

December 2009 Issue | Part 1 and Part 2

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Welcome to the December 2009 issue of *Functional Medicine Update*. This is an issue to remember for all of us. Never in the history of functional medicine have we had-on the same issue-two of the founding fathers of molecular medicine and functional medicine. In this issue, you are going to be privileged to hear from two people, both unfortunately now deceased, who made extraordinary contributions to the birthing of our field: Dr. Linus Pauling, two-time Nobel Prize-winning laureate (in fact, still, even today, the only person to have won two independent Nobel Prizes in two different fields-one in chemistry and the other in peace), and secondly, Dr. Abram Hoffer, MD, PhD, father of orthomolecular psychiatry and one of the extraordinary contributors to the whole paradigm of functional nutrition and its relationship to neurological activity.

With that as an introduction, let me presage the comments that you are going hear from Dr. Pauling. This is an interview that I had the privilege of doing with him back in the early 1980s, when I was a research associate at the Linus Pauling Institute of Science and Medicine on sabbatical from my teaching position at the university. This is a historical interview and I think you'll find it quite interesting to get Dr. Pauling's take, in the early 1980s, on what the status of affairs was as it pertained to vitamin C and orthomolecular medicine then, and his forecast of what it would be in the future. We'll wait for his own comments to see how good a forecaster he was. I think you'll find it an extraordinarily prescient discussion.

The True Pioneers of Chemistry and Medicine

Before we get into Dr. Pauling's interview, I thought it might set the tone if we go back and review the history that led up to this extraordinary 1982 interview, as well as my later interview with Dr. AbramHoffer in 2008. The theme derives out of the intellectual soil that existed at the end of the 19th century.

In terms of science and medicine, the 19th century was a period of time featuring people like Rudolf Virchow, the father of modern pathology, who explored the origin of disease as a pathological-based condition, and codified, in a systematic way, tissue pathology to define diseases as entities related to these pathologies. This was tied together with the development of the concept of human genetics as Gregor Mendel's discoveries (which had lain dormant for a hundred years because of the church) were resurrected and better understood. It was also a major theme in the work of Gregory Bateson at the end of the 19th beginning of the 20th century, in the connection with inherited traits and how that interrelated with Charles Darwin (the understanding of the nature of evolution and natural selection) during this same period. All of this early work comes together in the 20th century in what we consider to be the modern

concept of the origin of disease.

This period was also the time of origin of systematic organic chemistry Emil Fischer, the extraordinary German chemist, was starting to help us understand that there wasn't some vitalism in natural molecules- that they were interrelated with molecules that could be seen in a test tube. There was also the work of Wöhler on the conversion of cyanate into urea, and ultimately the recognition that the inorganic and organic world are connected through chemistry. The concept of vitalism was put aside as the concept of a reductionistic understanding of the milieu of life started to emerge.

The origin of the age of vitamins started to emerge right at the turn of the 20th century with the discovery of the anti-beriberi factors (the Eichman work on thiamine as an agent that could prevent and treat beriberi). The "vit amine" meant the substances that were derived vital amines from food. We then tie that together with Elie Metchnikoff, who was working at the Pasteur Institute and won a Nobel Prize in medicine for his discoveries about the origin of the immune system. Later, he developed his prolongation of life concept, which relates to the colon as a site of origin of many diseases through the alteration of the immune system.

All of this was happening during the latter portion of the 19th century. It was an epic period for setting new paradigms in place. The start of the 21st century has been a similar epic period as we start to look at systems biology, molecular medicine, and start the influence of various agents in the environment on genomic expression (nutrigenomics, nutriproteomics, and nutrimetabolimics-what we call the "trilogy of 'omics"). A new way of looking at the origin of dysfunction, metabolic disturbance, and ultimately chronic disease is being established.

The Contributions of Dr. Archibald Garrod

At the turn of the 20th century, an extraordinary person by the name of Dr. Archibald Garrod was also doing research. He was a third-generation medical doctor whose father was really the person given credit for discovering the first autoimmune disease (gout). On a thread put in a gout patient's urine, his father crystallized the first crystals of uric acid thanks to the birthing of organic chemistry. From that was born the molecular connection to the first autoimmune disease.

Dr. Archibald Garrod (the son) then took these concepts and actually wrote the first textbook on autoimmune disease that was set in the English literature back in the late 1800s and early 1900s. He then took this concept even farther by looking at colored compounds in urine. This started the age of spectroscopy and the understanding of chromophores and how light-absorbing compounds that gave rise to color could be used to identify chemical constituents.

Colored urine was a very interesting part of the application of this concept of spectroscopy in the late 19th century/early 20th century. Dr. Garrod was able to start looking at some of the porphyrias and at things that were related to colored compounds in urine. He identified the first genetic metabolism diseases of infancy, alkaptonuria. His article was published originally in *The Lancet* in 1902 and titled "The Incidence of Alkaptonuria: A Study in Chemical Individuality," and it really represented the birthing of the whole field of molecular uniqueness, biochemical individuality, and later what we called molecular medicine, which was a term coined by Dr. Linus Pauling.¹

I think if you went back and read the 1902 article by Dr. Garrod, you would find that many of things it

describes are as modern today as they were at the turn of the last century. I find it absolutely fascinating that when he looks at the concept of a genetic metabolism disease through the lens of that period of time and his own connection between the chemical world and the physiological and medical world, that from that emerges a platform for understanding the origin of many diseases that were previously not understood at all. This is what Thomas Kuhn called a "paradigm shift," a major shift in thinking. I quote from a part of Dr. Garrod's landmark paper. He says, "There are good reasons for thinking that alkaptonuria is not the manifestation of a disease but is rather of the nature of an alternative course of metabolism, harmless and usually congenital and lifelong. Witness is borne to its harmlessness by those who have manifested the peculiarity without any apparent detriment to health from infancy on into adult and even into advanced life." We can see that those individuals who excrete excess levels of homogentisic acid have a unique metabolism that is controlled by aspects of their family history.

I suggest that he is talking very beautifully about the nature of biochemical individuality, and how it can express itself into the phenotype over the course of living. In terms of genetic uniquenesses, some things are seen in infancy, and other things are seen later in life. What we might consider to be a genetic defect might actually be defined as a genetic uniqueness, requiring a specific environment in order to minimize the potential adverse effects of that uniqueness, or to optimize the positive nature of that genetic uniqueness.

I want you to recall when this was written in 1902 this was fairly early on. Bateson's argument was that we needed to look at genes and genetic lineages, and look at these dominant/recessive characteristics that were originally described in peas through the work of the great monk working in his garden, Gregor Mendel. From that extraordinary soil (to use the gardening metaphor) of Dr. Garrod, came the germination of this concept of molecular uniqueness and biochemical individuality.

