July 2002 Issue | Abram Hoffer, MD, PhD

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Welcome to Functional Medicine Update for July 2002. This month I will follow up on a theme from our Ninth International Symposium on Functional Medicine, which we held in May at the Diplomat Hotel and Spa in Fort Lauderdale, Florida. I refer to orthomolecular psychiatry, a topic Dr. Abram Hoffer brought to our attention at the symposium. Together with Dr. Linus Pauling, Dr. Hoffer was an originator of that field.

I begin with a quote from an article titled "Orthomolecular Psychiatry," which was published in Science magazine in 1968.[1] Dr. Pauling, the principal author of that article, won two Nobel Prizes, one for chemistry and one for peace.

"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, pentylenetetraze! shock therapy). I have reached the conclusion, through arguments summarized in the following paragraphs, that another general method or 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
"Orthomolecular psychiatric therapy is the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the human body." (The term orthomolecular means the same as, or identical to that which is found in natural organisms.) "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 catalyzing 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, possibly in conjunction with the decreased concentration of tyrosine, cause the mental and physical manifestations of the disease (mental deficiency, severe eczema, and others). A decrease in the amount of phenylalanine ingested results in an approximation to the normal or optimum concentrations and to the alleviation of the manifestations of the disease, both mental and physical.

"The functioning of the brain is dependent on its composition and structure; that is, on the molecular environment of the mind. 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.

Vitamin Deficiency in Mental Disease

"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: thiamin (B1), nicotinic acid or nicotinamide (B3), pyridoxine (B6), cyanocobalamin (B12), biotin (H), ascorbic acid (C), and folic acid. There is evidence that mental function and behavior are also 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 -aminobutyric acid.

"Several arguments may be advanced in support of the thesis that the optimum 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 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." Orthomolecular environment may control mental functioning.

Biological Psychiatry and the Nutrigenomic Concept

That was in 1968. Much has transpired in the 34 years since that article was written, in terms of mental health research and intervention therapies. We have seen the advent of new drugs, the SSRIs (selective serotonin reuptake inhibitor drugs) for use in the treatment of depression, and we are beginning to believe we are practicing biological psychiatry at some level. However, if we look closely, the orthomolecular model provides a different model of optimum functioning of the brain based upon biochemical coenzyme and enzyme function. This is a nutrigenomic concept, a nutraproteomic concept, a very modern concept in light of emerging 21st century technology. We have described this concept in FMU during the last two years, but it was presaged in 1968 by Dr. Pauling's insightful argument and article.

In the 1950s Dr. Abram Hoffer and Dr. Humphrey Osmond made extraordinary contributions in the emerging view later became orthomolecular psychiatry. Drs. Hoffer and Osmond wrote a paper that was published in 1959 in the Journal of Nervous and Mental Disease.[2] In this paper, which was titled "The Adrenochrome Model and Schizophrenia," they stated the following:

"So far medical research has met with little success in its attempts to discover biological mechanisms underlying schizophrenia. It is sometimes forgotten by those who glibly refer to schizophrenia as a faulty psychosocial reaction, a way of life, etc., that if their contentions were true, then it would be outside medicine and our speculations would be simply impertinent. Psychiatrists have seldom been prepared to relinquish this group of major illnesses but, baffled by its complexity, they have resorted to the dubious ruse of proclaiming under a specious holism inherited from Adolph Meyer, that all factors are or may be of equal importance. This has allowed them to avoid the danger of being wrong while ensuring that they will never be right.

"Unfortunately, as a prescription for scientific research, this is poisonous because the researcher is bound

to select those variables which he considers more important, or if not more important, at least more susceptible to study. A medical researcher must be alert to factors which are likely to be changed for the better by means available to his profession. A medical man may reasonably be expected to consider first the means of medicine and surgery."

Drs. Hoffer and Osmond go on to describe another hypothesis that emerged from their work, the adrenochrome hypothesis of schizophrenia, which they developed in the early 1950s.

"Chemicals were studied which were termed hallucinogenic, and more recently have been termed psychomimetic. Adrenochrome and adrenolutin might now be called schizogenic substances. When they are given they produce an experience which more closely resembles early schizophrenia than that induced by LSD-25 (thereafter LSD) or mescaline. We have studied experimental or model psychoses in humans which we consider resemble schizophrenia more closely than they resemble the toxic psychosis. The compounds which to our way of thinking do this were LSD, etc.

"We consider the crucial difference between the toxic and schizophrenic-like model psychosis lies in the presence of clouding and confusion in the former and their absence in the latter. Of the substances we included among the hallucinogens, three were indoles and the fourth, mescaline, may be indolized in vivo. Mescaline is similar in structure to epinephrine. We therefore examined body fluids for endolic substances derived from epinephrine. This led to a study of adrenochrome, and later adrenolutin."

Groundbreaking Research

Drs. Hoffman and Osmond go on to talk about the differentiation of schizophrenic fluids from those of non-schizophrenic individuals and the presence of these indolic substances. The early 1950s, when this article was written, was the period when bioorganic chemistry was just emerging to become a fundamental science. Therefore, this is prescient, groundbreaking research. It takes us to a new paradigm well beyond the dominant theme of the age for schizophrenia, which was psychosocial maladaptation and Freudian dysfunction.

In this paper and others they published over the years, Hoffer and Osmond presented an entirely different view of how illness may present through a series of molecular events that create a maladaptation of the environment of that physiological state and ultimately produce untoward signs and symptoms.

Vitamin B3 Therapy

In a paper following up on this research, Hoffer and Osmond looked at the result of a year's experience in intervention on schizophrenic patients, with a treatment that derived from the concept of endogenous hallucinogenesis. They described that treatment in a paper titled "Treatment of Schizophrenia with Nicotinic Acid and Nicotinamide," published in 1957 in theJournal of Clinical and Experimental Psychopathology.[3] (Nicotinic acid and nicotinamide are, basically, vitamin B3.) In that article they state the following:

> "Adrenochrome and adrenolutin, both oxidized derivatives of epinephrine, have been observed to produce in human volunteer subjects psychological changes that fall within the range of schizophrenic reactions. In animals, de Jong-type catatonia and trance-like behavior have been induced. Adrenochrome accentuates the electroencephalogram pattern of epileptic patients, disturbs the carbohydrate metabolism of rat brain tissue, prevents the decarboxylation of glutamic

> acid by brain tissue, and distorts the spider web pattern. These substances are classified as hallocinogenic or psychomimetic or, more recently, psychedelic compounds. The psychological properties of adrenochrome and adrenolutin suggest the hypothesis that in persons with schizophrenia there may be abnormal diversion of epinephrine into these oxidized derivatives."

