schizophrenics Anonymous is recommended when it appears the patient would benefit, and we suggest to family members that they join one of the schizophrenia associations, become acquainted with the other families, and attend the educational lectures. Many patients become interested in the hypoglycemic aspect of the illness and appreciate being referred to patient self-help groups concerned with this illness.

With the alcoholic-schizophrenic patients, treatment is first concentrated on the schizophrenia and they are referred to SA. In each of the SA groups, there are also members of Alcoholics Anonymous and, as the patient improves, these recovered alcoholics introduce the patient to AA. If the patient is not going to SA then he is referred directly to AA after his HOD score has gone down and the schizophrenic process has abated. Surprisingly, at that point the schizophrenic-alcoholic usually abruptly stops drinking without the prolonged struggle and battle typical of the nonschizophrenic alcoholic. The patient frequently attends both SA and AA groups and as the schizophrenic process dissolves, he usually drifts away from SA and continues in just AA.

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[2] Available from Health Frontiers Foundation, 149 Spindle Road, Hicksville, New York 11801.

[3] Adrenal Metabolic Research Society of the Hypoglycemia Foundation, P.O. Box 98, Fleetwood, Mt. Vernon, New York.

[4] Long Island Schizophrenia Association, 1691 Northern Blvd., Suite No. 203, Manhasset, New York 11030.

MEDICATION

Psychotropic Drugs

The academic drug researcher operates at a distinct disadvantage—he cannot employ the great variety of techniques which the clinician utilizes almost automatically in his daily practice. Also, the researcher can only handle very limited data and the number of controlled variables must of necessity include only those that are most obvious and that lend themselves to data collection and processing. The parameters of research designs are, therefore, arbitrarily quite limited, as are the results. Unfortunately, the results of such studies are often extrapolated beyond the confines of the data and the results are stated in terms which do not limit the results to the conditions of the study. Because he is unencumbered by such limitations, it is usually possible for the clinician to accomplish more with any given drug than the literature infers. The more complex the illness being treated, the more this general principle holds true, and it is especially so in schizophrenia.

Correct sequencing of medications is important in the psychopharmacology of schizophrenia. By changing the sequence it is often possible to obtain results with the same drug to which the patient was previously unresponsive. A similar observation has also been made by Kline (1969), who noted, in doing cross-over studies, that patients may react differently to the same dose of the same drug when it is later re-introduced and that this phenomenon creates a previously unrecognized problem for drug research. We have learned that this can be done deliberately—a patient can be "set up" to respond to a drug that we intend to administer at a later date. In doing this, advantage can be taken of certain readily observable principles of central nervous system activity such as the rebound phenomenon. For instance, a patient will often readily respond to an "up" drug if it is rapidly introduced during the immediate period following cessation of a "down" drug and vice-versa. Brain function, as a general rule, tends to be compensatory, and this natural tendency can be used to purposely "sensitize" a patient to the effect of the same or another drug. In attempting to induce this reaction, the action of the "sensitizing" drug should be in the opposite direction from the drug whose response we later need to effect a recovery.

Researchers who are not clinically experienced are often puzzled by the "polypharmacy" that they come across, because, from the limitations of a theoretical viewpoint, it "doesn't make sense." The clinician, however, often follows by "intuition" certain principles in drug usage which have been learned by experience. Besides sequencing, these include: utilization of mutual synergisms and antagonisms, balancing off of side effects, purposely utilizing desired side effects, extending dosage ranges by concurrent use of antagonists, calculating onsets and durations of action, predicting progressive loss of response, predicting development of tolerance or loss

of tolerance, estimating effective dosage ranges at different stages of the illness, and predicting phases of drug responses. Because of all these clinically important factors, which are not included in research designs, it is common for clinicians to obtain quite different results from those that are received from academic studies. In daily practice the clinician automatically compensates for biological individuality (Williams, 1971) and the difference between patients, which in psychiatric conditions are more marked than in other kinds of illness. In psychiatry it is common for patients to require 10 to 100 times the "average dose" of a given substance before they respond favorably.

Additional reasons for the traditional "town versus gown" difference in the results of treatment between clinicians and academic researchers are provided by understanding Joseph Wilder's "Law of Initial Value," which states that the pre-stimulus state of the organism determines the response as much as does the nature of the stimulus itself. The chemical importance of this concept has been reviewed by Lesse (1971). Because of the antipsychotic effect of the phenothiazines, all patients are placed on either a suitable phenothiazine or other antipsychotic medication if this has not been done previously. According to Hollister (1971), antipsychotic drugs "contribute the most therapeutic benefits in schizophrenia—there is little direct evidence that traditional therapies add more," and all antipsychotics produce a postsynaptic dopamine receptor blockade leading to stabilization of the membrane at the receptor site.

The site of action may also be an enzymatic protein in the presynaptic membrane adjacent to the intersynaptic cleft (Teller and Denber, 1968). They point out that the defective protein at the synaptic site is probably quite small and that the antipsychotic drugs are capable of changing protein structure even in minute doses. The change in structure then causes change in functioning of the enzymatic activity. Utilizing a "framework molecular model" (available from Prentice-Hall, Inc., Englewood Cliffs, N. J.) they demonstrated, for instance, that the "architectural" characteristic of chlorpromazine and mescaline allowed for a demonstration of their mutually antagonistic action by action at the cell's protein membrane discs.

