

(Contribution to the volume Functional Biochemistry of Cell Structures,
dedicated to the memory of Academician N.M. Sissakian.)

Orthomolecular Methods In Medicine

by

Linus Pauling

Center for the Study of Democratic Institutions,
P.O. Box 4068, Santa Barbara, California 93103

For over thirty years I have been interested in the problem of the molecular structure of the human body, the molecular basis of disease, and, more generally, the molecular basis of life. I shared this interest with my friend Academician N.M. Sissakian, and I am confident that, if he had known about them, he would have been interested in the ideas that are expressed in the following paragraphs.

A number of years ago my coworkers and I announced our discovery that a disease, sickle-cell anemia, ~~is~~ the result of the gene-controlled manufacture by the patient of a kind of hemoglobin different in molecular structure from normal adult human hemoglobin, which is manufactured by most human beings.¹ We entitled our paper Sickle-Cell Anemia, a Molecular Disease. I discussed this discovery and the concept of molecular disease in a public lecture in Moscow in 1957, shortly after the Symposium on the Origin of Life that had been arranged by Academician A. I. Oparin. The concept of molecular disease is, of course, a somewhat artificial one. We might say that every activity of the human body is molecular, that every disease is molecular, since the human body is composed of molecules, and vectors of disease, such as viruses and bacteria, are also composed of molecules. Moreover, the manufacture of the

abnormal hemoglobin, sickle-cell-anemia hemoglobin, that is characteristic of the disease sickle-cell anemia is the result of the presence in the patient of a mutated gene. The gene itself is a molecule, and the disease might be described as a molecular disease because it results from the presence of an altered, mutated, molecule of DNA, the gene. In this respect all of the diseases resulting from gene mutations, the inborn errors of metabolism, in the words of Harrod, might well be described as molecular diseases. Presumably, however, *a disease* resulting from macroscopic change in structure of the human body without any change in the nature of the molecules composing it (for example, insanity following the accidental cutting away of part of the brain) would not be described as a molecular disease. The discovery of the abnormal hemoglobin associated with sickle-cell anemia showed that some diseases of genetic origin involve the manufacture, under the control of the mutated gene, of a protein molecule with structure different from that of the normal protein molecule, manufactured under the control of the normal gene. The hemoglobin molecule contains four polypeptide chains, two alpha chains and two beta chains. The difference in structure of sickle-cell-anemia hemoglobin and normal adult human hemoglobin has been shown to be the change in a single amino-acid residue in the beta chain. Almost all of the approximately 100 abnormal human hemoglobins that have been discovered during the last eighteen years involve a single amino-acid replacement in either the alpha chain or the beta chain.

Many of the inborn errors of metabolism involve the failure to manufacture an enzyme, or involve the manufacture of an altered enzyme that has much smaller enzyme activity than the normal one. A great amount of information about the enzyme activity of normal and abnormal enzymes has been obtained from studies of wild-type and mutated microorganisms, especially the studies of Neurospora, initiated by G. W. Beadle and E. L. Tatum. In their first paper on the genetic control of biochemical reaction in Neurospora ² Beadle and Tatum reported their isolation of a mutant with decreased ability to synthesize pyridoxine (vitamin B6). This mutant strain grows on the basic medium that supports normal growth of the wild type at a rate only ten percent of that of the wild type. Its growth rate is rapidly increased by the addition of pyridoxine to the basic medium (Figure 1), and reaches the rate of growth of the wild type at a concentration such as to indicate that the ability of the mutant to synthesize the vitamin is only about one percent of that of the wild type. A simple explanation of this observation is that the mutated gene of the mutant strain synthesizes an abnormal enzyme, with decreased activity; if the abnormal enzyme is manufactured in amount equal to the normal enzyme, we may conclude that its structural defect decreases its activity to one percent of that of the enzyme manufactured by the wild type.