The Contributions of Dr. James Neel

Let's roll the hourglass forward into the middle 1900s. Now I'm in the 20th century (1949), and an extraordinary series of papers appeared in Science magazine. The first is by a gentleman by the name of James Neel, who was the chairman/director of the heredity clinic/laboratory, department of biology, at the University of Michigan. This is a paper that appeared in the July 15, 1949 issue of Science magazine, in which he wrote about the inheritance of a genetic metabolism-related disorder, sickle cell anemia.²

I want you to recall the timeline: We are 50 years downstream now from where Dr. Garrod was talking about the porphyrias, and alkaptonuria, and other genetic metabolism disorders that could be seen, clinically, as altered color of urine (with these colored compounds being excreted in the urine as a consequence of different metabolism). Some of these urine compounds, by the way, didn't develop as colored compounds until the urine was exposed to light because they undergo photochemical reactions with these metabolites to produce conjugated compounds that are colored, so this is a whole interesting chapter of evolution of the chemistry connection to medicine and to genetics.

In 1949, James Neel writes about what happens in a drop of blood from a member of a family who has sickle cell anemia. You get this bizarre clumping of the cells in this sickle, or holly leaf, shape. The ability of these erythrocytes to sickle is a phenomena that appears to be attended by no pathological consequences in the majority of these individuals until-and I want to emphasize this-they are thrust into some kind of unusual environment. This could be stress, sleep deprivation, dehydration, physical trauma, or infection. At that point of stress, this characteristic (this genetic tendency) for these blood cells to pack

in these unusual ways-these sickling configurations-can result in a pathological outcome that can have multi-organ involvement: it can affect the heart, the circulatory system, the musculature, the liver, and the kidneys. You get a multiple-organ influence from a biochemical uniqueness that is encoded in the genes of these individuals, who are triggered into this pathological state by environmental factors. Here is the genes/environment connection demonstrated through the concept of sickle cell anemia. We recognize these are inherited susceptibility factors. It doesn't mean that a person who has these genes for sickling situations will necessarily be in crisis. What it means is they have an increased susceptibility to certain environmental factors.

The Contributions of Dr. Linus Pauling and Dr. Harvey Itano

The companion paper that followed Dr. Neel's article in 1949 is, to me, one of the most dramatic "a-ha" papers that has appeared in the literature. It came from the pen of Dr. Linus Pauling, working with his post-doctoral student, Dr. Harvey Itano. This article is titled, "Sickle Cell Anemia, a Molecular Disease."³ This is the first time (as far as I know) that the term "molecular disease" was used in the English-speaking literature, following on from Archibald Garrod's work really that had been done way back when at the turn of the 20th century.

Dr. Pauling, then a professor at the California Institute of Technology (CalTech), developed an extraordinary way of looking at these sickling cells. Being a chemist, he looked at the uniqueness of these red cells and said, "What do they have in them that other cells don't have?" And of course all of us know that they have hemoglobin, and hemoglobin is an iron porphyrin molecule, and iron is a ferromagnetic element (it has effects in magnetic fields). He was able to demonstrate that there were different spin states in the iron and hemoglobin in the sickle cells versus normal red cells. By utilizing a very interesting way of evaluating the effect of the cell's biomagnetic field, he was able to start differentiating cells that would be sickled versus those not sickled, and start looking at the actual chemistry of how this whole process of altered hemoglobin was formed in the sickle cell individual. Eventually, because he was also a protein chemist and very interested in structure/function, he was able to isolate and analyze the protein structure (the beta globulin molecule of hemoglobin) and found that there was a single cell deletion (or substitution/mutation). As a consequence of this mutation of one amino acid for another, that single change in this large chain of amino acids was at a critical point of the structure of that protein, causing that globular protein (as part of the hemoglobin molecule) to then change the whole structure of hemoglobin, to make it more able to be packed into this configuration that led to sickling, and ultimately distorting the shape of the whole red cell: it looks like a sickle and it cuts its way through the vasculature, causing pathology when it starts packing together.

This concept that a single amino acid change caused by a single gene alteration could lead to a very serious series of crises and diseases that cut across multiple organs (the reason he called this a molecular disease) was a major paradigm shift in thinking about the origin of disease. Recall, if you would, the major theme about the origin of disease to that point was infectious disease. That was a major (obviously) breakthrough in understanding the origin of disease at the turn of the last century, with Louis Pasteur and others who had really helped us to understand that certain bugs can cause disease through this process of infection and the interrelationship with the immune system and so forth. From that, then, was later then born this additional concept of the origin of disease-this genetic metabolism disease-where genes and environment interrelate to give rise to the expression of an outcome in the phenotype called the disease (in this case, a sickling crisis).

The Contributions of Dr. Roger Williams

This follows on nicely-this intellectual lineage-from the soil that was first prepared by Archibald Garrod. Just to show you how there is consanguineous concepts of discovery that occur in great epic periods, in that same time period (1949) another well-known figure-someone we would consider one of the founding fathers of functional medicine-was doing his work, and this is Dr. Roger Williams. At the time, he was working as a faculty member at the Clayton Foundation for Research, in the chemistry department at the University of Texas, where he later was department chairman, in Austin, Texas. He was an esteemed biochemist who was actually credited with discovering pantothenic acid.

Dr. Williams had been the president of the American Chemical Society, the largest professional society for chemists in the United States. During the same period of time that Dr. Pauling was writing his paper on sickle cell anemia as a molecular disease with Dr. Itano on sickle cell anemia as a molecular disease (this whole concept of genetic uniquenesses giving rise to single changes in proteins that give rise to the expression, under certain environmental conditions, of disease), Dr. Williams was developing his concept of genetotrophic disease. Genetotrophic disease was an extraordinary concept for that time, and I believe, was published in 1950 for the first time in *The Lancet*.⁴ This was February 11 of 1950-a classic article. In this article, Dr. Williams wrote about this theme of disease occurring as a consequence of a genetic uniqueness and certain nutritional insufficiencies as another part of this paradigm shifting discovery. I quote, "Based essentially upon recent findings in genetics and biochemistry which have not yet been incorporated into medical thought, the concept of genetotrophic disease may, we believe, lead to an understanding of many diseases whose etiology is, at present, obscure."

What is this concept of genetotrophic disease? This is the concept that we each have genetic uniqueness for many things, one of which is the need for specific nutrients to promote proper functional physiology. And if, in fact, those needs that we each individually have, based on our genetics, are not met, then the result could be dysfunctional metabolism, which over time can lead to disease. This is very interesting if you think about it for a moment, because it almost goes back to HP Himsworth and his work. He was the person who was credited, as the head of the endocrinology department at the University of London School of Medicine (very highly esteemed director of medical research in England at the time), with discovering metabolic syndrome and insulin resistance. He was quoted as saying, "The history of modern knowledge is concerned in no small degree with man's attempt to escape from his previous concepts." He was talking about insulin resistance and hyperinsulinemia as a different form of diabetes than that of just frank insulin deficiency (what we now know to be called type 1 diabetes). He also said, "The history of modern knowledge is concerned in no small way with man's attempt to escape from his previous concepts," because he had a hard time getting his colleagues to understand there could be a second type of diabetes that was associated not with a deficiency of insulin, but an insufficiency of insulin promoting proper signaling or proper function.

