An Update of Megavitamin Therapy in Orthomolecular Psychiatry

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CONCEPTUALIZATIONS

When Dr. Hoffer asked me to give this talk on updating megavitamin therapy in schizophrenia, it occurred to me that there was probably very little that was really new to add to the extensive and thorough review of all aspects of megavitamin treatment presented last year at this same conference. Therefore I decided to look into my own thinking of the way I use megavitamins, the justifications I make in my own mind for using them in the ways that I do, and to share my own concepts of what I think 1 am doing to a patient when I prescribe various vitamins in extremely high doses to get certain effects.

In order to answer questions intelligent patients may ask me about what I believe is being accomplished by giving megadoses of certain vitamins, and also in order to justify to interested physicians my prescription of megavitamin therapy, I have come up with a conceptualization of what these vitamins are doing individually in the brains of those to whom I prescribe and the reason for the effects I see occur in those patients.

I'm not sure how common this kind of process is, but the birth of psychology with its conceptualizations of the ego, superego, and id, was an attempt to simplify and clarify complicated interrelationships. And in the same sense I have found it helpful to me to make some simple assumptions about the chemistry of human behavior and emotion, which may be at slight variance here and there with accepted current ideas, but which are useful to me primarily as a road map or general direction in treatment.

There is nothing original in my current concept of the chemistry of human behavior. It is relatively simple, it is naturally obtained from a variety of sources both within and outside the Orthomolecular movement, it is constantly being modified with my increasing past experience, and it is not at all complex; otherwise it would serve no useful purpose to me. It is a very personal simplification of the controversial and rapidly expanding biogenic amine theory of emotion and behavior, and its

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scientific validity is not of primary importance to me as long as it aids me, a majority of the time, in predicting the right things to do for my patients.

I find it very appealing to assume, as did Hippocrates, that the behavior of human beings may be affected by the condition of certain humors. The humors proposed by Hippocrates were blood, yellow bile, black bile, and phlegm. These do not quite fit my current needs, but Kety and Schildkraut noted that certain biogenic amines, notably dopamine, serotonin, and norepinephrine, had an importance in regulating mood states because reserpine produced a depletion of these amines in brain and other tissues while causing mental depression, and iproniazid produced an elevation of these same amines resulting in alleviation of depression.

These biogenic amines are affected by stress, by chemicals in the body, by vitamins, by foods, and mostly by what they come from, amino acids. There may very well be a pathway from the environment to behavioral disturbance that passes over a chemical bridge, or chemical bridges.

The biogenic amines we are talking about may be these chemical bridges, and they are called neurotransmitters. In order to think a thought or move a finger, many thousands of neurons must communicate with one another. At each junction between neurons there is a slight gap, known as a synaptic cleft. It is the neurotransmitters which cross this gap, thereby allowing the neurons to communicate.

Therefore, if one could learn how to control the neurotransmitters, one is capable of controlling all abnormalities in human behavior and consciousness.

BACKGROUND

In order to provide a background for how the Orthomolecular psychiatrist may conceive of megavitamin and Orthomolecular therapy in terms of research in the biochemistry of these brain humors, I would like to quote from a recent discussion by Seymour Rosenblatt, Associate Clinical Professor of Psychiatry, Department of Psychiatry, Mount Sinai School of Medicine of the City University of New York, prepared for Roche and recently distributed to American psychiatrists. He writes as follows: *"The past two decades have witnessed a revolutionary change in our understanding and knowledge of the central nervous system. The functional, topographic data accumulated during all the previous years of investigation are dwarfed by the relatively recent acquisitions of neurophysiological and neurochemical information. New findings are being integrated into a precise and exacting science of the nervous system. And basic research in this area is well on the way towards unravelling the molecular biology of memory, thinking, dreaming, sleeping, feeling, behavior and learning.*

"But what is the significance of this new knowledge, derived primarily from animal research, for the clinical psychiatrist? Can treatment of an asocial, withdrawn patient be helped by knowledge of the effects of early infantile experiences on the chemistry of the adult brain? Is there a clinical significance in knowing that inhibition of serotonin synthesis can produce aggressive and hypersexual behavior? Or that hyperactivity of dopaminergic systems can give rise to schizophrenic-like behavior in animals as well as man? Obviously, the answer is yes. It has been suggested, in fact, that the era of neuropsychopharmacology has had the greatest impact on psychiatric theory and practice since Freud."

(I would only like to insert a comment, here, that it simply hasn't made enough of an impact on psychiatric practice in the United States, where even some of these new concepts are being given Freudian, psychodynamic interpretations.)