Diagnosing the Many Forms of Schizophrenia

The concept of orthomolecular psychiatry gave rise to a rich history. The follow-up would suggest that by administering nutrients that serve as coenzymes for specific biochemical processes in the brain, one might optimize the molecular environment for individuals in need.

Part of the difficulty in studying these associations is that schizophrenia is, to some extent, a generic diagnosis. There are types of schizophrenia and there are schizophreniform-like presentations. It is not just one disease. It is a set of differing potential dysfunctions that may present with similar clusters of symptoms. To give it a one-disease label suggesting a single etiology would, in light of what we have learned about it over the last 30 or 40 years, be wholly inappropriate. One might ask, therefore, among the myriad of individuals who present with symptoms of schizophrenia, what percentage might have the subtype that will respond to cofactor therapy, i.e., orthomolecular nutrient addition?

Orthomolecular Management, a Viable Option

The answer to that question is still being investigated. It depends on a number of variables. Some percentage of those individuals who are relegated to chemical incarceration with schizophrenic management drugs certainly might experience complete remediation of symptoms with proper adjustment of the molecular environment of their minds. That seems certain. Although we don't know how many may be helped in this way, it is not likely to be an insignificant percentage. Therefore, for those individuals whose only options are institutionalization or dependence on chemicals with significant adverse side effects, orthomolecular management seems to represent an opportunity for remediation of the problem, not just treating its effects.

For empirical results and follow-up, we can again look at a number of papers Drs. Hoffer and Osmond published over years of collaboration. One such paper, titled "Schizophrenia: A New Approach. II. Result of a Year's Research,"[4] describes a remarkable investigation. It reminds me of the Goldbergers' work on pellagra. The Goldbergers were committed to their hypothesis that insufficiency of some nutritional substance (which they later found to be niacin) was associated with pellagra's dementia, but no one would accept that hypothesis.

The Goldbergers injected and ingested saliva, skin scrapings and blood from victims of pellagra. (Illinois State Penitentiary inmates were purposely put on a deficient diet to produce pellagra's dementia.) They took their blood, sputum, and urine and ingested them themselves to show pellagra was not a communicable disease, which was the principal belief at the time. That is real commitment to a hypothesis.

Testing Hypothesis with Adrenochrome Injection

By using a similar strategy, in the Hoffer, Osmond, and Smythies paper I am describing, Dr. Osmond used a comparable approach to test the hypothesis. Drs. Hoffer and Smythies evaluated Dr. Osmond after he was injected with 10 mg of adrenochrome, an oxidation product of adrenalin. In a summary of the

experience, Dr. Osmond reported the following:

"After the purple red liquid was injected into my right forearm, I had a good deal of pain. I did not expect that we would get any results from a preliminary trial so was not, as far as I can judge, in a state of heightened expectancy. The fact that my blood pressure did not rise suggests that I was not unduly tense. After about 10 minutes, while I was lying on a couch looking up at the ceiling, I found that it had changed colour. It seemed that the lighting had become brighter. I asked Abe and Neil if they had noticed anything, but they had not. I looked across the room and it seemed to have changed in some not easily definable way. I wondered if I could have suggested these things to myself. I closed my eyes and a brightly coloured pattern of dots appeared. The colours were not as brilliant as those which I have seen under mescal, but were of the same type.

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"The patterns of dots gradually resolved themselves into fish-like shapes. I felt that I was at the bottom of the sea or in an aquarium among a shoal of brilliant fishes. At one moment I concluded that I was a sea anemone in this pool. Abe and Neil kept pestering me to tell them what was happening, which annoyed me. They brought me a Van Gogh self-portrait to look at. I had never seen a picture so plastic and alive. Van Gogh gazed at me from the paper, crop headed, with hurt, mad eyes, and seemed to be three-dimensional. I felt that I could stroke the cloth of his coat and that he might turn around in his frame. Neil showed me the Rorschach cards. Their texture, their bas relief appearance, and the strange, amusing shapes which I had never before seen in the cards were extraordinary.

"My experiences in the laboratory were, on the whole, pleasant, but when I left I found the corridors outside sinister and unfriendly. I wondered what the cracks in the floor meant and why there were so many of them. Once we got out of the doors, the hospital buildings, which I know well, seemed sharp and unfamiliar. As we drove through the streets the houses appeared to have some special meaning, but I couldn't tell what it was. In one window I saw a lamp burning, and I was astonished by its grace and brilliance. I drew my friends' attention to it and they were unimpressed."

Adrenochrome and Liver or Gut Function

This report, which appears in the article, describes the effect of administering fairly small doses of adrenochrome on an individual of "normal mental health." According to other reports, an individual's response to adrenochrome may be prolonged as a consequence of his or her liver function. Dr. Roland Fischer reported that the prolonged effect of adrenochrome in some patients was due to a prior attack of infectious hepatitis.[5] This variability demonstrates that different people may have remarkably different responses to the same dose of the chemical based upon their sensitivity and detoxification capability.

These researchers also discuss the production of gut pyroles or indoles from gut detoxifying or toxifying bacteria. These bacteria convert tryptophan in the diet obtained from dietary protein into indoles and pyroles, including indoxyl and indoxyl sulfate, or indican. These compounds may contribute to the load of substances with potential effects on brain biochemistry.

Schizophrenia's Many Facets and the "Mystery Hypothesis"

Numerous factors, in any combination, can influence schizophrenia. These factors include genetic uniqueness, physiology, gut function, detoxification capability, and nutritional status. The fact that schizophrenia does not have a single, clear etiology makes it difficult to study. It may be one reason why

the orthomolecular hypothesis has remained a "mystery hypothesis" that has never been unequivocally confirmed and still remains an outlier in schizophrenia management.