Williams quotes Himsworth when he talks about the paradigm shifting concept of a genetotrophic disease in this fantastic article that appeared in *The Lancet*. In this article, he writes about etiology of diseases, like heart disease, diabetes, and arthritis, and other conditions such as alcoholism having their root origin in genetic uniqueness and nutritional insufficiency based upon the individual's own uniqueness that is not being met by their nutritional intake. Dr. Williams also writes about mental disease and various types of things like schizophrenia maybe being the result of inadequacy of specific nutrients to the genetic need of that individual. He says, "There is a prodigious amount of data to indicate combined genetic and nutritional influences in many forms of mental disease that an entire volume might be written on this

topic alone." For many years it has been seen that there are forms of dementia and other nutritional-associated symptoms of mental illness that could be tracked back to genetics not being adequately supported by proper nutrition.

Now, in the 21st century, I think we are witnessing a revisiting-a rediscovery-of these paradigms that were developed from the work of people like Archibald Garrod, and later Dr. Pauling and Dr. Williams. Dr. Williams took this concept of genetotrophic disease into an even more descriptive level in a wonderful review article he authored in Nutrition Reviews.⁵ This was in September of 1950, early on in the first publications of Nutrition Reviews. He writes about the extraordinary research that was in the literature that he believed supported the concept of genetic uniqueness and what he later called biochemical individuality.

This now takes us to 1968, and 1968 was an epic landmark period in the history of our field of functional medicine. That was the year that Dr. Linus Pauling authored what I consider to be one of the great papers-a paper that was probably not understood as well as it should have been in terms of its impact on the future trajectory of medicine. This paper appeared in Science magazine (April 19, 1968), and was titled "Orthomolecular Psychiatry: Varying the Concentrations of Substances Normally Present in the Human Body My Control Mental Disease."⁶

In this paper, Dr. Pauling really builds upon what Dr. Williams discussed "Genetotrophic Disease." Dr Pauling writes about optimizing molecular concentrations of what he called "orthomolecular substances," which are substances that are native to the human body, and how that then influences enzyme function, and how that enzyme function controls and regulates cellular activity in the phenotype of the individual. Also, how individuals with unique genetics might have enzymes that are slightly different in their structure and function from that of other individuals, and therefore their need for coenzymes to promote proper enzyme function may be slightly higher. This leads to the orthomolecular supplementation concept: It is not that individuals are getting superordinate amounts of supplements, but rather they are getting the level of nutrients necessary under their unique genes to promote proper enzyme function.

This is the application of Le Chatelier's Principle. Le Chatelier was the French chemist who lived at the height of the French Revolution, and whose concept was that you apply stress to an equilibrium, and the equilibrium moves in the direction to minimize the stress. (That's kind of a metaphor, isn't it, to the French Revolution?) The chemistry outcome of that is you add more of your substrate and you push that, then, through the equilibrium dynamics onto more product. In this case, increasing the activity and amount of a cofactor (or a coenzyme) can promote more of the apo enzyme becoming the halo enzyme (the active enzyme) that then catalyzes that specific reaction. This is the basis for things like the use of more B12 at hundreds of times the RDI for megaloblastic anemia, or for the use of oral B6 and folate for people with homocysteinemia. This is the specific applications of the conceptual framework that Dr. Pauling was speaking to: You can't change the genes, but you can change the environment that would then promote proper enzyme function.

The Contributions of Dr. Bruce Ames

This concept that is described in "Orthomolecular Psychiatry," this landmark paper, leads us into a period of nearly 40 years of debate and controversy, and up-and-down, and "What does this really mean?" This debate and controversy led us to a moment in time that I think is one of those "a-ha" moments, which I think was the publication in 2002 of a review paper by Bruce Ames, and Ilan Elson-Schwab, and Eli

Silver. It appeared in the American Journal of Clinical Nutrition in 2002, and the title of this paper was "High Dose Vitamin Therapy: Stimulating Variant Enzymes With Decreased Coenzyme Binding Affinity: Relevance to Genetic Disease and Polymorphisms."⁷

It was necessary that a paper such as this be written by a scholar such as Dr. Ames, an icon in the field, to help to support the lineage of the development of this theme--Archibald Garrod to Roger Williamsto Linus Pauling. In this review paper, which has 377 references, Dr. Ames and his co-authors did a brilliant job of really supporting this concept of genetotrophic disease, orthomolecular medicine, and molecular medicine, as it pertains to the role that nutritional supplements can have in specific cases for promoting proper function. In this paper he writes, "As many as one-third of mutations in a gene result in the corresponding enzyme having an increased Michaelis constant [this means decreased binding affinity] for [its respective] coenzyme," which is generally vitamin-derived. This results in a lower rate of reaction. "About 50 human genetic diseases due to defective enzymes can be remediated or ameliorated by the administration [he says] of high doses of vitamin component of the corresponding coenzyme, which at least partially restores enzymatic activity." He then writes about single-nucleotide polymorphisms, in which the variant amino acid "reduces coenzyme binding and thus enzymatic activity" and these can be remediable by raising cellular concentrations of the cofactor. This is the very concept that Linus Pauling discussed in 1968 in his Science article. Dr. Ames gives many examples and applications of this, clinically, that have been proven in the literature. And with 377 references, anyone that says there is no science needs to do their homework.

That leads us, now, into the 21st century, with the development of nutrigenomics and nutriproteomics and nutrimetabolomics, and how this relates to individual need for nutrients to promote individual function. It ties to the vitamin C controversy. It ties to all the things that we have seen debated, including the niacin and schizophrenia controversy, and the B6 and folate controversy (the homocysteinemia)-all the things that are still being debated today. With that, let's go to the father of this whole concept, Dr. Linus Pauling, and hear what he had to say in 1982.

INTERVIEW TRANSCRIPT

Clinicians/Researchers of the Month

Linus Pauling, PhD

1901-1994

Recipient of the Nobel Prize in Chemistry, 1954

Recipient of the Nobel Peace Prize, 1962

Interview recorded at the Linus Pauling Institute of Science and Medicine, 1982

JB: Hello. I'm Dr. Jeff Bland. I'm a Senior Research Fellow at the Linus Pauling Institute of Science and Medicine. It's a great pleasure today to be with Dr. Linus Pauling, the Chairman of the Board and the chief visionary influence on the Linus Pauling Institute's activities. I'm here today to really engage in a fireside chat with Dr. Pauling to discuss some of the areas of his interest and some of his research progress that he's making and, really, hopefully acquaint you with some of things that are not only going on here at the Institute, but in the field science and health care in general.

Without further ado, let me thank Dr. Pauling very much for being with us today and for sharing this

moment of his precious time. Nice to have you with us, Dr. Pauling.

LP: Well, thank you! I'm glad to be here.

JB: I'm going to start, if I could, just for the sake of the listeners, asking you if you might review for us some of your recent activities. I know you have been traveling all around, and you have been speaking to many groups. I'm sure we'd all like to hear some of the things that have occupied your time.