He goes on to say:

"In time this wealth of emerging research information will be integrated into concepts of human behavior which the psychiatrist now sees *primarily in a developmental and psychodynamic context."*

(This last statement, however, is an obvious contradiction to the previous statement, because if the impact is so great on theory **and practice,** why does the typical psychiatrist, today, still see human behavior primarily in a developmental and psychodynamic context?)

I think that what he is saying here is that in another 20 years there may be some humane application of these theories and facts to alleviate the suffering of inadequately treated depressed and schizophrenic patients. The rest of his discussion, however, is of great interest.

"Of more immediate consequence: investigators have recently been concentrating, for the most part, on developing greater understanding of the pathogenetic factors underlying the affective disorders. A great deal of progress has already been made. Interest has centered particularly on certain biogenic amines—most notably norepinephrine, serotonin and dopamine.

"Rising in the brain stem are a number of distinct nerve systems which directly or indirectly influence a wide variety of physiological functions. Each of these systems employs a distinct chemical substance, or amine, for the transmission of nerve impulses within its own network. And the proper balance and functioning of these neurotransmitters appear to play an important role both in the governing of the states of consciousness and alertness of the mind and in the modulation of emotional experience and behavior.

"The three major central amine systems on which most laboratory studies have been carried out are: norepinephrine (NE), dopamine [DA] and serotonin [5-HT). All three are intimately involved with centers of the brain—such as the limbic system—and regulate a variety of behaviors, including affects, arousal, cognition, aggressive and sexual drives.

"All monoaminergic neurons have similar structural characteristics. They differ primarily in the complement of enzymes which produce their respective neurotransmitters. The enzymes are synthesized within the cell body and are carried by an axoplasmic flow to the nerve terminals. The latter consist of numerous fine, unmyelinated branchings. Each branch has a profusion of discrete segmented dilations, termed varicosities.

"Each varicosity has granular vesicles which contain the neurotransmitter. The storage granules have both a binding and protective function. Formed in the cell body and transported down the axon, they actively take up amines in the cytoplasm by a process requiring adenosine triphosphate (ATP) and magnesium (Mg). *The granules extrude a portion of their substance along with their amine content into the synaptic cleft during the neurotransmission process. This process occurs when the nerve is excited and depolarized."*

(I would like to insert the observation here that the marked increase in the production of NE, and probably the other amines, by ECT which causes a total, massive excitement and depolarization of nearly all the neurons perhaps accounts for the amazing and dramatic response of severe depressions and acute schizophrenias to this type of treatment.)

"During depolarization, vesicles in the nerve endings move to the cell membrane and fuse with it. The transmitter is released into the junctional gap and received by receptors on the effector cell. The storage granules of the NE neurons, in addition, contain the enzyme dopamine-beta-hydroxy-lase which mediates the synthesis of NE from DA (which requires adequate amounts of oxygen and ascorbic acid).

"Besides the existence of the uptake storage mechanism of the granule, another uptake mechanism is present along the cell membrane. Unlike that of the granule, it is not reserpine-sensitive, and serves to recapture released extraneural amines."

Rosenblatt then goes on to define the anatomical locations in the brain of the NE systems which are both ascending and descending, the DA systems which are at least three definable systems, and the 5-HT systems whose neurons tend to have a distribution similar to the NE systems.

"From the distribution of the central biogenic amine tracts, it is apparent that an interaction exists between them in many areas of the brain. The effect on any

behavioral components can be conceptualized as a vector, with these amines as components, which modulate the dominant cholinergic systems."

He then takes up the known effects of each neurotransmitter in its own system on behavior.

"Noreprinephrine—This neuronal system has a major role in affective states. Destruction of NE neurons can result in withdrawn, asocial, anhedonic, 'depression-like' behavior in primates. A deficiency in turnover, reflected by lowered levels of a norepinephrine metabolite in the cerebrospinal fluid, is found in depressive states in man. Electroshock treatment leads to an increased synthesis and release of NE in the brain. During states of emotional stress, an increase in NE turnover also occurs. Since NE is involved in the pleasure or reward centers of the hypothalamus, it seems likely that a dysfunction in its metabolism could result in distinct mood changes.

"Dopamine—A deficiency of DA in the corpus striatum, secondary to a degeneration of cells in the substantia nigra, is involved in the pathophysiology of Parkinson's disease. The disease's rigidity and akinesia result from decreased dopamine inhibition of cholinergic systems in the striatum (which is nearly the same as saying an increase in acetylcholine, the levels of DA and acetylcholine being balanced in the healthy state). Administering L-dopa, a precursor of DA, increases the amount of DA and thereby reverses the disinhibition of cholinergic neurons.