Dr. John Smythies published a couple of papers following up on this concept. One, a brief review which appeared in the Journal of the Royal Society of Medicine six years ago, is titled "Endogenous Neurotoxins Relevant to Schizophrenia."[6]

The Search for a Psychotomimetic Agent
In that article he stated the following:

"The search for an endogenous psychotomimetic agent that might play a role in schizophrenia has failed for 40 years to show one. Previous candidates have included O-methylated derivatives of catecholamines, and N- and O-methylated derivatives of indolealkylamines, which for various reasons failed the test. In 1954, Hoffer, Osmond and Smythies reported that adrenochrome, the in vitro oxidation product of adrenaline, was psychotomimetic in humans. This was confirmed by three groups and denied by one. The latter, however, used adrenochrome semicarbazone, a quite different compound, so its finding is not relevant.

"However, there is now clear evidence that close relatives of adrenochrome (namely noradrenochrome and dopaminochrome) occur in the brain. First, neuromelanin is a complex polymer made up mainly of benzothiazine units derived from 5-S-cysteinyldopamine and an indole derived from an aminochrome. (dopaminochrome in the substantia nigra and noradrenochrome in the locus coeruleus). Secondly, the enzyme prostaglandin H synthetase, during the initial stage of prostaglandin synthesis in the brain, co-oxidizes dopamine to dopaminochrome or its dihyhroxy leuk isomer. These quinones are highly toxic to neurons and bind covalently to DNA and to several enzymes and microtubular protein.

The Role of Neuromelanin
"Neuromelanin has for long been regarded as an uninteresting inert cellular pigment with no clear function. However, recent interest has focused on its power to chelate heavy metals, in particular iron, and the hypothesis has been advanced that it normally plays a role in protecting the cell from heavy metal toxicity. The fact that it is made up in part of potentially toxic oxidation products of catecholamines now suggests that it may play an additional role in protecting the cell from these compounds.

"Some failure in this function may lead to the cellular damage now reported in the brains of schizophrenics, e.g. loss of spines on cortical paramidal cell dendrites and, in particular, damage to catecholamine pathways."

Toxic Oxidation Products of Dopamine
The suggestion is increasingly made that the toxic oxidation products of dopamine produced in the pigmented neurons may play a role in a variety of disorders, including potentially the genesis of Parkinson's disease. These neurotoxic quinones formed by the auto-oxidation of catecholamines can go on to catalyze and be involved in a variety of adverse effects, both at the neurochemical level and at the neuropathological level.

There is also a link between this pathway and hyperhomocysteinemia. We have talked about the interconversion and relationship between homocysteine metabolism, degenerative neurological disorders,

and the endogenous indole hypothesis.

Directions for Future Schizophrenia Research
Exciting things are happening. Smythies closes his article by saying:

"Clearly further research is needed. Do noradrenochrmome and dopaminochrome (and related compounds) share the neurotoxic and psychotomimetic effects of adrenochrome? Are there any demonstrable abnormalities in neuromelanin synthesis, or in the protaglandin H synthetase system, in schizophrenia? Does neuromelanin occur in adrenergic neurons in the brain, and if not, why not?" (That could be aggravated by stress, which could play a role in increasing schizophrenic reactions. That could explain the modification of schizophrenia by lowering stress, which reduces schizophrenic crises.)

"What is the role of 5-cysteinyl dopamine in the neuron? Are these cytotoxic aminochromes related to apoptosis? Vanillylmandelic acid, the O-methylated metabolite of dopamine, is a close chemical relative of potent antioxidants such as ferulic acid: Perhaps it has an important antioxidant role itself?"

Cross-Disciplinary Research
Many lines of thought are beginning to converge. These lines of thought began in the early 1950s when Hoffer and Osmond developed their extraordinary model of schizophrenia based on endogenous psychomimetic, schizophreniform, or schizophrenigenic effects. In following this line of reasoning through papers in associated fields, one discovers that other investigators are following parallel lines of thinking in their areas. This research is crossing the boundaries of medical disciplines into the areas of substance abuse and detoxification in hepatology. In hepatic encephalopathy, which is really gastrointestinal hepatic encephalopathy, you can see a convergence of that line of thinking with regard to middle-molecular-weight molecules produced in the gut that are not properly detoxified or scrubbed by the liver, which produce altered brain biochemical function.

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We are witnessing the emergence of this concept at a level of specificity we have never seen before. This spring, when I read a paper in the American Journal of Clinical Nutrition, I told my colleagues it was the most significant article on biochemical nutrition I had seen in 30 years of reading the literature. The principal author, appropriately, is a very responsible investigator, Dr. Bruce Ames, a professor of biochemistry at the University of California, Berkeley. Dr. Ames has twice been a presenter at our annual international symposium on functional medicine. His name is affixed to the Ames Test, a test for mutagenicity of chemical compounds that uses special strains of Salmonella typhimurium.

When Dr. Ames was a FMU COM, he spoke to us about nutrition and aging. The important article he recently published is titled "High-Dose Vitamin Therapy Stimulates Variant Enzymes with Decreased Coenzyme Binding Affinity (Increased Km): Relevance to Genetic Disease and Polymorphisms."[8]

Dr. Bruce Ames
I could devote an entire issue of FMU to discussion of this article. It is a tour de force, a seminal work that compiles and condenses 50 years of nutritional biochemistry into a cogent model built around the genomic and proteomic theme of today. This article will set the stage for the next generation, underpinning the observations that Hoffer, Osmond, Pauling, and Williams made years ago.

In this paper, Dr. Ames states:

"As many as one-third of mutations in a gene result in the corresponding enzyme having an increased Michaelis constant, or Km (decreased binding affinity) for a coenzyme, resulting in a lower rate of reaction."

Most coenzymes are derived from, or at least related to, specific micronutrients that are essential vitamins and/or minerals.

Human Genetic Diseases and Remediation of Defective Enzymes
"About 50 human genetic diseases due to defective enzymes can be remedied or ameliorated by the administration of high doses of the vitamin component of the corresponding coenzyme, which at least partially restores enzymatic activity." (This occurs through Le Chatelier's principle. By overcoming through mass action the sluggish enzyme steps and pushing on a sloppy equilibrium, stress is applied to an equilibrium to move it in the direction to minimize the stress, moving reactant to product more effectively in these genetic mutations or polymorphisms.)