Projects at the Linus Pauling Institute, 1982

LP: Well, you know, I divide my time, it turns out, into thirds. One-third of the time I work on basic problems of science, which I have been interested in for a long time (since 1922 when I carried out my first research). So I still make quantum mechanical calculations about molecular structures and crystal structure, the nature of metals, and the structure of nuclei. Then, one-third of my time is devoted to collaborating with other people here in the Linus Pauling Institute in our attack on medical problems. Right now, we are just finishing up a big study of the effectiveness of vitamin C in controlling cancer in mice. It has turned out, I'm glad to say, that the vitamin C has great value. It slows down, greatly, the development of spontaneous breast cancer in a strain of mice that develop these cancers. I collaborate with many people in the Institute in their research, in considerable part by talking with them about what they are doing and giving them advice, perhaps, or making suggestions on the basis of my years of experience. The job of answering letters from people who write in for advice is a considerable one that takes up a good bit of my time. Then, the other third of my time, I travel. I travel to give talks, largely about vitamins and health, or about health in general, especially in relation to nutrition. Some of them about world peace, because why should I be working on improving the health of people if the world is going to be destroyed in a great nuclear war? We need to have a future, to believe that we are going to have a future, that the human race will have a future in order to justify our trying to control cancer, and heart disease, and other diseases. And of course, some of the talks that I give on these trips that I take are about science.

JB: I'd like, if I could, to sort of switch the topic and ask you...you alluded to this exciting study here at the Institute that has been ongoing for a couple of years as it relates to vitamin C's impact upon spontaneous mammary cancer in mice. That's but one of a number of exciting types of work that are going on in the Institute. I'm sure that our listeners would like to hear a little bit more about some of the other things happening at the Institute. Could you say a few words about that?

In His Own Words: Dr. Pauling's Views on Vitamin C

LP: Some of the investigators in the Institute are working on the question of, "Just what is cancer?" How does cancer originate in the human body? During recent years (the last 20 years), it has been possible to get information about genetic influences. About the role of genes, which are polynucleotide DNA (strings of DNA molecules) in causing cancer and in achieving almost everything else that goes on in the human body. Our investigators have been involved in the recent work on oncogenes. Oncogenes are genes that are involved in cancer. They are closely related to genes that are present in every human being or in every animal of the species under study. When one of these pro-oncogenes (a gene that might become an oncogene) undergoes a genetic mutation, it becomes an oncogene, a gene that changes the nature of the organism in such a way that a cancer develops. There may be some second effects that also must occur (more than one change is usually involved in the production of cancer). So this very modern technique of studying the DNA molecules that determine the nature of an individual human being, including the

cancers that he might produce, is being used by workers/investigators in our Institute.

A different attack is being made by Dr. Constance Tsao and her associates. This is to study certain chemical substances that are produced by oxidation of vitamin C. It was discovered 10 or 15 years ago by Dr. Omura-well, in fact, by his teacher, who then retired, but Dr. Omura has continued-that oxidation products of vitamin C, which are found in the human body after vitamin C is ingested, have greater anti-cancer activity in animals than vitamin C itself has.⁸ This hasn't been followed up by anyone. There are a number of these oxidation products, different substances that you get by reaction of vitamin C and oxygen. We don't know whether all of them have greater anti-cancer activity than vitamin C or only one or two of them, and we don't understand at all how they work in controlling cancer. It may turn out that much of the anti-cancer activity of vitamin C results from its oxidation in the human body to these oxidation products.

So I have hope that this will turn out to be a really significant effort that will lead to an advance in our ability to control cancer. Vitamin C, itself, of course, works in other ways than just through the oxidation products. It is required for the efficient operation of the immune system. We know that when the immune system is functioning well, the probability of dying from cancer is less than when the immune system is not functioning well. After an operation for removal of a cancer, in almost every patient, there are, in the blood stream, millions of malignant cells. And yet, only some of these patients then later develop metastatic cancer. Others do not. Why? It is believed-and I think quite rightly-that if your immune system is working well, then that system can detect the malignant cells, prepare them for destruction, and then carry out their destruction. And so in the people who have a well-working immune system, the malignant cells are destroyed and metastases do not occur.

Vitamin C is known to potentiate the immune system in various ways. An English investigator named Vallance showed that more antibodies that can identify the malignant cells are formed with a high intake of vitamin C than with a low intake.⁹ More molecules of complement are formed as a result of additional vitamin C. Molecules of complement have to attach themselves to the complex of a malignant cell, or a group of malignant cells, and antibodies, in order that these malignant cells be destroyed. With a high intake of vitamin C, you produce more of the T-lymphocytes that can destroy these marked malignant cells (the complex of the antibodies complement and the malignant cells). And it has been known for 40 years (more than 40 years-nearly 50 years) that vitamin C is required in these T-lymphocytes and phagocytes and white cells, generally, in the order that they be able to destroy infected cells and malignant cells. Vitamin C is intimately involved in the process of protecting the human body against infections and against malignancies because the only way the human body has of destroying these infected cells and malignant cells is with use of vitamin C.

So vitamin C is important to cancer in many ways. Now we are just embarking on a new project that I am especially interested in. This is vitamin C in relation to heart disease. Evidence has been turning up during recent years about the involvement of vitamin C in heart disease. There is a good correlation between incidence of heart disease and the amount of cholesterol in the body, and also the amount of low-density lipoprotein. This low-density lipoprotein is the protein that consists of molecules that can carry cholesterol molecules out to cells in the body where they are required for proper functioning of the cells. Cholesterol is a very important substance. Sometimes, however, the amount of cholesterol is too great and it gets involved in laying down plaques in the blood vessels. There is another protein (a lipoprotein) whose molecules have a function of picking up cholesterol and carrying it back to the organs where it is

destroyed in the liver, converted into bile acids that are then eliminated from the body. Well, vitamin C has been shown to speed up the rate of conversion of cholesterol to bile acids, and that means you are bleeding off the cholesterol, so that level in the body goes down. It has also been shown to cause the production of more high-density lipoprotein. That means you have more of the protein that removes cholesterol from the blood vessels and carries it to the liver to be destroyed. Also, it cuts down (slows down) the rate of production of low-density lipoprotein so that you have a smaller number of the molecules that carried the cholesterol out to the blood vessels where the plaques can be formed. It also cuts down the amount of triglycerides in the blood, and there is a correlation between triglycerides and heart attack. So with all of these correlations, we can see cutting down the total cholesterol, the low-density lipoprotein, and the triglycerides, and increasing the high-density lipoprotein and speeding up the rate of destruction of the cholesterol (converting it to bile acids), we can see that vitamin C might well be correlated in a very striking way with heart disease. A high intake of vitamin C may turn out to be the best way of protecting yourself against heart disease.