"Excessive amounts of DA may result in abnormal motor and mood states. In animals, a form of stereotyped motor activity ensues, suggestive of a 'hallucinatory' process. Latent schizophrenic states in patients have been activated by L-dopa and manic-like states have been evoked in depressed manic-depressive subjects.

"Several of the more effective antipsychotic drugs appear to be DA-blocking agents as well. These drugs—which include the phenothiazine compounds and haloperidol— tend to block the action of DA on its receptor cells and, by so doing, often produce varying degrees of DA deficiency in the corpus striatum. This results, at times, in a reversal of the schizophrenic symptoms—but unfortunately in the induction of parkinsonian symptoms. Nevertheless, the fact the DA-blocking agents are particularly effective in the treatment of schizophrenia has led some researchers to suggest that an abnormality in the dopaminergic system may be involved in the pathogenesis of the psychosis.

"Serotonin—There also appears to be significant disturbance of 5-HT as well as NE metabolism in depressed patients: evidence indicates a basic deficiency in 5-HT turnover in the central nervous system of these subjects during both remitted and depressed states.

"A number of psychotomimetic drugs, including LSD, have a significant effect in increasing brain 5-HT. At the same time, there is a decrease in the firing and, therefore, the release of 5-HT by the neuron. This decrease in the activity of 5-HT (serotonin) neurons obviously results in a marked imbalance of the central biogenic amine modulatory systems.

"One result of inhibited serotonin synthesis is a marked impairment of sleep. Since disturbances in sleep patterns are commonly found in psychotic states, several recent studies suggest that administration of the amino acid tryptophan, a serotonin precursor, may well have a beneficial action in some schizophrenic patients.

"Disturbances in the functioning of these three amine neurotransmitters would, from existing evidence, obviously appear to be implicated in a variety of psychiatric disorders. On the other hand, recent findings suggest that not even the manic and depressive illnesses can be explained solely by a specific amine etiology. Certainly, much more research is needed before we can approach full understanding of these complex illnesses. But the current interest in the biogenic amines can do much both to advance knowledge in this area and to stimulate further research efforts."

This is the end of Rosenblatt's discussion. What is disturbing about it to me is the impression I get that we ought to wait and see what new information may come out to clarify some of the confusion and apparent contradictions that are inherent in this fragmented **medical model before we** use any of this

information in clinical treatment.

However, Rosenblatt's discussion is too narrow, and there are a number of other facts about these neurotransmitters and about other neurotransmitters which he has ignored, and which provide a considerably more comprehensive understanding of how manipulation of these neurotransmitters can be accomplished in such a way as to achieve dramatic improvements in many psychiatric illnesses.

Another interesting thing about neurotransmitters is how chemically similar some of them are to well-known hallucinogens. For example, DMT (dimethyltry-ptamine), a powerful hallucinogen, is tryptamine with two methyl groups added, and tryptamine is an amino acid which is a precursor of 5-HT, one of the neurotransmitters. Bufotenin, another hallucinogen, is serotonin with two methyl groups added. And mescaline, a well-known hallucinatory drug, is chemically similar to NE with three methyl groups added, NE being one of the most important of all the neurotransmitters.

Authorities, as already pointed out, have pretty well accepted the level of neurotransmitters as being related to mood. No less an authority than Judd Marmor, who is the newly elected president of the APA and who is also the Franz Alexander Professor of Psychiatry at University of Southern California has stated, unequivocally, that "happiness and sadness are not just states of mind; they are also specific neurochemical states, as are all emotions." But these same nonorthomolecular authorities do not even admit the possibility of methylated neurotransmitters or methylated breakdown products of neurotransmitters causing an alteration of perception. Yet, in many cases, methyl-accepting substances capable of removing methyl groups from such products will cause a disappearance of hallucinations and delusions, at least in the acute schizophrenias.

Not only that, Axelrod, at the NIMH, has shown that everyone has a substance, a methyl transferase, capable of adding methyl groups to neurotransmitters (possibly) circulating in their platelets and that non-schizophrenic people have a dialyzable inhibitor in their platelets which blocks the methyl transferase. Whether these isolated facts are truly relevant or not, treating patients as though they were works often enough to use these concepts as a workable hypothesis.

