Molecular Medicine

ORTHOMOLECULAR PSYCHIATRY

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

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

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The proper functioning of the mind is known to require the presence in the brain of molecules of many different substances. For example, mental disease, usually associated with physical disease, results from a low concentration in the brain of any one of the following vitamins: thiamine (B1), nicotinic acid or nicotinamide (B3), pyridoxine (B6), cyanocobalamin (B12), biotin (H), and ascorbic acid (C; mental depression accompanying scurvy). There is evidence that mental function and behavior are affected by changes in the concentration in the brain of any of a number of other substances that are normally present, such as L(+)-glutamic acid, uric acid, and y-aminobutyric acid.

Optimal Molecular Concentrations. - Several arguments may be advanced in support of the thesis that the optimal molecular concentrations of substances normally present in the body may be different from the concentrations provided by the diet and the gene-controlled synthetic mechanisms, and, for essential nutrilites(vitamins, essential amino acids, essential fatty acids) different from the minimal daily amounts required for life or the "recommended" (average) daily amounts suggested for good health.

Evolution and Natural Selection. - The process of evolution does not necessarily result in the normal provision of optimal molecular concentrations. Let us use ascorbic acid as an example. Of the mammals that have been studied in this respect, the only species that have lost the power to synthesize ascorbic acid and that accordingly require it in the diet are man, other primates (rhesus monkey, Formosan long-tail monkey, ring-tail or brown capuchin monkey), the guinea pig, and an Indian fruit-eating bat (Pteropus medius). Presumably the loss of the gene or genes controlling the synthesis of the enzyme or enzymes involved in the conversion of glucose to ascorbic acid occurred some twenty million years ago in the common ancestor of man and other primates, and occurred independently for the guinea pig and for this species of bat, in each case in an environment such that ascorbic acid was provided by the food. For a mutation rate of 1/20,000 per gene generation and for even a very small advantage for the mutant (0.01 percent more progeny) the mutant would replace the earlier genotype within one or two million years. The advantage to the mutant of being rid of the ascorbic-acid-synthesis machinery (decrease in cell size and energy requirement, liberation of machinery for other purpose) 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 optimal supply of dietary ascorbic acid would not prevent the replacement of the earlier species by the mutant. Hence, the amount of the vitamin provided by the diet available at the time of the mutation might be less than the optimal amount. Moreover, it is possible that the environment has changed during the last twenty 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.

Individual Variation. - The human race is characterized by large genetic heterogeneity. Enzyme concentrations in tissues of different persons often differ by the factor two or even 10 or 100. Heterozygosity in the gene for phenylketonuria halves the amount of the enzyme phenylalanine hydroxylase, and homozygosity reduces its amount or effectiveness by two or more orders of magnitude. Roger J. Williams especially has emphasized the significance of individual variation of human beings in relation to health, nutrition, and therapy.

Molecular Concentrations and Rate of Reactions. - The rate of an enzyme-catalysed reaction is approximately proportional to the concentration of the reactant until concentrations are reached that largely saturate the enzyme. The saturating concentration is larger for a defective enzyme with decreased combining power for the substrate than for the normal enzyme. For such a defective enzyme the catalysed reaction could be made to take place at or near its normal rate by an increase in the substrate concentration. Also, an increase in concentration of an enzyme inhibitor can decrease the rate of a reaction; for example, an increase in nicotinamide concentration, with the consequent inhibition of the enzyme diphosphopyridine nucleotidase, decreases the rate of hydrolysis of diphosphopyridine nucleotide.

The functioning of the brain and nervous tissue is more sensitively dependent on the rate of chemical reactions than the functioning of other organs and tissues. I believe that mental disease is for the most part caused by abnormal reaction rates, as determined by genetic constitution and diet, and by abnormal molecular concentrations of essential substances. The operation of chance in the selection, for the child, of half of the complement of genes of the father and mother leads to bad as well as to good genotypes, and the selection of foods (and drugs) in a world that is undergoing rapid scientific and technological change may often be far from the best. I believe that significant improvement in the mental health of many persons, especially those with borderline or mild mental illness or mental retardation, may be achieved by the provision of the optimal molecular concentrations of substances normally present in the human body, especially those that are not toxic or have low toxicity.

Among these substances, the essential nutrilites may be the most worthy of extensive research and more thorough clinical trial than they have yet received. The use of L(+)-glutamic acid (not an essential amino acid) in treating mental retardation suggests also that other substances normally present in brain and nerve tissue and either synthesized in the body or normally provided in the diet may be of value in increased or decreased amount.