Our epidemiological associate, Dr. James Enstrom, has published a paper describing a study that he made of several hundred people who had been ingesting larger amounts of vitamin C than the population as a whole (on the average about a gram and a half of 1500 milligrams of vitamin C).¹⁰ They had only about half the probability of dying of heart disease at each age as the control population (similar sub-populations in California), who were on an ordinary diet with an ordinary intake of vitamin C. There are other differences between the two populations that he compared, but it seems likely that this high intake of vitamin C is largely responsible for their having only half as much mortality from heart disease (age standardized, age corrected mortality). Well, they had only half as much mortality from cancer, too, and from other diseases. Vitamin C is not a specific remedy—a wonder drug—against cancer, or against the common cold, or against the flu, or hepatitis, or viral pneumonia, or herpes infections, or heart disease. It is not a specific wonder drug. What it does is to build up the human body to the state of health that all human beings ought to be in. When I read what the Food and Nutrition Board says, that 60 milligrams of vitamin C a day is enough for all persons in ordinary good health, I think they should say, "All persons in ordinary poor health." If you want to be in what ought to be ordinary good health, you have to take additional vitamin C. Of course, I believe that the arguments that support this conclusion are really thoroughly convincing. They are the sort of arguments that appeal to me as a scientist. I am accustomed to looking at the facts and trying to draw some logical conclusions from them. Other people, perhaps, are not so accustomed to doing that. I would say that the evidence that high intake (many times the usually recommended amount—RDA—of vitamin C) is needed for good health. That conclusion is thoroughly justified by the evidence.

JB: I'd like to respond and say that this relationship between vitamin C and heart disease is a very interesting controversy recently in the literature that I believe falls right in line with what you are talking about—that some people interpret data differently. There was a report in the *American Journal of Clinical Nutrition* by some supposed responsible investigators saying that vitamin C did not increase high-density lipoprotein cholesterol and did not lower total cholesterol.¹¹ However, in examining the protocol of the study, it was found that the average starting cholesterol of this group was about three-quarters the value of the standard average American cholesterol level, meaning it was about 175 where the normal value is about 220 for the average person. And it had already been pointed out in 1976, through another series of investigations, that vitamin C is most effective in lowering cholesterol and raising HDL when a person has an elevated blood cholesterol level, meaning that the study population selected in this study was already almost guaranteed to show a negative result, which I found to be something that was either

naiveté on the part of the investigators, or more likely that they were trying to make a certain political statement through the misuse of science.^{12,13}

LP: Yes. It is true that if you want to find out what some investigators have observed, you have to go back and read their entire paper, not just read a statement that someone has made, even the investigators themselves have made, about what results they have obtained. People are often misled by statements that some investigator showed that this substance did not have any value, when, in fact, he had observed some value, but not so great as he had expected to observe, or when the number of subjects was so small that he was not able to show, with statistical significance, that there was a positive effect. Very often the mistake is made that when an investigator has used a certain number of subjects, which might be rather small, and has failed to show benefit from the treatment at what is considered a statistically significant level, the results are described as his having shown that there was no effect, when, in fact, he hadn't that there was no effect, he had just not succeeded in showing that there was an effect. The statistical treatment that you give if you are trying to answer these two questions is quite different.

Response to View that Vitamin C Has Toxic Effects

JB: One of the most common questions, Dr. Pauling, that the average person asks about vitamin C therapy, particularly today, in light of a lot of the published information in the wire service and in magazines and newspapers, is surrounding vitamin C's supposed toxic effects. I think that there are several notable reports that have occurred in the literature lately. I know you responded very eloquently to a paper that appeared in Seminars on Oncology lately by a Dr. Mary Sestili, who has commented that vitamin C has toxic effects, potentially, when used in cancer therapy.¹⁴ And you have also previously responded to Dr. Victor Herbert, hematologist, who says that vitamin C supplementation may destroy vitamin B12.¹⁵ We also hear that vitamin C supplementation supposedly causes kidney stones through its metabolism to oxalate. And recently there has been the report by Professor Cerklewski at Oregon State University that somehow vitamin C supplements cause an antagonism of copper metabolism in the body and leads to copper deficiency anemia.¹⁶ I think it would be very useful for our listeners to sort of put this into perspective. Could you comment on vitamin C's toxicity for us?

LP: Human beings differ from one another. There may well be a few human beings who should not take very large doses of vitamin C. But they are so rare, in my opinion, that it is justified for me to say that vitamin C is essentially completely non-toxic. Some of the arguments that have been presented are based on a misunderstanding. We know that the common sort of kidney stone has a greater tendency to form in alkaline urine than in acidic urine. But uncommon forms have a greater tendency to form in acidic urine. When my book *Vitamin C and the Common Cold* came out it was immediately attacked in a publication mainly for doctors.¹⁷ The statement was made that vitamin C, in the form of ascorbic acid, keeps the urine acidic, and so increases the tendency to form certain kinds of kidney stones (the less common kinds). That is true, but it isn't an effect of vitamin C. Vitamin C is the ascorbate ion. You can't take pure vitamin C because you can't get hold of a large aggregate of negatively charged ion; there always is a positive ion along with them. And that can be either hydrogen ion, or sodium ion, or calcium ion, or some other ion. Ordinary vitamin C tablets contain ascorbic acid, which is vitamin C with hydrogen ion. They make the urine acidic. It isn't the vitamin C, then, that increases the tendency to form these uncommon stones. It is the hydrogen ion that you are taking along with the ascorbate ion. But, to keep the urine acidic decreases the tendency to form the common stones. Not many people form stones, anyway. And fewer still know what kind they might have a tendency to form. If you happen to know that you have a tendency to form common kidney stones, then you would be wise to take ascorbic acid (vitamin C in the

form of ascorbic acid-the common way in which it is available), or to take some other acidifying agent. But the ascorbic acid is the best thing to take to cut down the chance of forming the common kidney stones. If you know that you have formed one of the uncommon kind, then the doctor may well advise you to keep the urine alkaline. You could take baking soda as an alkalinizing agent, or you can take sodium ascorbate. And when take sodium ascorbate you are not only protecting yourself to some extent against forming additional kidney stones of that uncommon kind, but you are also benefitting from the vitamin C. With the oxalate stones, there may be one person described in the medical literature as having an oxalate stone formed because of a large volume amount of vitamin C that he took. That is possibly a real effect for that person of a special genotype. The number of these cases is so small that I don't think that that is a reason not to take vitamin C.

For some of these other statements, Dr. Victor Herbert saying that vitamin C destroys vitamin B12 and you may get pernicious anemia was based on an error that he and his associate made when they analyzed their foods for vitamin B12. They just didn't use the standard procedure for making the analysis for vitamin B12. And when other investigators repeated their work, when they used Dr. Herbert's method they got the same results he had gotten, but when they used the standard method they found that practically none of the vitamin B12 had been destroyed. Only a small amount of loosely bound vitamin B12 had been destroyed. So the statement that vitamin C can cause pernicious anemia, or B12 deficient anemia, is just not in accordance with the facts; it was based on an error.

With the investigator at Oregon State University, Dr. Cerklewski, who reported that the copper level in the blood went down when the subjects were given large doses of vitamin C, the situation has been exacerbated by a writer in one of the popular newspapers who misrepresented Dr. Cerklewski's work. First he said that Dr. Cerklewski took the subjects off the vitamin C after 60 days (or whatever period) in order to protect them from dying of anemia. Dr. Cerklewski says this just isn't true. He said that in his paper he mentioned the possibility that this lower copper level would lead to an iron deficiency (anemia-failure to incorporate iron in the red blood cells and the hemoglobin for the red blood cells). But he didn't think that it would occur; he just mentioned that as a possibility (a rather distant possibility). The scare statements that you will get anemia (die of anemia) if you take large doses of vitamin C are not justified by the statements of the investigator himself. Vitamin C improves the workings of the human body so much, that it may well be that people will produce as much hemoglobin as they need, even though their copper levels are somewhat less than in other people when they are on a smaller intake of vitamin C. So there is no evidence, really, to support that conclusion about vitamin C and anemia.

