Neurotransmitter Theory and Orthomolecular Practice

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The practicing clinical psychiatrist must make a decision, when he confronts a patient with certain symptoms, as to what he should do about these symptoms. In the past 25 years, it has been traditional for psychoanalytically oriented psychiatrists to assume that psychotic behavior represents unconsciously caused reactions to unconscious psychological events and that, somehow, elucidation, clarification, and insight remove the need for such behavior. Biologically oriented psychiatrists and most so-called eclectic psychiatrists have deduced that such an orientation leads to inadequate results, and have found more dramatic and effective reduction or cessation of symptoms from the use of major tranquilizers.

An explanation of how major tranquilizers work, which I prefer to think of as antipsychotic, antihallucinatory, antidelusional, or antischizophrenic (depending on the type of symptoms which are relieved), has not been forthcoming and, at best, is only in the rudimentary stages, but this has not discouraged the use of such medications except by those purists who continue to regard schizophrenia as a myth or as a way of life. Hawkins, in the Journal of Orthomolecular Psychiatry (1977), has eloquently defined schizophrenia from an Orthomolecular point of view, and this paper will not attempt to recapitulate that excellent definition. However, the biological and genetic implications of that definition lead one to look hard at the kind of information that the clinician needs to obtain about the patient behaviorally, perceptually, and biochemically in order to make the most sophisticated and objective decisions possible in initiating his treatment.

Both mood and perception are beginning, gradually, to succumb to the intricacies of biological and biochemical explanation, and although many gaps, contradictions, and confusions still exist in the diverse biogenic amine theories, few can argue that emotions and perceptions are merely psychological events; they are also, ultimately, specific neurochemical events. Three-quarters of a century ago a Cambridge University graduate student introduced the concept of the neurotransmitter, or biochemical vehicle of neuron impulse transmission, a hypothesis which eventually led to the identification, by Axelrod in 1972, of norepinephrine (NE) as being centrally involved in this physiologic event. Since the identification of norepinephrine (NE), at least

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eight other chemicals have been characterized as neurotransmitters (Maas, 1975): serotonin (5-HT), dopamine (DA), acetylcholine (ACh), histamine, excitatory amino acids (e.g., glutamate, aspartate), inhibitory amino acids (e.g., aminobutyrate, GABA), substance P (a polypeptide of about 1400 mol. wt.), and prostaglandins.

Maas believes dopamine (DA), norepinephrine (NE), and serotonin (5-HT) are somehow related to mental illness, the first to the psychoses and Parkinsonism, the last two specifically to depression.

Starting out with depression, if it is of sufficiently severe nature that the examining psychiatrist feels that the presenting symptoms are not clearly accounted for by the ensuing circumstances of the patient's life, he most frequently initiates a tricyclic antidepressant. Looking at the patient's response to such an approach, we find situations where not infrequently musical chairs with medications occur. One tricyclic medication not working leads, after adequate trial, to another tricyclic, eventually to a third or fourth with inadequate response, and finally the right one or combination is found and both patient and physician may be pleased by a remission of the symptoms and a successful outcome. On other occasions, no need for experimentation occurs if the initial medication tried lives up to its expectations. Because of this unpredictable situation, it is easy to see why the chemical explanation of depression as a single neurochemical event with merely quantitative differences does not hold. In fact, there is a combination of factors which might clarify the situation if one looks at the biochemically different effects of the different tricyclics.

For example, amitriptyline (e.g., Elavil) has a 4+ effect on a scale of 0 to 4 on inhibiting re-uptake of serotonin and none on norepinephrine. Nortriptyline (e.g., Aventyl) has a 2+ effect on serotonin re-uptake inhibition and an equal effect on inhibiting norepinephrine re-uptake. Imipramine (e.g., Tofranil) has a 3+ inhibiting effect on serotonin re-uptake and a 2+ effect on inhibiting norepinephrine re-uptake, and desipramine has no inhibition on re-uptake of serotonin, but 4+