CAUSE OF DYSPERCEPTIONS

The best evidence available today, as reviewed by Dr. Hoffer in **Orthomolecular Psychiatry** in 1973, is that alerations in perception are always due to one of three broad effects on the neurotransmitters, or a combination thereof: 1) A reduction of 5-HT concentration as compared with the concentration of epinephrine in the brain (another neurotransmitter —the methylated by-product of NE) results in an increase in oxidation of epinephrine to adrenochrome which is hallucinogenic, whereas an increase in the ratio of 5-HT to epinephrine inhibits this oxidation or even prevents it. 2) NAD deficiency allows epinephrine to be easily oxidized to adrenochrome, whereas adequate levels reverse the reaction. 3) Methylated indoles which are methylated breakdown products of the catecholamine neurotransmitters have been found in increased quantities in urine of schizophrenics.

There are a wide variety of well-known drugs that will affect neurotransmitters and will also affect a number of other substances in an undesirable way, leading to many unpleasant and sometimes dangerous side effects. But, in Orthomolecular psychiatry, we look to vitamins, minerals, amino acids, and dietary measures to alter health in a favorable way, and I have found it most satisfying to consider the ways that megavitamins and diet can favorably alter neurotransmitters.

Niacin or niacinamide in megadoses might impede the breakdown of

tryptophan leading to higher serotonin levels, correcting the imbalance leading to overoxidation of epinephrine to adrenochrome; could enhance deficient NAD levels; and being excellent methyl acceptors could demethylate toxic and hallucinogenic indoles.

Adequate levels of B6 are necessary for the synthesis of 5-HT and for the conversion of dopa to DA. Ascorbic acid is essential along with oxygen in the conversion of DA to NE by dopamine-beta-hydroxylase.

This, then, provides the rationale for megadoses of B3, B6, and C therapy in disorders with altered perception and at least some of the affective disorders where levels of NE may be deficient.

However, a large proportion of affective disorders and also perceptual disorders where there is a large affective component fail to respond to megavitamin therapy alone, and for some time now affective abnormalities have had to be controlled with mood altering drugs with all of the concomitant undesirable side effects. Drug therapy and ECT with drug failure has been, until recently, the main resource. Now, with the advent of lithium carbonate, we have a powerful and effective adjunct to use with megavitamin therapy. The alleged aggravation of schizophrenic symptoms in latent schizophrenics or overt schizophrenics with prominent mood disorders is easily controlled with the concomitant use of megavitamin therapy.

Here we have a mineral which undoubtedly has profound effects on neurotransmitters although the mechanism of action is not clearly known. The suggestion has been made that lithium may decrease NE at critical receptor sites in the CNS, thus reducing the mood-elevating or disinhibiting effect of NE. It has been alleged also that lithium produces a shift of NE metabolism from O-methylation to oxidative deamination, and also a possible increase in turnover of the catecholamine. Corrodi and coworkers in 1967 reported that although lithium does not alter the NE content of the brain, it inhibits tyrosine hydroxylase (an essential enzyme which aids in manufacturing precursors of NE). Lithium does not influence the content of DA or 5-HT in the brain although 5-HT turnover appears to be increased.

Lithium can substitute for sodium in the process of cell membrane depolarization. One hypothesis is that intracellular sodium levels are moderately elevated in depressed states and markedly elevated in manic states. By replacing the elevated sodium levels with lithium, sodium is brought back toward normal resulting in a normalization of mood. Whether this, in turn, has a balancing effect on the levels of the neurotransmitters is certainly not known yet, but it is an appealing idea. If lithium increased the turnover of NE to epinephrine, thereby altering the ratio of concentration of epinephrine to the concentration of 5-HT which would be unchanged by lithium, the increase in adrenochrome produced by this alteration could explain the occasional accentuation of schizophrenic symptoms by lithium used alone.

Our own experience, however, has been that lithium in conjunction with megavitamin therapy in several hundred cases has only accentuated latent schizophrenia when megavitamins were intentionally delayed for some reason. The addition of megavitamins immediately relieved the precipitated schizophreniclike symptoms.

Excessive 5-HT may cause as pronounced behavioral alterations as a deficiency. Richard Wurtman, John Fernstrom, and several colleagues at the Massachusetts Institute of Technology found that the availability of the amino acids tyrosine and tryptophan in the brain is a major factor in determining the rate at which four neurotransmitters are produced. The production of neurochemicals in the brain was once thought to be insulated from the meal-to-meal vagaries of amino acid intake. Within one hour after a meal, the levels of these chemicals begin to change as the amounts of tyrosine and tryptophan in the blood rise and fall.