The same thing is true for many other statements that are made about possible dangers of vitamin C, one of which is that if you take large doses of vitamin C and then stop you will develop scurvy. Or if a mother-a pregnant woman-takes large doses the child is apt to have special needs for vitamin C such that that child will be ascorbutic on the ordinary intake of vitamin C that would not permit scurvy to develop. There just is no evidence to support this. There is a rebound effect, which, in fact, was discovered ten years ago by my associates. It is a rebound effect that occurs after you have been taking large doses of vitamin C and stop suddenly, the level in the blood goes below that corresponding to the ordinary low intake, and it stays low for a few days. I recommend that people taper off if they want to stop a large dose instead of stopping. Dr. Anderson, in Toronto, carried out a study in which he checked whether people have an increased probability of developing the common cold (respiratory illness) during this period after they have stopped a large intake, than they have ordinarily on the ordinary low intake. He found he couldn't detect any increased incidence of respiratory illness during this period when the level in the blood is lower than usual.¹⁸

So, there is an effect. It's not an important effect. Nevertheless, I suggest that people should taper off over a period of a week or two if they have been taking large doses. And then I say, "But better still, don't stop the large doses." If a patient goes to the hospital (a person who has been supplementary vitamins), the doctor is apt to stop the supplementary vitamins. This is wrong. The doctors should be giving larger amounts of vitamin C and other vitamins to patients in hospitals. You know, we are troubled about the fact that the cost of medical care in the United States is very high. We are spending hundreds of billions of dollars on medical care, hospital care: six-, seven-, eight-hundred dollars a day for patients in the hospital. It has been known for forty years that you can cut down the length of stay in the hospital by two or three or four days (or by thirty or forty or fifty percent for a longer stay) if the patient receives large amounts of vitamin C. After a surgical operation, the wounds heal faster with vitamin C. It has been known for about fifty years that vitamin C is required for wound healing. You can't manufacture collagen, connective tissue, scar tissue. You just can't heal wounds if you don't have vitamin C. When a person not getting vitamin C begins to die of scurvy, if he has an old scar, it is apt to break open again because he is not manufacturing collagen. In fact, his joints fall apart, his blood vessels burst, because he is not making the collagen which is required for the strength of these organs and tissues. And vitamin C is needed-absolutely needed-to make collagen. So your body is stronger when you take vitamin C.

Now, about what my associates are doing. Dr. Cameron, when he first gave large doses of vitamin C to terminal cancer patients in Scotland (and he deserves the credit for having discovered, by his clinical observations, that vitamin C really has value for cancer patients), one of the things that Dr. Cameron noticed was that the patients said, "Doctor, I feel so strong!" They not only didn't feel sick (have this cachexia, just feeling miserable that is characteristic of cancer), and not only developed good appetites instead of being anorexic (not able to eat because the food didn't taste good), but they also got strong. Dr. Cameron wondered, "What can vitamin C be doing that makes the patient say that they feel strong?" And they were strong. He mentions that one of his patients, who, in Scotland, liked to play golf, was able to lower his golf score after he got out of the hospital. And another (a retired man) took on the job of chopping wood (not as a job, but just because he liked doing it-he felt strong and he brought chopped wood around to Dr. Cameron and other people). Also, Cameron noticed that in the accounts of scurvy, when sailors used to die on ships with scurvy, the first sign of the scurvy was lassitude and lack of muscular strength, and then the body began falling apart, later. The gums ulcerated and the teeth fell out, and the joints, and so on, and the person died.

What about this lack of muscular strength and regaining strength in Cameron's patients? There is a simple chemical substance named carnitine, which is present in muscle juice to the extent of about one percent. (If you squeeze meat, the juice that you get out contains carnitine.) Carnitine is required for muscular activity. You know, you burn fuel in the body to provide the energy for muscular work. This is burned in the cells in the muscle. The fuel that you burn is fat (at least, one of the fuels). Carnitine is required to carry molecules of fat into these cells where they can be burned to provide muscular energy. Just a couple of years ago, a biochemist showed that carnitine can be made from lysine, an amino acid present in the body (present in meat, too). Lysine, by chemical reactions that take place in the human body, catalyzed by certain enzymes, two of which are hydroxylation reactions that require vitamin C. You can't make carnitine from lysine without vitamin C. The fact that people sometimes say, "I have to eat red meat to be strong," it may be that they are getting carnitine from the meat and that helps them to be strong, or also getting lysine, which is present in larger amounts in meat protein than in vegetable protein. And if they have enough vitamin C, they can convert the lysine to carnitine and thus have even greater muscular strength. One of the investigations that we are carrying out as a result of the various observations by Dr.

Cameron and by others is to study human beings. How much carnitine is in their bodies? How much is floating around in the blood? And if you give a person extra lysine and extra vitamin C, does he then produce more carnitine and become stronger, too?

Vitamin C and Selenium

JB: Dr. Pauling, one of the other very commonly asked questions surrounding vitamin C's use in supplemental doses has to do with another antioxidant (knowing that vitamin C is considered a biological antioxidant that works in the water soluble portion of cells). This other antioxidant is the trace element selenium, which is receiving quite a bit of attention recently because it is supposedly a cancer-preventive nutrient. It has suggested by Dr. Walter Mertz at the USDA that high-dose vitamin C therapy antagonizes selenium status, or at least prevents selenium absorption from the diet. Do you have any comments on that relationship?

LP: I'm not sure that my comments are as significant as those that you would make. I would think that selenate or selenite might well be reduced to elementary selenium by ascorbate. That selenium...an organic molecule such as selenium methionine or some other organic compound would probably not be affected by the ascorbate. But I'd be interested to know your opinion on this point.

JB: I concur with your comment. In fact, a paper in which the oxidation reduction relationships between inorganic selenium and selenite, selenate, and selenious acid in vitamin C and the organics (organoselenium, selenium methionine, selenium cysteine) confirmed exactly what you just pointed out and that is that there was not a reduction in the organic forms of selenium to selenium metal, where there was in the inorganic selenite, selenate forms. So it would seem to me that if you were supplementing with a sodium selenite preparation and taking high-dose vitamin C that you may render some of the selenium unabsorbable, but if you were taking the organically bound form it would be a very small probability reaction.

LP: Yes, and of course, the organically bound form probably is selenium minus one, already as far reduced as possible so that ascorbate couldn't reduce it any further.

JB: Exactly right. One of the other things, quickly, that you might want to comment on is the suggestion that you can utilize a fat soluble form of ascorbate called ascorbyl palmitate, where the ascorbic acid molecule is a esterified palmitic acid, and that this is supposedly a very useful antioxidant in the fat soluble milieu of cells. That you should be taking a supplement of ascorbyl palmitate. Do you have any comment on that?