"Several single-nucleotide polymorphisms, (we have been calling them SNPs, of which nearly 2,000,000 have now been identified through the human genome studies) in which the variant amino acid reduces coenzyme binding and thus enzymatic activity, are likely to be remediable by raising cellular concentrations of the cofactor through high-dose vitamin therapy."

This is where the biochemical individuality and diversity occurs that Roger Williams talked about 50 years ago.

Validation for Hoffer, Osmond, Pauling
Does this sound like what Hoffer and Osmond were talking about in 1950? What Dr. Pauling was referring to in his landmark 1968 article is now, some 50 years later, finally beginning to see the light of day through the Human Genome Project and the proteomics that are being done.

SNPs and Nutrient Management
This is a B12/folic acid interrelationship. Folic acid in particular, and 5-methyltetrahydrofolate, can overcome or work around that block. The specific form of folic acid as 5-methyltetrahydrofolate is on the other side of that genetic polymorphism and therefore is an orthomolecular treatment for individuals with a genetic polymorphism of the 677C—>T methylenetetrahydrofolate reductase enzyme.

As we pointed out in previous discussions, approximately 20 percent of the population are people who have that polymorphism. The percentage could even be higher. Some studies have that indicated up to one third of the population has either the heterozygous or homozygous form. Ten to 15 percent of the population has the more dramatic homozygous form, in which both the mother and father gave the

offspring this alternate way, or let's call it a slower way, of metabolizing folic acid to 5-methylenetetrahydrofolate. According to Dr. Ames, other disorders, related to cardiovascular disease, migraines, mental illnesses, cancer, arthritis, and diabetes, involve SNPs. And these SNPs are nutrient-modifiable as a basis of increasing the cellular levels of cofactors that ultimately become the activating agents for specific enzymes that are genetically modified through and have different function.

Genetic Polymorphisms and Chronic Diseases
Pauling called it molecular medicine in his 1949 article in Science magazine on sickle cell anemia. He discovered for the first time how a single amino acid substitution in the heavy βglobin chain could create diverse symptoms and signs that we associate with sickle cell crisis-a single genetic polymorphism. Some genetic polymorphisms are very serious. Others occur at less serious places along the polypeptide chain or the genomic message, so their symptoms are milder. They may just accumulate injury over time, increasing the risk of degenerative disease, heart disease, dementia, arthritis, diabetes and cancer.

The Ames paper discusses at length such topics as alcohol and drug sensitivity, Alzheimer's disease, cancer, and relationships to the immune system that might translate into autoimmune disorders. All of these disorders may be treated by assessing the genotype of the individual and recognizing how their expression patterns can be modified by specific nutritional environments. An extraordinary new field is emerging. Let's turn to Side II for the interview with Dr. Hoffer

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INTERVIEW TRANSCRIPT

Abram Hoffer, MD, PhD

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JB: Among all the individuals I've had the privilege of knowing professionally in the last 25 to 30 years, this month's Clinician of the Month is at the head of my list of those I admire. Along with Linus Pauling and Roger Williams, Dr. Abram Hoffer has been a founding personality in the field we are all now involved in.

Dr. Hoffer was born in 1917 in Saskatchewan. He received his PhD in chemistry at the University of Minnesota in 1944, his MD from the University of Toronto in 1949. In about 1950 Dr. Hoffer's name first began to appear in the literature, together with that of Humphrey Osmond. Those publications represented their first significant contribution to the area of brain biochemistry, brain function, physiological and neurological function, and, ultimately, psychiatric diseases. They moved away from the Freudian view to a more physiological view of psychiatric disorders.

In 1950, most psychiatrists had little or no chemistry background. This research represented an entirely new language for them, and it met tremendous resistance. Time, vigilance, a good idea, and truth ultimately win out, however, and perhaps also longevity. Dr. Hoffer outlasted a lot of his critics from years ago. They have gone by the wayside, and Dr. Hoffer, who is now 85, has continued to be a beacon for us all. Dr. Hoffer, welcome to FMU.

Origins of Dr. Hoffer's Brain Biochemistry Research
How did you make the extraordinary discovery that endogenous hallucinogenesis and brain biochemistry had something to do with schizophrenia?

AH: Thank you very much for inviting me, Jeff. The research we developed in Saskatchewan rolled out of a desperate need to develop a treatment for schizophrenic patients. In 1950, when I started out, if you were admitted to a mental hospital, that was a lifetime sentence; you never got out. There were no treatments. The modern drugs had not yet been developed. Insulin coma was going into disfavor. Electric shock treatments were still being used, but the results were only temporary.

My mission was to see if I could develop a research team to look into the problem of schizophrenia. It's easy enough to say, but it's a very difficult problem. There isn't any disease more complex than schizophrenia. I was very lucky at that time because a couple of young psychiatrists in Great Britain, Dr. John Smithies and Dr. Humphrey Osmond, had been doing some work with mescaline. They had been taking it themselves and also studying the impact of this particular hallucinogen on normal volunteers.

Mescaline Research
Although the association was not original with them, they highlighted the fact that there was a similarity between the mescaline experience and the schizophrenic experience. They made another very important observation that had also been made previously. This was the chemical similarity between mescaline and adrenaline. They're not identical, but there's a similarity. You remember the old rule that compounds that have similar structures tend to have similar properties. These were their two observations.

They put these two observations together, and this was unique. The uniqueness of their observations was that they now claimed it is possible that in the schizophrenic body, there is a compound derived from adrenaline that has the properties of mescaline. That was a very imposing idea. This is the idea Dr. Osmond brought to Saskatchewan in the fall of 1951 when he came to join us as superintendent of one of our two major mental hospitals.

Research on Hallucinogens
At that time, I was director of research, and I had my training in biochemistry. I'd gotten my PhD in the field of vitamins. I knew whatever we had to know at that time about vitamins. This hypothesis made a lot of sense to me. I began to look at it. I began to collect all the known hallucinogens. There were only five in those years. The literature was very scarce. I distinctly recall sitting at my kitchen table and drawing the structures of these compounds. Suddenly I said to myself, Oh, my God, there it is! They were almost all indoles.