The observed rate of growth of the "pyridoxineless" Neurospora mutant as a function of the amount of pyridoxine added to the medium, as reported by Beadle and Tatum, is shown in Figure 1. The

mutant equals the wild type in growth rate at vitamin concentration 10 micrograms per liter, and achieves a growth rate about 10 percent higher for a four-fold increase in concentration. We may draw the conclusion that the amount of the growth substance that is synthesized by the wild type is not the optimal amount, but is somewhat less.

In Figure 1 there is shown also the dependence of growth rate on concentration of para-aminobenzoic acid for the mutant strain of Neurospora crassa that has decreased power to manufacture this substance, and also the growth rate of the wild type of Neurospora crassa as a function of the amount of a growth substance, biotin, that it is unable to synthesize. These two growth-rate curves are similar in form to that for the pyridoxineless mutant (of Neurospora sitophila), and also similar in form to the theoretical curve that is shown. This theoretical curve represents the Michaelis-Menten equation, $R = \frac{R_{\infty}c}{(c + K)}$, in which R_{∞} is the limiting rate for high concentration of the reactant in an enzyme-catalyzed reaction, c is the concentration of the reactant, and K , the Michaelis constant, is the assumed dissociation constant of the complex of reactant and enzyme. The two lower calculated curves in Figure 1 correspond to the same value of R_{∞} and to values of K ten-fold and fifty-fold greater, that is, to a ten-fold and fifty-fold decreased combining power of the enzyme for the reactant molecule.

The studies of the abnormal hemoglobins and of the many inborn errors of metabolism show that human beings differ from one another in their genetic constitution and the nature of the enzyme molecules and other protein molecules that they synthesize. Let us consider the functioning, physical or mental, of a "normal" person, *in relation to* the amount of a particular vitamin (thiamine, nicotinic acid, pyridoxine, ascorbic acid, or some other vitamin) that he ingests. We may compare him with the pyridoxineless strain of Neurospora sitophila, and conclude that his functioning will depend upon the amount of the vitamin that he ingests. If we use the Michaelis-Menten curve as the basis for our description, and take the rate of the enzyme-catalyzed reaction as a measure of his state of well-being, we may say that he will show signs of poor health (poor state of well-being, less than fifty percent of the maximum) if he ingests less than 2 units of the vitamin per day (using the scale for the horizontal axis of Figure 1), that he will have what probably might be called normal health (eighty percent of the maximum) if he ingests ten units per day, even better health (ninety percent of the maximum) for twenty units per day, and a small but perhaps significant further increase in health for a larger amount of vitamin ingested. Here the possibility must be kept in mind that for large amounts of the vitamin some deleterious side reactions could occur. This possibility would be shown, for example, by the observed toxicity of large amounts of the vitamin. It is interesting in this respect that some vitamins are essentially

non-toxic. Ascorbic acid and nicotinic acid are examples of vitamins that are not toxic when taken in amounts of the order of 100 grams, *which* *is* 1000 or 10,000 times the usually recommended daily requirement. *Let us*

consider a person who is homozygous in a mutant gene, such that the enzyme that is manufactured under its control has a combining power for the vitamin that is only two percent as great as that of the normal enzyme. The state of health of this person would be represented by the lowest of the three theoretical curves shown in Figure 1. If he received the normal ten units per day of the vitamin, he would be in the region of vitamin deficiency, with reaction rate only one-tenth of that of a normal person on the same diet. To be raised to the normal level of well-being, eighty percent of the maximum, he would need to receive fifty times the normal amount of the vitamin, 500 units per day instead of ten units per day. (Similar conclusions may be reached if the vitamin functions not as the reactant in an enzyme-catalyzed reaction, but as ~~a~~ *coenzyme*, with the mutated apo-enzyme having a decreased combining power for the *coenzyme*.)

We are accordingly led to the conclusion that some molecular diseases might be controlled by the increase in the concentration in the human body of molecules that are normally present in the body, and are normally required for life and good health. These molecules might be molecules of vitamins, as discussed above, molecules of amino acids, or molecules of other substances normally present in the human body.