inhibition of norepinephrine re-uptake. Cerebrospinal fluid studies of depressed patients have confirmed two chemically different patterns in metabolites of serotonin and norepinephrine, and several investigators have demonstrated that low urinary levels of MHPG (3-methoxy-4-hydroxyphenyl glycol), a metabolite of norepinephrine, are correlated with successful desipramine and imipramine treatment, and high or normal levels of MHPG with successful amitriptyline treatment. Twenty-nine percent of a group of 68 depressed patients had below normal concentration of 5-HIAA (5-hydroxyindo-leacetic acid), a metabolite of serotonin, and there was a significant correlation between the CSF concentration of the metabolite and the severity of the depression in the subnormal group. This is a group which would be expected to respond most favorably to amitriptyline (e.g., Elavil) therapy. If the clinical psychiatrist, who does not have at his beck and call the means and tools of the research psychiatrist, uses musical chairs with his antidepressants, he may find, as the Orthomolecular psychiatrist has, that musical chairs with high doses of water-soluble vitamins and a diet for relative hypoglycemia, as well as checking and treating for low normal or subnormal thyroid function, can bring about a certain percentage of remissions from depression. One may look for the effects of vitamins and diet on neurotransmitters for a possible explanation. Niacin or niacinamide in mega-(meaning massive) doses impedes breakdown of tryptophan, a precursor of serotonin; thus it would possibly be helpful in those depressions with deficiency of serotonin, the type of depressions expected to respond to a drug blocking serotonin reuptake such as amitriptyline (e.g., Elavil). The relationship of nicotinic acid to tryptophan was emphasized by Graham (1966) when he pointed out that, with adequate pyridoxine, tryptophan can protect against pellagra even with insufficient nicotinic acid.

Adequate levels of pyridoxine (vitamin B6 are necessary for the synthesis of serotonin and for the conversion of dopa to dopamine, the precursor of norepinephrine;
therefore vitamin B6 is potentially helpful in both chemical types of depression, the "serotonin depression" and the "norepinephrine depression." Ascorbic acid (vitamin C) is essential, along with oxygen, in the conversion of dopamine to norepinephrine by dopamine-beta-hydroxylase. Therefore, both vitamins B6 and C in megadoses conceivably could have beneficial effects in those patients who have shown a reduction of depression in response to drugs inhibiting norepinephrine reuptake such as desmethylimipramine (e.g., Norpramin or Pertofrane). Vitamin B6 has been proven helpful in relieving the depression sometimes brought on by oral contraceptives because of the blocking of B6 which, in turn, impairs subsequent tryptophan metabolism.

The studies of Wurtman and Fernstrom at the Massachusetts Institute of Technology have shown the relationship of amino acid intake and brain blood levels of at least four neurotransmitters. Since insulin reduces the blood levels of all the amino acids except tryptophan, and the precursors of dopamine and therefore norepinephrine would be reduced, hyperinsulinism brought about by a diet high in sugar would tend to aggravate a depression that might be responsive to imipramine or desmethylimipramine. Wouldn't it be wonderful if avoiding sugar and refined starches, thereby lowering surges of insulin in the blood, thereby raising levels of phenylalanine and tyrosine and eventually the norepinephrine that comes from them, could remove the need for those excellent and indispensable medications, imipramine and desmethylimipramine? Orthomolecular psychiatrists have been able to do this, at least in some cases.

Fasting, which lowers and stabilizes blood insulin levels, and of course, removes many potential food allergens, probably has profound balancing and/or stabilizing effects on neurotransmitter synthesis and functions. The Russian use of these techniques is apparently empirical rather than based on any kind of neurotransmitter theory.

Orthomolecular Theories

The Orthomolecular theorists have their own biogenic amine hypotheses of the causes of the distorted perceptions that characterize schizophrenia, and these have been extensively described by Hoffer (1973) in Orthomolecular Psychiatry; Treatment of Schizophrenia edited by Hawkins and Pauling. Granted, the theories seem to be made to fit, or partially fit, the treatment methods advocated and used, and perhaps, someday, other explanations may turn out to be better or more correct. But what works cannot be discounted, and patients, their families, and their doctors soon find what works when everything else has failed and when relapses follow overconfidence and discontinuation of treatment.