That's very important because there are thousands of compounds in the body. If you tell a scientist to find one that might be connected to schizophrenia, it's a hopeless task. But if you're looking at indoles, you can narrow the field to perhaps five or six. We then developed the adrenochrome hypothesis of schizophrenia, which stated very simply that there was an abnormal diversion or conversion of adrenaline by oxidation to adrenochrome, and that adrenochrome was a hallucinogen. So we maintained, in fact, that schizophrenia was due to a kind of endogenous intoxication from the compound formed in the individual's own body. That became known as the adrenochrome hypothesis.

Testing the Adrenochrome Hypothesis

We knew it would take a long time to establish whether this was true or not. The odds were perhaps 1000 to 1 against us, and we couldn't wait that long. We still needed a treatment. From my position as a chemist, I realized that if this hypothesis were true, we might be able to reverse the reaction by putting in compounds that would prevent the body from making that conversion. I immediately thought about vitamins, which had been my specialty. Of all the vitamins, we hit upon two. The first was vitamin B3 or niacinamide. We selected it because of its known connection to pellagra. We also knew it was a methyl acceptor. We felt that by putting in large amounts of this vitamin, we could decrease the production of adrenaline from noradrenaline. I don't know if that's true. That was merely our idea at that time.

The second idea was to use large amounts of vitamin C, which is an antioxidant, to see if we could slow down the oxidation of adrenaline to adrenochrome. That led to our first use of large quantities of vitamin B3 and vitamin C as a treatment for schizophrenia. It's a long story, but we then began to run the first double-blind, controlled experiments in the history of psychiatry. Between 1952 and 1960, we ran six double-blind experiments, using placebo controls. In every case, we showed that adding this vitamin to the treatment of the day, which was ECT and later a tranquilizer, we could double and triple the two-year recovery rates. That was really the beginning of the whole movement.

Biological Psychiatry in Today's Practice

JB: Biological psychiatry, as it's practiced today, seems to differ considerably from the biological psychiatry you are describing. Today's practice often involves mood-manipulating medications such as SSRIs to block certain physiological functions rather than to promote normal biological or biochemical function in the brain. Have you been surprised by the way this model has been woven into the practice of psychiatry?

AH: Yes, I have been. I have been not only surprised but also very disappointed. It seemed to us that our hypothesis was easy to examine. I should go back a bit. We weren't only biochemists; we were also psychiatrists. We were aware, and many psychiatrists have known this, that in order to help schizophrenic patients get well, you need four things. You need shelter, not the streets, but shelter. You need good food, which is seldom found in hospitals. You need respect, dignity, and treatment with humanity. These three alone will allow schizophrenic patients to have a very high natural recovery rate.

We thought that by adding vitamins to this approach we would improve the recovery rate immeasurably. But when tranquilizer drugs came along, they were so impressive, so powerful, and you could see the results so quickly, that they swept the field. I can remember the major enthusiasm that swept across psychiatry between 1955 and 1965, when it was believed that we now had the answer. We had the cure. An amazing race developed among mental hospital superintendents to discharge as many patients as possible into the community, because they were sure that by placing them on these drugs, they would get the cure they wanted. As a matter of fact, although these drugs are very helpful if used carefully, they do not cure. They merely help control the symptoms. With the medications, along with modern tranquilizers and also the old ones, very few schizophrenic patients ever recover.

The Tragic "Cure Rate" of Modern Psychiatry

King County in the State of Washington passed a law two years ago that will promote orthomolecular treatment in their mental hospital system. At a recent hearing in Seattle, one of the senior psychiatrists was asked about the results of treatment with their schizophrenic patients. He told them he had treated more than 10,000 schizophrenic patients. When they asked him how many got well, he reported honestly

that none had. That's with the use of the most modern medication there is.

I think this is a tragedy. Modern psychiatrists will use drugs, but they still hold the basic belief that psychotherapy, by itself, is even more important. They merely use these drugs as a way of controlling the basic symptomatology. I hope this is going to correct itself. I sense that at the international level, there is a major drift now toward orthomolecular treatment, which will be a combination of the use of vitamins and nutrients, and also the use of medication. The use of medication will be much more focused and much more careful.

A Testimonial for the Benefits of Orthomolecular Medicine

JB: I have studied this field and been the beneficiary of much of your wisdom and your contributions. I believe you are describing the drift accurately. I once met a psychiatrist who told me how big an impact your work had on his life. He had been schizophrenic and was institutionalized. His wife asked the attendants if they could give him higher doses of B6, B3, and ascorbate. They said absolutely not; they didn't allow that on the ward. She began sneaking it in, and he had a complete recovery.

He said in the last 26 years since he's been on this program, he's had no problem. He's been in clinical practice and he owes his life to your work. Your 600 papers and 19 books speak volumes. We need to get people to read about your work and have experience with it.

AH: I think so, too. And, Jeff, I want to give you a lot of credit for spreading the word. With the massive educational effort you have put on, this has made it so much easier to get these matters before the profession.

Continuing Research

JB: It's easy to be enthusiastic about discoveries of the type you have made. I think we make a good team. You are still in practice, which in itself is remarkable. Most people would say you deserve to have more spare time to do whatever you want. Obviously, you're still very passionate about your work. What kinds of things are you doing now in your clinical work?

AH: I'm continuing to explore the limitations of the orthomolecular movement. As you know, we don't think schizophrenia is just one disease. It's a syndrome that can be caused by a variety of factors. What we need are more scientists like yourself to help us work out the exact biochemical abnormalities, which can then be corrected. We have to use vitamins, minerals, and essential fatty acids. We have to combine these in the best possible ways. I'm continuing to explore that.

I work more than with just schizophrenics. I also see a lot of cancer patients who come to me for nutritional counseling. I've seen about 1250 in the past 25 years. I see all sorts of cases. For example, I see people with Huntington's disease. You may be surprised to know, but with the few cases of Huntington's disease I've seen, individuals got well with the combination of massive doses of vitamin E (4000 units per day) and niacin. It's what I would call a multiple, double-dependency disease. I continue to write; I continue to lecture.