The treatment of disease and the prevention of disease *at* the present time are largely accomplished by the use of synthetic drugs or physiologically active substances extracted from plants; that is, by chemotherapy. Mental disease is controlled by synthetic drugs such as chlorpromazine or powerful natural products such as reserpine. Electroconvulsive therapy, insulin coma therapy, pentoline tetrazol shock therapy, and related methods of changing the structure of the brain are also used. In addition, patients with mental disease may be treated by psychotherapeutic methods, to provide insight and to decrease environmental stress.

We may use the expression orthomolecular medicine to describe the general method of treatment and prevention of disease referred to above, the provision in the right concentration of the molecules that are normally present in the human body and are needed for life and good health. (The word orthomolecular might be criticized as a Greek-Latin hybrid; I have not, however, found any other word that expresses so well the idea of the right molecules in the right amounts.)

An example of orthomolecular therapy is the use of very large amounts, five grams to twenty-five grams per day, of ascorbic acid in helping to control colds and other infectious diseases. The treatment of diabetes by injection of insulin might also be considered to be an example of orthomolecular medicine. Another 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 catalyzing the oxidation of phenylalanine to tyrosine. The patients, when kept 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 in the food results in an approximation to the normal or optimal concentrations and to the alleviation of the manifestations of the disease, both mental and physical.

In the case of phenylketonuria the concentrations of substances in the patient are larger than the optimal concentrations, and the orthomolecular therapy requires a diminution in the concentrations. This is more difficult to achieve than the increase in the concentrations of ascorbic acid or insulin, mentioned above. I believe that there are several general arguments that can be presented in support of the contention that most patients with a disease that can be treated by the methods of orthomolecular medicine are in the second category, such that the treatment involves the increase in the amounts of certain molecules, rather than in the more difficultly treatable first category.

One argument has already been given. Geneticists have observed that favorable mutations occur far more rarely than unfavorable mutations: the enzyme manufactured by a mutated gene almost always shows decreased activity, relative to that of the wild type. From the argument given above we conclude that the orthomolecular therapy for such a disease would involve an increase in the amount of the

substrate for the reaction catalyzed by the enzyme, to bring the rate of the reaction back towards normal, or possibly the provision of the enzyme itself. (I do not know of any disease that can be treated by providing the enzyme itself, although in the case of insulin therapy a closely similar treatment is involved, the provision of the hormone itself, identical with human insulin or closely similar to it.)

Also, the example of the pyridoxineless strain of Neurospora, in relation to the wild type (Figure 1), shows that the wild type does not manufacture the optimal amount of the essential substance pyridoxine, but an amount *some what* less than optimal. We may explain this observation by considering the processes involved in the evolution of species. The machinery for manufacturing the essential substance is itself a drain on the organism. Presumably the amount of drain on the organism increases roughly proportionately to the rate of manufacture of the substance. The differential disadvantage associated with a small increase in the amount of synthesizing machinery is presumably balanced in the wild type by the differential advantage resulting from the larger amount of the growth substance, pyridoxine, that is synthesized; that is, the slope of the growth-rate curve in Figure 1 at the concentration 10 micrograms per liter, where the growth rate of the mutant is equal to that of the wild type, is just, with changed sign, the differential disadvantage associated with increase in the synthetic machinery. Some increase in well-being can accordingly be expected through the increase in

concentration even of substances that are not essential nutr^lites.

In the case of vitamins and other essential nutr^lites, we may consider the evolutionary process resulting in the loss of the ability of the organism to manufacture the substance. Let us assume that the substance is available in the food normally accessible to the organism, but in amounts somewhat less than the amounts manufactured by wild type. A mutant organism unable to manufacture the substance would be liberated from the drain associated with the machinery of manufacture. The advantage accompanying this liberation could outweigh this disadvantage accompanying the somewhat decreased concentration of the substance. Accordingly, the mutant would replace the wild type even though the concentration of the essential substance provided by the food normally ingested were somewhat less than the concentration manufactured by the wild type. Increase in state of health would accordingly result from an increased supply of the vitamin or other essential nutr^lite.