LP: I would need to be convinced that we need that fat soluble form of ascorbate if we are taking enough of the fat soluble antioxidant vitamin E. My recommendation would be to spend your money on vitamin E and save money by buying the cheap form of vitamin C, rather than to buy a more expensive form of vitamin C. Moreover, I don't think anyone should rely entirely on this fat soluble form. It might be taken as an adjunct to an amount of ascorbate, itself (ascorbic acid or sodium ascorbate or calcium ascorbate, itself).

JB: What dosage level would be considered for the average consumer who is reasonably well (let's say not sick)? What dosage level of vitamin C would be considered at a range they would have concern about excessive intake? Is there some range that we might say, for the average person, would be the desirable

range?

LP: Vitamin C isn't very expensive. What I buy costs about a cent-and-a-half a gram (the ascorbic acids crystals) and one-gram tablets you can get for around three cents a tablet (three cents a gram). So it isn't very expensive. My twelve grams a day comes to about eighteen cents a day. Nevertheless, people may not want to spend too much money on vitamins. I say a little extra vitamin C does a lot of good. To take even 250 or 500 milligrams does a lot of good. To take 1000 milligrams a day does more good. To take 5000, 10,000 milligrams still more good. But in general, I don't complain about a person telling me that he takes 1000 milligrams a day, or 2000 milligrams a day. As people get older I think it would be wise for them to increase the intake. I've already mentioned, I think, that I think that the twelve grams (12,000 milligrams) that I take is probably the right physiological amount. You can get along pretty well with a somewhat smaller amount. I think that's the right one.

Now, a person can find his own upper limit from the gastrointestinal response that was observed ten years ago by Dr. Cameron and more recently by Dr. Cathcart.¹⁹ Dr. Cameron observed that a sick person can take much larger amounts of vitamin C by mouth without it acting as a laxative or having too much of a laxative effect (producing looseness of the bowels) than the same person when he gets well.

Consequently, it might be good for a person to find out what his gastrointestinal limit is, and if it's unusually high it may well mean that he has a special need for vitamin C, that he really is not in the best of health. I can take only about twelve grams a day (well, I could take more if I split it up into a succession of small doses, but not much more). Some people can take twenty or thirty grams a day before they get this response, even though they consider that they are in good health. A really sick person, Dr. Cathcart reported, might have to take as much as 200 grams in a day to get this response, but he can't do that day after day. In a few days he is well if he has mononucleosis or hepatitis or some such disease and has had to cut down his intake.

This man who comes to see me every few months (the chemist down in San Jose) still has metastatic cancer. It's clear that he is not well, both because you can see the metastases when he has CAT scans made and also because he can take his 130 grams a day without having far too much looseness of the bowels. So he is not well. He is able to work, to stay alive, for eight years, but he hasn't been able to get rid of the cancer and get back into good health. Some people do, apparently, succeed in that.

JB: I know that the listeners would probably like this to go on indefinitely, but we certainly have to recognize that you have many, many other responsibilities today and we appreciate your time. I would like, however, to leave with one last question being put to you before we have a chance to get together to do this in the future. That is: I think a lot of people see the rate of change of information occurring and how quickly science is evolving and developing and we all probably feel a little bit of a state of overwhelm. As a visionary, as a person who has been a major contributor to the field of science and health care and had your finger on the pulse of what's been happening for 70+ years, what is your vision as to what is occurring right now and the kind of future that you see for health care?

Dr. Pauling's Thoughts (in 1982) about the Future of Medicine

LP: I think that it will be recognized before long that the greatest contribution to medicine made in the last quarter of the 20th century is the recognition that nutrition, including nutritional supplements, can be used in a far more effective way to improve health, prevent disease, and even in the treatment of disease, usually as an adjunct to a conventional therapy, than had been possible than it had been used in the past.

In particular, I think vitamin C, which is unique among the vitamins in two or three respects, will be found to have very great value. The estimate that I have made about the value of nutritional supplements, vitamin C, and some other health practices has been increasing. That is, the value of these (my estimate of their value) has been getting greater year after year. In an article that I wrote recently, I made the estimate that in this way it should be possible to increase the length of the period of well-being and the length of life by 35 years, which would mean around 110 years as a life expectancy rather than 75 years.²⁰ And this, I feel, is desirable. There are periods in life when you are miserable. When you were young you were miserable—at least I was miserable before I found the proper relationship to the world as a whole, to the opposite sex, and so on. I was not happy as a child and as a teenager; I was miserable. I expect that there may well be a period of misery associated with the decline in health that culminates in death. It may be that this could be shortened (this second period of misery). The first, I think, has got worse in the last twenty years with the relaxation of the social pressures on young people to behave that kept them from getting involved with problems so intimately as they are now involved. I believe that we can then increase the length of the period of well-being with respect to the period of less well-being, that is, we'll win out in this way by being happier over a greater fraction of our lives than at the present time.

So now going from this extraordinary discussion with Dr. Linus Pauling concerning his view of orthomolecular medicine, vitamin C, and the future of this molecular medicine concept, let's move to the next important founding father of this concept in the 20th century, and that is Dr. Abram Hoffer, who, as you know, as a psychiatrist and a PhD in chemistry, birthed the concept of orthomolecular psychiatry. And also, he was in practice, seeing patients up to the end of his life. An incredible contributor to our field, who I had the great fortune of being able to interview just very shortly before his transition and moving on.

With that, let's talk in the 21st century, with Dr. Abram Hoffer and his view of this whole field.

Clinicians/Researchers of the Month

Abram Hoffer, MD, PhD

1917-2009

Interviewed in his office in British Columbia, Canada, December 2008

JB: This is a great privilege for me. I'm representing the Institute for Functional Medicine. We've been very fortunate, at the Institute for Functional Medicine, for the past 14 years, to, every year, honor someone who we feel has provided meritorious distinction in the field of functional medicine. We've named this award for a person who is really one of the founding fathers of functional medicine and that is Dr. Linus Pauling. There is probably no recipient that would be more deserving for this Linus Pauling Award than the person I'm so privileged to be able to honor today, and that is Dr. Abram Hoffer.

Dr. Hoffer, this is the 14th Linus Pauling Functional Medicine Award. We wanted to save it for when it got rich enough to be really worth something. We think that you—as one of the founding fathers of the whole paradigm upon which functional medicine is built—really represents the core of what we are trying to teach doctors in the future. The plaque says, "For a lifetime of pioneering work that has elucidated the important role of biochemical uniqueness and orthomolecular therapies in a wide variety of chronic mental health conditions, the Institute recognizes Dr. Abram Hoffer's significant contribution to the evolution of functional medicine's knowledge and intellectual architecture for the prevention and

treatment of complex mental health disorders." We want to thank you for your many decades of extraordinary leadership in developing this field.

AH: Dr. Bland, thank you very much. This is one of the highest honors I never expected to receive. Linus was a fantastic person, a major fantastic person-my mentor-and I think he not only changed medicine, he certainly changed my life as well. Thank you very much.

JB: Thank you very much. Well deserved and, as I said, there would be no functional medicine if not for Abram Hoffer, Linus Pauling, and Roger Williams.