There are several ways research psychiatrists have tried to explain the relationship of abnormal brain chemistry to psychotic symptoms. The first and most obvious way has been to look for a psychotogen or a way psychotogens could be metabolized by the brain of the schizophrenic. Another way is to assume that an excess of the substance or substances which most antipsychotic drugs antagonize or block, somehow, inherently, results in the development of the primary symptoms of the disease. The amphetamine psychosis has been suggested as a model, but offers no real advantage over the dopamine excess theory in view of the effects of amphetamines on dopamine release. Data are reported as consistent with the cause of amphetamine psychosis being amphetamine itself and not a metabolite. A two-factor theory, with one of the factors being dopamine, the other being a second substance, perhaps a false neurotransmitter such as DMPEA (di-o-methylamphetamine) or CPK, was suggested by Davis (1975). The first factor, the false neurotransmitter, could represent the "turning on" of schizophrenia; the second factor, dopaminergic stimulation, "turns up" the gain. Therefore, one needs both factors to have an overt schizophrenic episode. Phenothiazines, in blocking dopaminergic stimulation, turn down the gains, which in turn allows the normal reparative processes to occur so that the basic schizophrenic pathology heals after weeks or months. However, by this theory, factor one is an as yet unknown process (such as DMPEA or CPK), and factor two would be dopamine-mediated, possibly
stress-related "activation of psycho-
pathology."

The chronology of evidence to support the early hypothesis of Osmond and Smythies (1952) has emerged from several areas according to Friedhoff and Schweitzer (1975).

(1) Cantoni (1952) identified S-adenosyl-
methionine as an active methyl donor in biological methylation reactions. This substance is formed enzymatically from methionine and ATP.

(2) Armstrong et al. (1957) identified urinary 3-methoxy-4-hydroxy-mandelic acid as a metabolite of adrenalin.

(3) Axelrod (1957) demonstrated in vitro that catecholamines form mono-0-methylated metabolites.

(4) Pollin et al. (1961) produced exacerbations of schizophrenic symptoms upon feeding methionine to iproniazid-treated patients.

(5) Axelrod (1961) detected an enzyme in rabbit lung capable of converting tryptamine to N, N-dimethyltryptamine, and serotonin to bufotenin.

(6) Friedhoff and Van Winkle (1962) detected DMPEA in the urine of schizophrenics, but not in the urine of normal subjects. Subsequently, they showed the possible origin of urinary DMPEA by means of in vivo and in vitro studies with labeled dopamine (Friedhoff and Van Winkle, 1963).

(7) Daly et al. (1965) converted several catecholamine metabolites to trioxy metabolites, thereby demonstrating a confluence between catecholamine and mescaline metabolism in mammalian tissues.

(8) Various investigators have implicated dopamine overproduction in the etiology of schizophrenia.

(9) Recently it has been demonstrated that mescaline can be formed in mammalian tissues from an appropriate precursor. Friedhoff and Schweitzer (1975), whose laboratories have added some considerable information to previous research, conclude that it is possible that the various outward manifestations of schizophrenia relate to the dominant biogenic amine in a particular individual. For example, perhaps in some individuals excessive dopamine, in relation to acetylcholine, might lead to excessive methylation and thereby produce hallucinations in that individual. Some, such as Mandell (1975), have suggested that classical theories of the role of central biogenic amines do allow that one manifestation of an "overfunctioning" system might be a pathological state of activation. Such a theory would have to accept the possibility that psychotropic drugs would act to protect the receptors rather than directly altering neurotransmitter levels.

Hoffer (1973) pointed out that methylated breakdown products of neurotransmitters have been found in increased quantities in the urine of schizophrenics. Other points he made were that a reduction of serotonin as compared with the concentration of epinephrine in the brain results in an increase in oxidation of epinephrine to adrenochrome (which is hallucinogenic) whereas a reversal of this ratio inhibits or prevents it; and that NAD deficiency allows epinephrine to be easily oxidized to adrenochrome whereas adequate levels inhibit adrenochrome formation.

I have found it appealing to consider, as we do in Orthomolecular psychiatry, the way diet, vitamins, and minerals, used in perhaps more dramatic ways and dosages than ordinary, may favorably alter various levels of different 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. Heyman (1964) reported that schizophrenic patients oxidized more niacinamide to N-methyl-2-pyridone-5-carboxamide than normal controls and that tranquilizers decreased this oxidation whereas hallucinogens increased it. Adequate levels of vitamin B6 are necessary (as already indicated earlier) for the synthesis of serotonin and for the conversion of dopa to dopamine, and ascorbic acid
(vitamin C) is essential along with oxygen in the conversion of dopamine to norepinephrine by dopamine-beta-hydroxy-lase. This, then, provides the rationale for megadoses of vitamins B3, B6, and C therapy in disorders with altered perception as well as the affective disorders discussed previously.