As an aside, because of my age there was a movement here in the government of British Columbia, which decided that doctors over 75 ought not to be trusted. They tried to take away my billing number. That made me angry, so I organized a little group and we took it to the Supreme Court of British Columbia,

and we beat the government down.

Niacin Flush Test

JB: Back in the mid-1970s I first had the pleasure of meeting you at the Northwest Academy of Preventive Medicine meeting in Bellevue, Washington. You spoke about something that over the years has continued to be an interesting clinical model. That is the niacin flush test for evaluating potential niacin needs.

AH: Yes. I want to give credit to David Horrobin for that. It's based upon my observation. You couldn't fail to observe that when you gave schizophrenic patients niacin, they didn't flush nearly as badly as others do. I've had patients who didn't flush at all until about two years after they started therapy. This coincided with their recovery. In 1960, I published a brief statement to the effect that schizophrenic patients didn't flush nearly as much as others.

Some time after that, at a meeting in Montreal, David Horrobin asked me if schizophrenic patients flushed as much with niacin. I was surprised at the question, but I simply said no, they did not. I didn't follow that up any further, but David has done a fantastic job. He took it further, and he and his colleagues developed a skin-patch test for schizophrenia. This test has now been validated at about six universities around the world. It's a plastic strip of four pockets containing different concentrations of metal nicotinate. You put it on your arm, leave it on for five minutes, strip it off, and see how many of the spots are red. As a rule, normal people tend to turn red in every one of the four areas. Schizophrenic patients tend not to turn red. This is a very important finding, which has been validated. It's not yet available, but they hope that one day it will be available as a simple diagnostic test.

Methyl Hypothesis

JB: You talked earlier about niacin being a methyl acceptor. You've also had clinical success using niacinamide, which is a methylated derivative of niacin. Is the methyl acceptor hypothesis still valid, or do you feel there are other things going on?

AH: I don't think the methyl hypothesis is as valid as we originally thought. I think it was just a way we had of getting at it. I really don't know how it works. I have at least 10 different reasons why it could possibly work. I think the main one is based on tests we did in 1952 with the electroencephalogram. We took some of our patients and injected them with adrenochrome while they were attached to the EEG. We could see the remarkable change in the EEG.

At the height of this experience, we only let them stay in that state about 5 to 10 minutes. We then injected them with 100 mg of niacin intravenously, and within a minute, their EEG was normal. Niacin tends to protect the brain against the effect of excessive quantities of adrenochrome. I think that's one way.

Another mechanism involves the synapses and the oxidation/reduction cycle between oxidized adrenaline and adrenochrome. There are many possible reasons. Basically, none of them is that important. The most important thing is the observation that it does work. I've often heard stories similar to the one you told about the psychiatrist. One of my patients as a teenager was very psychotic. He made a complete recovery and eventually became president of a major psychiatric association. No one in the organization knew his previous history.

Nutrients and Dosages

JB: What doses do you use, and do you use these nutrients in combination generally, or as single nutrients?

AH: We used to start it as a single nutrient because we looked upon it as a drug. We were still steeped in the drug culture. We used niacin and vitamin C. Now I don't any more. We realized by 1960 that we were not dealing with just one vitamin. We were dealing with the whole field of nutrition. If you have a need for one, it's likely you will need several others as well. We use either form of niacin; they both work equally well for schizophrenics, but there are certain reasons for using one compared to the other. It could be the flushing or for cosmetic reasons.

We also add vitamin C as a major antioxidant and anti-stress factor. I like to put in a B complex preparation. I use the B complex 50 or B complex 100 because of all the other Bs, which I think are very important. For certain types of schizophrenia, and these can be characterized by laboratory tests, we use large amounts of pyridoxine, up to 1000 mg per day.

Pyridoxine

Contrary to the few reports I've read about how dangerous it is, I haven't ever seen a severe reaction to pyridoxine. Some children tend to become more active with pyridoxine, but we can easily control that by giving them magnesium.

So we use all the vitamins that are needed. This is based upon clinical experience and trying various things out. I also use minerals and essential fatty acids. David Horrobin has been working with the essential fatty acids, omega 3 type. He has a superb preparation I've been using for both depression and schizophrenia. It is enriched in EPA compared to DHA. I find it is a remarkable preparation, very helpful to the whole vitamin treatment program. We use everything they need to help patients get well. We also aim, in every case, to get them off tranquilizers as quickly as possible, because as long as they stay on heavy doses of tranquilizers, they're not going to get well.

Criticism by the American Psychiatric Association

JB: I recall a critical, and from my perspective imbalanced, review of orthomolecular psychiatry by the American Psychiatric Association. It referred to your work and that of Dr. Linus Pauling. The tone set in that document, back in the early 1970s, seems to have continued as a theme of the American Psychiatric Association ever since. Why is this the case in the face of the mounting evidence?

AH: An APA report issued, I think, in 1971, attempted to destroy us. It was full of lies, innuendo, and wrong conclusions. It wasn't based on any data. They did not make honest references to data. Dr. Osmond and I replied two years later, but our reply didn't receive the same publicity. Their report became gospel. Everyone believed that when a respectable organization like the APA issued a report, it must be like the Bible, like God speaking.

It reminds me of my cancer patients who are given chemotherapy. When you give someone chemotherapy, you almost kill the patient. You use a sub-lethal dose of a very toxic compound to kill the tumor. You hope that the tumor won't come back, but that the patient will. I think the APA hoped they were giving us chemotherapy, but I think we have survived. We're beginning to come back again. There was an amazing sense of enthusiasm between 1960 and 1970, with many, many doctors coming into it.

But in 1970, attempted to kill it outright.

The APA has to be held responsible for the hundreds of thousands of patients who could have been well today had they not taken that particular attitude. Why they did it, I don't know. I can't begin to explain it. It was led by the NIMH, as well.

Dr. Hoffer's Background
JB: I know you began life in rural Saskatchewan, and your siblings were born in a sod shack. You completed your public school education in one-room schools.

Do you think your rugged background has given you independence and the ability to survive all the travails and criticism you have faced over the years?