Moreover, fluctuations from the normal situation might result in an increased need for the nutr^lite; an example is the state of infection, mentioned above, that leads to an increased need for ascorbic acid. Ascorbic acid is required for the proper functioning of the leucocytes of the blood, and an increased amount of ascorbic acid is required for the proper increase in the number of functioning leucocytes made in the effort to control the infection.

Orthomolecular psychiatry may turn out to be an important branch of orthomolecular medicine. It has been reported, for example,

that the ingestion in amounts of five to fifteen grams per day of L(+)-glutamic acid, in addition to the amounts provided by the normal food, by patients with mild mental retardation leads to a significant increase in intelligence and significant improvement in personality. This sort of orthomolecular therapy, which was discussed by various investigators some twenty-five years ago³, seems not to be used at present to the extent that would seem to be justified by its simplicity, freedom from dangerous side effects, and low cost.

Another aspect of orthomolecular psychiatry that, in my opinion, deserves more attention than it has received is the treatment of schizophrenia and other forms of mental illness by the ingestion of three grams to fifteen grams per day of nicotinic acid or nicotinamide as well as of three to six grams per day of ascorbic acid.⁴ These substances are non-toxic and cheap, and they are normally present in the human body. The reports of great improvement in mental health accompanying their use, together with the rationale for this sort of therapy that has been developed in the arguments of the present paper, suggest that a thorough study of the effectiveness of this therapy should be carried out. I believe that for those patients for whom it is effective the control of mental disease by varying their concentrations in the brain of non-toxic substances that are normally present, such as nicotinic acid, nicotinamide, ascorbic acid, ^{and} L(+)-glutamic 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.

There are many other orthomolecular treatments that need to be given a thorough trial. The mental deterioration accompanying aging and cerebral vascular disease may be alleviated by supplementary bioflavonoids (vitamin P) and ascorbic acid. The use of cyanocobalamine (vitamin B12) in the treatment of mental disease has been reported, as has also the use of pyridoxine (vitamin B6). The study of the functioning of the brain in its relation to the concentrations and intake of the vitamins, the essential amino acids, non-essential amino acids, and other substances normally present in the human body constitutes a field of research in which a great amount of work needs to be done.

End

(References + Figure will
be mailed to you soon.)

Legend for Figure

Figure 1. The top curve, with the associated points, represents the experimental measurements of Beadle and Tatum of the rate of growth (centimeters per day) of the pyridoxineless mutant of Neurospora sitophila, as a function of the concentration of pyridoxine added to the basic culture medium, in micrograms per liter (horizontal scale). The second curve is the growth rate of the amino benzoateless mutant of Neurospora crassa, as a function of the concentration of para-aminobenzoic acid added to the medium, same scale; the third curve from the top is the growth rate of Neurospora crassa as a function of the concentration of ~~bioin~~ bioin in the medium, same scale (47 micrograms per liter on the scale corresponds to 1 microgram per liter of bioin added). The fourth curve from the top is the theoretical Michaelis-Menten curve, described in the text, and the fifth and sixth curves from the top are the theoretical curves with tenfold and fiftyfold decrease in combining power of the enzyme for the substrate, respectively. The large circle on the upper curve indicated the growth rate of the wild type of Neurospora sitophila, on the medium without added pyridoxine. The experimental values for the top curve are from Reference 2, those for the next curve from E. L. Tatum and G. W. Beadle, Proc. Natl. Acad. Sci. U.S. 28, 234 (1942), and those for the third curve from the top from F. J. Ryan, G. W. Beadle, and E. L. Tatum, Am. J. Bot. 30, 784 (1943).