The Treatment of Mental Disease by Use of Substances Normally Present in the Body. - L(+)-glutamic acid is a non-essential amino acid that is present at rather high concentration in brain and nerve tissue, and plays an essential role.[9] It is normally ingested (in protein) in amounts of 5 or 10 grams per day. It is not toxic; large

doses may cause increased motor activity and nausea. In 1944, Price, Waelsch, and Putnam[10] reported favorable results for glutamic acid therapy of convulsive disorders (benefit to one out of three or four patients with petit mal epilepsy[11]).

Zimmerman and Ross then reported an increase in maze-running learning ability of white rats given extra glutamic acid.[12] Zimmerman and many other investigators then studied the effects of glutamic acid on the intelligence and hebaviour of persons with different degrees and kinds of mental retardation.[13-20] L(+)-glutamic acid is apparently more effective than its sodium or potassium salts. The effective dosage is usually between 10 g and 20 g 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. Improvement in personality and increase in intelligence (by 5 to 20 IQ points) have been reported for many patients with mild or moderate mental deficiency by several investigators.[21]

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 mg per day (70 kg male). In 1940 Streitwieser et al.[25] reported some success in the treatment of severe depression and other forms of mental disease by use of large doses of nicotinic acid (3 g or more per day). Other investigators, especially Osmond, Smythies, and Hoffer, have advocated and used nicotinic acid in large doses for the treatment of schizophrenia.[26-30] The dosage recommended by Hoffer is 3 g per day (or more, up to 18 g per day, as determined by the response of the patient) of either nicotinic acid or nicotinamide, together with 3 g per day of ascorbic acid. Nicotinic acid and nicotinamide are nontoxic (LD50 not known for humans, but probably over 200 g; LD50 for rats 7.0 g per kg for nicotinic acid, 1.7 g per kg for nicotinamide), and their side effects, even in continued massive doses, seem not to be commonly serious. The advantages of nicotinic acid therapy have been summarized by Osmond and Hoffer[31]: "Niacin (nicotinic acid) has some though not all the qualities of an ideal treatment: it is safe, cheap (less than one cent per gram), and easy to administer, and it uses a known pharmaceutical substance which can be taken for years on end if necessary... It does not seem to affect the more chronic illnesses, and even in acute illnesses its action is often less dramatic than that of some of the phenothiazenes. Its protective qualities, continuing long after patients have stopped taking it, are puzzling... It has been proved to reduce the level of cholesterol in the blood. It seems to benefit some deliria not obviously associated with vitamin lack, and is claimed to improve many cases of intractable rheumatism. In our view it is a useful adjunct in the treatment of schizophrenia, both for acute cases and to reduce the chance of relapses..."

It is my opinion, for reasons presented in the opening arguments of this paper, that, for those patients for whom it is effective, the control of mental disease by varying the concentrations in the brain of nontoxic substances that are normally present, such as nicotinic

acid and ascorbic acid, is to be preferred to the use of phenothiazenes and other means of therapy that involve a greater insult to the body and mind.

Varying the intake of other vitamins has also been used in psychiatry. The mental deterioration accompanying aging and cerebrovascular disease may be alleviated by supplementary bioflavonoids (vitamin P) and ascorbic acid.[32] The use of cyanocobalamin (B12) in the treatment of mental disease has been reported.[33] The observed decreased level of pyridoxyl phosphate enzymes in the brain tissue of mental patients, especially the aged, suggests that pyridoxine (B6) therapy would be useful. A field of research in which much more work needs to be done is that of the functioning of the brain in its relation to the concentrations and intake of the vitamins, the essential amino acids, and other substances normally present in the body.

Summary. - The functioning of the brain is affected by the molecular concentrations of many substances that are normally present in the brain, such as L(+)-glutamic acid, nicotinic acid, and some other vitamins. Some of these substances are nontoxic. The optimal concentrations for a person may differ greatly from the concentrations provided by his normal diet and genetically determined biochemical machinery. It is known that massive therapy with L(+)-glutamic acid benefits many mental retardates and that massive therapy with nicotinic acid or nicotinamide, together with ascorbic acid, benefits many schizophrenics and other persons with mental disease. Biochemical and genetic arguments support the idea that orthomolecular therapy, the provision for the individual person of the optimal concentrations of important normal constituents of the brain, may be the preferred treatment for many patients, especially those with mild mental retardation or mild psychosis. I suggest that this therapy, to be successful, should involve the thorough study of and attention to the individual, such as is customary in psychotherapy (psychoanalysis), but not in conventional chemotherapy.[35]

References

(The list of references is incomplete)

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The word orthomolecular may be criticised as a Greek-Latin hybrid. I have not, however, found any other word that expresses as well the idea of the right molecules in the right amounts.

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In the course of time it should be possible to develop a method of diagnosis (analysis of blood and urine, etc.) that could be used as the basis of calculating the optimal molecular concentrations for the individual.