Tyrosine and tryptophan, however, must compete with three other amino acids for the limited places available on the transit system from the blood to the brain. As the ratio between these amino acids fluctuates, the likelihood of getting a ride into the brain changes, much as the odds at a race track change as each bet is placed. When a group of rats were given a diet high in tryptophan but without competing amino acids, the brain content of the neurotransmitter 5-HT and the tryptophan from which it is produced rose substantially. When they ate food with competing amino acids, there was no increase in either substance.

A high-carbohydrate diet produces hyperinsulinism, and one of the most interesting effects of insulin is that it depletes the blood of all the competing amino acids except tryptophan. With virtually unhindered transit into the brain, tryptophan becomes 5-HT at a vastly increased rate. This can result in hostility, aggressiveness, and paranoid trends. This is a good justification for a hypoglycemic diet.

Another substance having value in behavioral problems, especially hyperkinetic, distractible, inattentive children is 2-dimethylaminoethanol (also known as Deanol), a precursor of acetylcholine which is a neurotransmitter. There is another balance system in the brain, in the basal ganglia, between DA and acetylcholine, and relative suppression of cholinergic neurons either by elevation of DA or high doses of anti-cholinergic drugs results in either schizophrenic-like symptoms or interference with concentration and learning abilities. Perhaps this is one of the reasons why Deanol may have some value as a treatment resource. Deanol may be looked upon as a vitamin and is chemically similar to choline, a B vitamin.

L-glutamine is another amino acid which has a place in the treatment of neurochemical dysfunction. Glutamic acid seems to be the only amino acid metabolized by brain tissue. However, it is of considerable importance in brain metabolism and is a major acceptor of ammonia produced either in the metabolism of the brain or delivered to the brain when the arterial blood ammonia is elevated. In the latter reaction, glutamic acid accepts 1 mol of ammonia and is thus converted to glutamine. Although it has been shown that the brain can form urea, the formation of urea does not play a significant role in removal of ammonia from the brain. This is accomplished almost entirely by reactions involving the formation of glutamic acid as well as by the formation of glutamine. When levels of ammonia in the brain are elevated, usually as a result of increased ammonia in the blood, the supply of glutamic acid available from the blood may be insufficient to form the additional amounts of glutamine required to detoxify the ammonia in the brain. L-glutamine readily passes the blood brain barrier and is very useful and effective in some kinds of neurotoxic conditions. Four grams a day has been beneficial to some patients. Propranolol, a beta adrenergic blocking agent, which is a false neurotransmitter normally blocking those receptor sites sensitive to epinephrine (or adrenalin), is used to slow down an overexcited heart (a heart being overexcited by adrenalin); in so doing it can reduce palpitations of the heart and has some definite anti-anxiety as well as anti-tremor effects. Even in low doses, however, it has the ability to slow the heart sufficiently that a hypoglycemic reaction could constitute an added risk to the patient's health. Yet this drug was tried in England at doses of 500 to 3500 mg daily and resulted in six out of 14 chronic refractive schizophrenics recovering. The usual dose of this drug is 10-40 mg a day, and no one in the United States could risk such a dosage without government approval. Apparently its effectiveness is at least partly its ability to block the effects of an overproduction of adrenalin.

When the simplest and most direct forms of Orthomolecular psychiatry fail, that is the use of megavitamins for

reasons already described, the addition of lithium when there is a prominent mood disorder, the use of only judicious levels of antipsychotic and antidepressant medication when a response is needed rapidly, and a nutritious hypoglycemic diet, then fasting and food allergy testing is the ultimate weapon in the Orthomolecular arsenal. In a sense, it probably should be first, but it represents such a drastic change in the patient's life pattern that patients may only accept this method when everything else has failed.

I have no idea what fasting does to neurotransmitter levels, but one thing it does is to bring about a marked stability of both blood glucose and blood insulin levels. Also there is a tremendous stabilization of FFA (free fatty acids) and circulating amino acids from proteolytic breakdown of muscle. All amino acids except leucine are potential glucogenic precursors in man.

If allergic-like reactions to foods have profound effects on the neurotransmitters of the central nervous system, which facts seems to suggest, it is yet to be confirmed, but one can certainly hypothesize that certain enzyme systems essential in the metabolism of the neurotransmitters are profoundly affected or interfered with by these allergic reactions. Naturally, removal of the allergens allows normal neurotransmitter synthesis and function. Perhaps someday this type of supposition may be proven. The results of this type of treatment so far are primarily empirical.

We can now look at the humors of the central nervous system and say that in some respects Hippocrates was not very far from wrong, all he would have had to do was change the names.

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