Since lithium is normally present in trace concentrations in the human body, one might consider the use of massive doses of lithium or mega-lithium therapy as comparable to megavitamin therapy and simply another aspect of Orthomolecular psychiatry. This mineral undoubtedly has profound affects on neurotransmitters although the mechanism of action is not clearly known. The suggestion has been made that lithium may decrease norepinephrine at critical receptor sites in the central nervous system, thus reducing the mood-elevating or disinhibiting effect of norepinephrine. It has been alleged also that lithium produces a shift of norepinephrine 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 norepinephrine content of the brain, it inhibits tyrosine hydroxylase (an essential enzyme which aids in manufacturing precursors of norepinephrine). Lithium does not influence the content of dopamine or serotonin in the brain although serotonin 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 levels of sodium 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 or performance of the neurotransmitters is certainly not known yet, but it is an appealing idea. For example, if lithium increased the turnover of norepinephrine to epinephrine, thereby altering the ratio of the concentration of epinephrine to the concentration of serotonin 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 schizophrenic-like symptoms.

All of these speculations and embryonic theories lead us, finally, to face the problem of how to cope with this most enigmatic and frightening illness. In the schizophrenias, we have the most horrible of human afflictions, a distortion of the mind which often affects the patient's own ability to cooperate with needed treatment. At least depression and anxiety encourage patient cooperation. Schizophrenia, on the other hand, often makes of society, family, and doctor, enemies for the patient. When treatment finally can be instituted, dramatic results are often needed rapidly just to be able to work with the patient. Drugs and ECT are therefore sometimes unavoidable, but the ultimate goal is still to bring about healthy mental functioning without the need for chemicals not normally present in the brain. If every psychiatrist finding a justification for using an antipsychotic drug on a patient would also add megadoses of niacin or niacinamide, approximately equal amounts of ascorbic acid, high doses of pyridoxine and all the other B vitamins, he would rapidly discover what Orthomolecular psychiatrists have known for a long time: that lower doses of drugs are possible to get the same beneficial effects desired, that as a result side effects of the drugs are less, and that sometimes patient response is faster, cooperation greater, feeling of well-being more probable, and even avoidance of drugs or discontinuation of drugs already started more likely.

In "Seminars in Medicine of the Beth Israel Hospital, Boston" in the June 16, 1977, issue of The New England Journal of Medicine, in an article entitled "Vitamin Homeostasis in the Central Nervous System," Reynold Spec-tor states, and I quote:
"Several groups of investigators have suggested that pharmacologic doses of certain water-soluble vitamins, including vitamins B6, B12, C and niacin, may be useful in the treatment of schizophrenia. Oral doses of 10 to a thousand times the minimum daily requirements have been advocated. Moreover, blood levels of vitamin C have been correlated with mental 'alertness' or 'sharpness.' Dr. Linus Pauling has developed a hypothesis to rationalize the use of pharmacologic doses of vitamins in patients with mental illness and in certain normal subjects. According to this hypothesis, the brain is sensitive to its molecular environment, and, in some subjects, 'megavitamin' therapy may improve the molecular composition and thus function of the brain. If Dr. Pauling's Orthomolecular theory is correct, it has broad implications not only for patients but also for normal persons. If, for example, it could be demonstrated that large, oral doses of vitamin C improved the alertness of the mind, millions of people would be tempted to take it." Spector goes on to state, "A task force of the American Psychiatric Association has reviewed the results of megavitamin therapy in patients with schizophrenia and concluded that this treatment was not helpful. However, the use of megavitamin therapy persists."