Spontaneous disinhibition of neuronal circuits, because they are connected in series rather than parallel, can result in clinically significant symptoms even though only a few sites are involved. This may lead to production of reverberative circuits in which apparent perceptions may occur, for instance, without external stimulation. Also, in chronic schizophrenia there is a disturbance of internal inhibitory activity (Saarma, 1968), and Saarma and Vasar (1970) have demonstrated that this disturbance is positively influenced by nicotinic acid. Teller and Denber conclude that the symptoms resulting from the endogenous genetic defect in schizophrenics are similar, from the viewpoint of molecular biology, to those that are exogenously caused by the psychotomimetic drugs. Bradley and Johnston made a valuable contribution to future research in this area in their work on "The Molecular

Pharmacology of Hallucinogens" (1968). Animal research until this time had been based only on gross behavioral changes in response to the drugs being investigated. Bradley and Johnston introduced the use of operant conditioning techniques to determine more subtle behavioral changes in response to a series of possible psychotogens. By correlating these more subtle responses to a series of structural changes in the molecules being studied, they have come closer to approximating the human condition in drug research with experimental animals.

It is explained to the patient that the phenothiazines are being prescribed, not as tranquilizers, but for their effect in reducing the HOD score and for their antischizophrenic action. Intelligent patients appreciate a brief explanation of the action of the phenothiazines so that they get to know that chlorpromazine has a "down" action and is, therefore, useful when they are agitated, or upset, or have insomnia, whereas fluphenazine, especially in lower doses, has an "up" action. An explanation is given of extra-pyramidal side effects and the reason for prescribing anti-Parkinsonian medication.

Patients are told that if they get blurred vision, the anti-Parkinsonian drug dose is too high, and that if they get restless legs or cannot sit still, it is too low. An explanation is given that the phenothiazines are not properly called tranquilizers and that that term should be reserved for drugs of the meprobamate type. This removes the common prejudice against taking tranquilizers. Many patients are either fearful of tranquilizers or they have reaction formations against them and do not want to become dependent on them. Clarification of this issue is often of considerable importance because some patients will discontinue antipsychotic drugs, with dire results, for these reasons.

The dose of phenothiazines is reduced as the patient improves and his medication is shifted from one end of the phenothiazine spectrum to the other, depending on what phase of illness or recovery he is in currently. We have seen many patients whose impairment was impeded by their being kept on the wrong phenothiazine due to the mistaken notion that all phenothiazines are interchangeable. As an example:

> A 28-year-old schizophrenic man was admitted to a hospital with paranoid symptoms. He was placed on 600 mg of chlorpromazine, following which the paranoid symptoms disappeared. He then became depressed and apathetic. During the next year-and-a-half he had psychotherapy three times a week, but did not improve and so was discharged at the end of that time as having achieved maximum hospital benefit. Medication remained the same throughout the entire hospital stay and he was discharged on the same dosage.
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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 (1956), Sourkes (1962 1970), Lochner et al. (1963), Minde (1966), Cookson et al. (1967), Jenner (1967) Vestergaard (1969), and Hoffer (1967). Thyroid can be used in treatment of the recurrently ill schizophrenic as well as for other types of schizophrenia.

Hoffer and Osmond (1967) reviewed the literature and noted that the average dose of thyroid used was 5 grains daily. Danziger and Kindwall (1953, 1954) gave doses of 2 to 20 grains but found that few patients required more than 10 grains. All researchers have commented on the considerable resistance of the schizophrenic to thyroid hormone and in our own work we have observed the same phenomenon. Our most common dose is 3 to 5 grains daily, and many patients who were previously unresponsive to treatment will recover when this amount of thyroid is added. Many of these are patients who do not present the classic periodic pattern; one will be described later.

Megavitamins

We routinely use mega doses of four vitamins for a variety of reasons in treating schizophrenic patients, and this has resulted in increased rates of recovery. It is still not possible to predict exactly which patients will benefit by megavitamins and it remains for future researchers to give us the useful clinical indicators to identify these patients in advance. Work supported by the Canadian Mental Health Association (Ban, 1969; Ananth et al., 1969; Ban and Lehmann, 1970) is proceeding in that direction and preliminary results indicate that there is a segment of the schizophrenic population that responds to either nicotinic acid and pyridoxine or pyridoxine alone and may eventually be identifiable.

Ananth, Ban, and Lehmann report (1972) that the therapeutic effect of nicotinic acid in chronic schizophrenics is potentiated by pyridoxine. This was demonstrated in a 48-week double blind control study in which pyridoxine alone, nicotinic acid alone, or the two together were demonstrated to have a statistically significant therapeutic effect. The therapeutic effect was demonstrable even though the patients had been hospitalized for an average of 10.9 years, were not on hypoglycemic diets, and the doses of both pyridoxine (75 mg daily) and vitamin B3 (3 g a day) were considerably below the dosages we routinely prescribe.

In general, it can be said from our own experience that the higher the patient's HOD score, the greater the likelihood of response to an overall megavitamin treatment regimen. The schizophrenic patient whose illness could be called "metabolic

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 phenothiazines may be augmented by the megavitamins. Demonstration of the effectiveness 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, 19. 8b). Similar negative experiences have been reported by Roukema d Emory (1970) and Greenbaum (1970b), who also demonstrated that nicotinamide 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 schizophrenia has been precipitated by LSD. Although the flushing side-effect of niacin can be controlled by cyproheptidine (Periactin®) 4 mg four times daily (Robie, 1967), the flush unnecessarily alarms patients even when it has been previously explained to them. Niacin also appears to be more beneficial than niacinamide in treating the alcoholic-schizophrenic, although we do not have statistical studies to prove that this is so.

Recent studies (Davis and Walsh, 1970; Lieber and DeCarli, 1970) have demonstrated metabolic pathways in alcoholics which may account for nicotinic acid's

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[5] Hypoglycemic episodes, for instance, will trigger post-LSD "flashbacks."