AH: I think it has. I also think it requires the right genes. I got those from my parents. I liked the spirit of my father. He came out in 1904 to the bald prairie when there was absolutely nothing there. When I consider what they did and what I've done, I've done nothing compared to what they did.

Being on the farm also helped. I was really a farmer until I finished my first degree at university. On a farm, you spend many, many hours alone. If you're putting in eight hours a day sitting on a tractor plowing, you have only yourself. You get used to thinking, and you get used to being independent. I think this has been extremely helpful to me.

Also, I tend to be very stubborn. If I have an idea that I think is a good one, then I am persuaded. I tend to be logical. If someone can show me the errors of my thinking, I'm delighted to receive their criticism, but I think that when I have a good idea, I tend to pursue it right to the end.

Support for the Adrenochrome Hypothesis
The adrenochrome hypothesis has been valuable in directing my work for the past 45 to 50 years. I should tell you that the adrenochrome hypothesis is now very current. There is no way to measure it in the body. It's known to be there.

There's a study in Japan, for the first time showing a genetic link between adrenochrome and schizophrenia. This is very exciting. And Dr. John Smythies, my colleague, has published six or eight very important documents reviewing the whole adrenochrome hypothesis. It is more than just adrenochrome, because many catecholamines can be oxidized in the brain-adrenochrome, dopachrome. All of these have to be examined very seriously.

Smythies Research
JB: I saw a review paper by Dr. Smythies in the Journal of the Royal College of Medicine a year or two ago. He presented the more contemporary view and gave attribution to your initial discoveries, saying that as we learn more about the chemistry, your work seems more and more prescient because it's documented truth through time.

AH: He's done a remarkable job. He's had more time; he's a retired physician from Alabama. He's now doing his work in Los Angeles. He's published a remarkable series of papers. I'm really glad you read that one, Jeff.

Humphrey Osmond Book
JB: Another interesting book for our listeners is Humphrey Osmond's book, Understanding Understanding. It reviews the whole nature of psychiatric illness and perception and its relationship to brain chemistry, which, from a more traditional psychotherapy perspective, puts brain biochemistry into an interesting concept. How do we understand what we understand?

AH: It's an amazing book. Of course, Humphrey was an amazing scientist.

Osmond and Hoffer's Combined Work
JB: Obviously, you two worked well together. The field was created by the synergy of your minds probably feeding off one another.

AH: It was interesting from the first day we met. These things do happen by some strange coincidence. Here I was, born in Saskatchewan, and I've had primitive training; I've gotten my job; I'm kind of a fluke. And here was this English psychiatrist, trained in England, who had been in the British Navy. He came to work with us because he got so fed up with the research climate in Great Britain. He spoke with the typical English accent, which I couldn't understand, and I doubt that he could understand my Western prairie accent.

He came along and the first time we met, on a hot, dusty fall day in Regina, he pulled out this manuscript that he and John Smythies had written on mescaline. He was so enthusiastic. The idea was so solid that within five minutes after we met, we were close friends. It was the most amazing phenomenon.

The Hoffer/Osmond Diagnostic Test
JB: That was a remarkable moment for all of us. Do you find the Hoffer/Osmond diagnostic test is still used?

AH: I use it a fair amount. It's being used, though not by too many people. You'd be surprised to learn that the major people using it are chiropractors in the Southwest United States. They find that patients with high perceptual scores respond so well to nutrition that they combine it with their chiropractic treatment.

An Optimistic View of the Future
JB: When you look back on conversations you've had with Linus Pauling in years gone by and assess where we are today, do you have an optimistic perspective?

AH: I've always been optimistic. I think it's built into my genes, but I've also been a student of history. I realized very soon after I started that a medical discovery takes between 40 and 50 years to be established. If you look back at all the major paradigm shifts in medicine, you're looking at 40 to 50 years. The first idea about antibiotics was about 1906. It wasn't until the war that the idea became popular, and this is true of most medical discoveries. There was a major push to slip tranquilizers into the field. It was done quite easily because the drug companies were able to pour millions of dollars into advertising. New ideas are given short shrift in medicine. If an idea is going to survive it has to be good and it has to be promoted.

Linus Pauling, of course, was one of my most important mentors. He also tended to be very optimistic and forward-looking. When he had an idea, unless you could persuade him by logic that it was wrong, he

hung onto that idea. I also learned that from him. He was one of the greatest Americans ever. I've always been sorry he was never given an honorary medical degree. He had numerous others, but he never had a single medical degree given to him.

Linus Pauling
JB: I share your thought. Having had the privilege of working under him at the Pauling Institute in the early 1980s, I realize there were not enough awards to give to Dr. Pauling and his wife for all of their humanitarian contributions.

AH: I have an amusing story to share about Dr. Pauling. My son John, a professor of medicine at McGill in Montreal, and I became close friends with Linus Pauling. One day, Dr. Pauling and John happened to be in the bathroom together, standing at the urinal. John, who was very young and a very good physician/scientist who had great respect for Dr. Pauling, said one day he would tell his grandchildren about this great moment. Linus Pauling continued to stand there a moment and then, very casually, said, "John, we are all peers."

JB: Yes, we are all leveled by the act of putting on our pants one leg at a time.

AH: When people talk to me about the importance of peer-reviewed articles in journals, I think of that story.

Praise for Dr. Hoffer
JB: On behalf of all of us who hear this interview, I want to thank you for your diligence, commitment, and perseverance throughout your long career. You have opened a number of doors for people who were in darkness. I hope we will see this concept emerge to become widely understood and practiced to help people in need.

AH: Thank you very much. With the help of yourself and your amazing organization, I think we can't lose; we're going to win

Endocrinology of Aging

Dr. Hoffer is a model for all of us. His combination of spirit, liveliness, passion for life, and an extraordinary gift of good health have enabled him to make contributions over eight decades, and hopefully beyond.