The article then goes on to clarify the brain barrier systems, and makes the point that since no folate or ascorbic acid is synthesized in brain or cerebrospinal fluid, studies performed indicate that vitamin transport systems exist in the central nervous system and maintain rather well-defined concentration gradients. The mechanism and location of vitamin transport systems are discussed, and the importance of the choroid plexus in this regard; also the fact that there is no evidence of carrier-mediated transport of ascorbic acid across the cerebral capillaries. Once it has entered the cerebrospinal fluid and the extracellular space of the brain, ascorbic acid is concentrated by brain cells by an active-transport system. The brain cells themselves are capable of transporting ascorbic acid intracellularly from the extracellular space of the brain (and the cerebrospinal fluid) in vivo. There is also evidence that, even at very low plasma levels of ascorbic acid, the brain levels are well maintained by the active-transport systems, which pump relatively more of the vitamin into the cerebrospinal fluid and brain to replace what is lost by diffusion. On the basis of this, Spector concludes that unless a small change in the brain's concentration of ascorbic acid (and by implication other tested water-soluble vitamins) makes a large functional difference, it is difficult to see how megavitamin therapy could alter brain function in a patient who was not markedly deficient. Spector does concede, however, that it is possible that megavitamin therapy could alter brain function indirectly, by changing the concentration of some other substance that secondarily enters the brain from blood. He also concedes that, if there are patients who respond to megavitamin therapy, it is more likely that such patients have deficient or altered vitamin-transport systems with high half-saturation concentrations or low maximal-transport velocities or both, as may be the case in some retarded children unable to transport folates from blood into cerebrospinal fluid. Nothing in these particular studies indicates that the ratios between CSF and plasma vitamin levels in humans were done on schizophrenic patients.

**Task Force Report**

But, for the moment, I should like to return to the Task Force report which, as previously mentioned, concluded that megavitamin therapy was not helpful in schizophrenics, but that the use of this therapy persists, it persists for the simple reason that it works, and our experience has shown that, in many patients who have responded and become confident that the inconvenience of taking such large doses of vitamins is no longer necessary, a discontinuation often results in an unhappy and totally unexpected relapse. Then return to therapy will just as effectively bring on a remission. Patients, families, and concerned physicians need little more than this to acquire conviction.

For those who need the support of scientific literature, the evidence against
megavitamins is totally without foundation. The negative report by the Task Force of the American Psychiatric Association was largely, if not entirely, based on the NIMH two-year double-blind study at the New Jersey State Hospital at Marlboro directed by J. R. Wittenborn and described in the Archives of General Psychiatry Vol. 28, 1973. This study included randomly both so-called acute and chronic schizophrenics. Based on reconsideration of Orthomolecular psychiatry's claim, which has long been emphasized by Hoffer, that the significant beneficial response to megavitamins (specifically in this case mega-niacin) is seen in the acute schizophrenics, or reactive schizophrenics with good premorbid personalities, rather than chronic or process schizophrenics, Wittenborn undertook a post-hoc study of his data, and presented his results in an article entitled "A Search for Responders to Niacin Supplementation," reported in the Archives of General Psychiatry, Vol. 31, 547-552, October, 1974. His conclusions are that the good responders in the niacin group showed a premorbid history with relatively strong interpersonally oriented commitments; the good responders in the controls did not. He felt that perhaps patients with dissociative psychosis and a history of interpersonal participation may respond well with high-dosage niacin as supplementary to the other medication and treatment. He then states as follows:

"When patients with a good predictor score (meaning positive premorbid adjustment) are considered, there were twice as many with a good outpatient adjustment score in the niacin supplementation group as in the control group. In this sample, it was advantageous for patients who had a high positive predictor score (i.e., who had a good premorbid adjustment) to receive niacin supplementation."

This post-hoc study was supported in part by a public health service grant. To sum up, the latest scientific review of an extensive double-blind study by the original architect of the study, when refined to meet criteria for niacin always advocated by orthomolecularly oriented psychiatrists, showed twice as many patients benefiting from niacin than the control group. This more recent finding has not been answered by the Task Force, and in view of the safety of the treatment, the devastation created by the illness when inadequately treated, and even the severity of the side effects from other available chemotherapy, widespread use of niacin supplementation in this category of patient would appear to be inevitable.

Headaches have never been proven to be due to a deficiency of aspirin in the body, depression to a deficiency of a tricyclic antidepressant, and schizophrenia due to a deficiency of chlorpromazine. Although the Orthomolecular psychiatrist tries to provide the optimum environment for the mind and brain in as natural a manner as possible, replacing what is needed, and removing what is harmful, he is not adverse, as some critics have implied, to using any technique which can bring about favorable results, fulfilling Claude Bernard's requirements for human experiments: "Those that can only harm are forbidden. Those that involve no foreseeable harm to the patient are innocent and therefore permissible. Those that may do good are obligatory."

REFERENCES