That leads me to the concept of the endocrinology of aging. An interesting paper titled "The Endocrinology of Aging" appeared in Science magazine in 1997.[9] The authors talk about the fact that most aging individuals die from atherosclerosis, cancer, or dementia. But in the oldest old, we start to see other factors come into play that reduce their ability to function properly. These are often modified due to hormonal dysfunctions-insulin, growth hormone, insulin-like growth factor-1, adrenaline, and thyroid hormone activity. Therefore, there has been a tendency to want to replace all these substances found in the plasma and the biological fluids of older people that are low, to restore them to the level they were when the individual was young in the hope of restoring youth and vitality.

Dr. Hoffer provides a different model. He has had an active life of the mind and nurtured himself well

with love, passion, and commitment. He has also followed his own nutritional guidelines. From his example we might conclude the replacement of substances is not as important as doing the right thing-matching one's genes with his or her environment.

Lifestyle Effects on Aging

According to the authors of this article on the endocrinology of aging, we should be mindful that most things we associate with andropause in men or menopause in women, such as dementia, heart disease, arthritis, and cancer, are modifiable by lifestyle intervention. This is the concept of successful or healthy aging. There is considerable variation of the effect of aging on healthy individuals, and the most powerful modifiers of the aging process are the things we do every day, how we think, how we act, what we eat, and how we move.

Genetic factors, lifestyle and societal investments, and a safe and healthy environment are the important aspects of successful aging. The modifiable aspects are the things we do every day-eating, thinking, and acting correctly, matching our environment with our genes. This is a lot less expensive and more controllable than any drug that takes over our physiology and for which there may be some risk/benefit relationship.

Compression of Morbidity

In this paper, Lamberts and his colleagues state that in recent years it has become evident that it might be necessary to accept the grim stereotype of aging as an unalterable process of decline and loss. As life expectancy increases further in the coming decades, the goal should be increased years of healthy life, improving health span, with full range of functional capacity at each stage of life. Dr. James Fries, in his landmark 1980 article in the New England Journal of Medicine, described what he called the compression of morbidity. It can often be achieved through lifestyle measures and proper nutrition, exercise, and enhancing endocrine/gene expression function, which promotes a phenotype of healthy aging.

We have a tendency to want to find a simple solution, which is the drug, hormone, or medication we should replace so we can be as vital in our ninth decade as Dr. Hoffer. If we trace his life from his youth on the Saskatchewan prairie and to today, we find lineage that combines his legacy of good health with the way he has treated his genes.

Walter Willett

Dr. Walter Willett from Harvard, our COM in the May 2002 issue of FMU, recently published a paper titled "Balancing Lifestyle and Genomics Research for Disease Prevention."[10] In that article he states:

> "Genetic and environmental factors, including diet and lifestyle, contribute to cardiovascular disease, cancers, and other major causes of mortality, but various lines of evidence indicate that environmental factors are most important. Overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health. However, integration of new genetic information into epidemiologic studies can help clarify causal relations between both lifestyle and genetic factors and risks of disease. Thus, a balanced approach should provide the best data to make informed choices about the most effective means to prevent disease."

Individualizing Therapeutic Nutrition
In certain cases, particularly the schizophrenic patients Drs. Hoffer and Osmond were studying, the environment of the mind may require considerably higher than average levels of particular nutrients. For them it is not vitamin therapy or pharmacology. Their genetic uniqueness and polymorphisms cause them to require high levels of folate, B12, B6, vitamin C, niacin, or niacinamide.

Dr. Hoffer referred to doses in the thousands of milligrams a day of niacinamide, the 1000 mg dose potential for pyridoxine, a range of zinc as high as 50 to 100 mg, and vitamin C in the thousands of milligrams. For folate and B12, one may require milligram doses of folate as 5-methyltetrahydrofolate and hundreds if not thousands of micrograms of vitamin B12 as cobalamin. Some people suggest these doses merely produce expensive urine, that they would just be washed out of the body and have no impact. If one's unique single nucleotide polymorphisms (SNPs) whose function depends on specific nutrients, however, then those levels do more than produce expensive urine. They bounce through the molecular process on their way through the body and create positive outcome on function. That is the paradigm of molecular medicine.

Nutrients That Modify Brain Function

We also owe credit to Dr. Richard Wurtman for the concept of nutrient modification of brain function. He discovered that nutrients can be precursor substances to the neurotransmitters. Tryptophan, for example, is a precursor to the serotonergic family of neurotransmitters. Phenylalanine and tyrosine are precursors to the dopaminergic family of neurons. And the B vitamin choline is a precursor to acetylcholine.

Dr. Wurtman made another major contribution to this field in an article that appeared in Scientific American in 1982.[11] In that article, titled "Nutrients That Modify Brain Function," Dr. Wurtman stated the precursors of neurotransmitter molecules can be essential nutrients, and nutritional inadequacy can modify brain signals and nerve system function. They can ultimately produce abnormal physiological function. He goes through the whole pathway of serotonin synthesis and dopamine synthesis and acetylcholine synthesis. This article caused many individuals to view the molecular environment of the mind from another perspective, that of neurotransmitters and their precursor, not just their coenzymes.

Carbohydrates and the Serotonergic Pathway
Dr. Wurtman also talked about how carbohydrates relate to the serotonergic pathway, and through their insulin activity lead to different uptake at the neuron of tryptophan and its conversion to serotonin.

This was the topic of another paper, published in Scientific American in 1989, which Dr. Wurtman wrote with his wife, Judith Wurtman. They discuss behavioral disorders recognized as disturbances of appetite and mood, which may be tied together with carbohydrate and protein ratios and serotonin.[12]

Brain Effects of Foods
Dr. Wurtman wrote another combination paper with Dr. John Growdon at MIT, titled "Treatment of Brain Disease with Dietary Precursors of Neurotransmitters." They showed again that higher levels of tryptophan, phenylalanine, or choline can be used to treat a variety of neurological disorders associated with insufficiency of these neurotransmitters.[13] "Ways That Foods Can Affect the Brain" is the title of another paper by Dr. Wurtman that appeared in Nutrition Reviews in 1986. Food can modify the

molecular environment.[14]

In this issue of FMU with Dr. Hoffer's interview, we received a vision of the future direction of medicine-away from remediation of symptoms and chemical incarceration into true management of the molecular environment. Dr. Williams, Dr. Pauling, and Dr. Hoffer predicted and pioneered this vision.

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