AH: Thank you.

JB: This is a really special opportunity, Dr. Hoffer, for me. As you probably know I've valued (as have, literally, tens of thousands of practitioners) from your work and your insight. To sit down in your office, here, in Victoria, British Columbia and know that you are still practicing psychiatry at the level of wisdom that you can bring to this discipline is absolutely amazing. It's something that we all aspire to do in our own professional lives. Not many of us will be as successful in creating a whole new concept as you have created, but certainly your model of "stick-to-it-ness," and discipline, and dedication to your patients is a model for all of us.

I'd like to just start-we can go all the way back, obviously, to before 1957, but 1957 is kind of, for me, where I started my understanding of you by reading your first paper published on niacin and schizophrenia. How would a psychiatrist even be interested in niacin?

Dr. Hoffer's Unique Background and His Collaboration with Dr. Osmond

AH: Well, I would say, luckily for me, Jeff, I got my first degree as a PhD, and later on I got my MD. Now, there is a different set up, as you know. You learn to do things differently. A PhD is taught how to think and a doctor is taught how to remember. And having taken my PhD first was a great thing for me to have done it that way. After I was made director of psychiatric research for the province of Saskatchewan in 1950, I had the following qualification: I knew absolutely nothing about psychiatry. Which I think (looking back on it) was superb, because I hadn't been taught all the things that you could not do. So it was my job to do something about these poor schizophrenic patients. Half of them at our mental hospitals would never get up; none of them would get up. We had no treatment. It was absolutely awful what happened to them.

Luckily, at this time, Dr. Humphry Osmond was brought out from England. We were desperately short of doctors to man our mental hospitals in Saskatchewan, and Dr. Osmond came out. I didn't know he was coming, nor did he know that I was interested in research. When he arrived in the fall of 1951-a very hot, dusty Saskatchewan day-I met him at Dr. McKericker's offices in Regina, and it turned out he brought with him a very important paper. He and his friend, John Smythies-John Smythies is still alive and living in California-they had done some work with mescaline, the active principal of peyote.²¹ And they had concluded that the experience induced by mescaline was in many ways similar to the one induced by schizophrenia. Now, this was an interesting observation. It had been made before by another doctor-Dr. Taylor Stocking-some years before, but what he and John Smythies did was even more unique after that. They then looked up the chemical structures of mescaline, which in many ways is similar to adrenaline (it's what you might call a catecholamine). They concluded that the question with the question: was it

possible that in the body of the schizophrenic patient there might be a compound with the properties of mescaline and some similarity in structure to adrenaline? He brought that paper with him.

Now he had first presented that idea in England, but they thought it was so absolutely awful that he was told they rejected it. He was so unhappy at this that he told his wife that he would have to get out of England as far as he could. And when he saw in The London Times an ad asking for psychiatrists to come to Saskatchewan, he said to his wife, "That's far enough. I think I can go there." So he came there hoping that he could do some research.

We met. And after we learned how to understand each other (because he spoke with an English accent and I spoke with a prairie accent), so after we learned to communicate we became very close friends. I looked at the idea very carefully and it made sense. It made so much sense. And so I began (since I was in charge of the research and had time to do the reading and the study and collecting money-all the other stuff you have to do)...so I looked up formulas for all of the known (at that time) hallucinogens, and they all had-and I remember just thinking, one day I'm sitting at my kitchen table and my wife was doing the dishes and I'm sitting at the table, all covered with papers, and I'm drawing down formula, and I said, "Oh my God. There it is." They were indoles. They were indoles, and you know what that meant. Because there is a law in chemistry that compounds with similar structures tend to have similar properties. I said, "Oh God. There it is." So we said, "We now have a new formula. The hypothesis will be: look in the body for something which has the properties of mescaline and is similar in structure to adrenaline. It's got to be an indole." Now, indoles in the cells (there are many of them found in the body-as you know, they are made in the gut, and not all of them would be that important). We had to narrow it down to indoles that might be derived from adrenaline. And in those days there were only two that we knew about: one was called adrenochrome (which later on we discovered could be converted into adrenolutin), and the other one was (by theory) noradrenochrome. So that gave us the hypothesis.

It's kind of long-winded, but I will speed it up a bit. We didn't really care about the hypothesis. We wanted a treatment. We didn't care about the hypothesis. I knew then that most hypotheses turn out to be dead wrong. That's the way it goes in medicine. We wanted a treatment, and since I had taken my PhD in Minnesota, and my PhD thesis had been on B complex vitamins and wheat, I was familiar with the vitamins and I knew all about pellagra and the diseases it causes. We said to ourselves, "Well, let's try niacin." Maybe if we get niacin we can protect the body against the impact of this hallucinogen that we thought was present, but we didn't know its structure. We didn't know yet about that. So that's how we hit upon niacin.

And I recall (it's still vivid), that there was a very middle-aged woman. She was the head stenographer of a large company in Regina and she became paranoid. Right after the war they used to have Christmas parties (maybe they still do). One day after the party this very moral, good woman got the idea that her boss was in love with her. They had never had a relationship. She became so depressed because she thought it was going to break up her marriage. She went into a deep depression and was admitted to our hospital (under someone else). There, she had shock treatment and she was better for six months. Then she went to another Christmas party. Same thing, again. Went into a depression. Came back to the hospital again. Had shock another time. Nothing happened. And then she came under my care. So I said, "Okay. She's going to be number one. I'm not going to give her anymore shock treatments; she already had three series. She hadn't responded." We had no drugs (no tranquilizers). We had barbiturates and we had the narcotics; that's all we had. And so I started her on niacin. She didn't like to take it (most people

didn't like to take it-the flushing kind-that's all we had). But anyway, she took it and she gradually got better. And after about two or three months in hospital, she was okay. Discharge her.

A couple of years later, her sister brings her back again. She is getting paranoid one more. What happened? She had stopped taking her niacin. So I called her into the office, and I'm very rough and I yell at her and tell her I'll do all sorts of terrible things to her, including shock, if she doesn't go right back onto the vitamins again. She went back onto the niacin. She gets well. And after two years she stops taking it. Another relapse. Same thing: put her back on niacin and she gets well. So now she stays on it and after about five or six years of niacin, she says, "Dr. Hoffer, I've been doing so well for four or five years, do you think it is okay for me to go off?" I said, "Okay, let's try." And she went off her niacin and she remained well thereafter. She went back to her senior job, looking after thirty stenographers in this stenographic pool.

Jeff, when you see one person like that get well, there's no doubt anymore. I mean, there was some doubt, but there was no evidence for scientific doubt because if one person can do it, surely there are going to be more who respond the same way. And that led us to our first controlled studies that we did (the first double-blind, controlled studies in the history of psychiatry and the first in the United States). In England they had done double-blinds on arthritis, but they had never done any in any other fields, so we were the first. And our double-blind experiments showed that we could double the two-year recovery rate of patients when we gave them niacin or niacinamide compared to placebo controls. So that was basically how we got started, and we published that paper, and we were lucky that we got that published because the editor was a close friend of mine (otherwise he wouldn't have taken it).²²

JB: When I look back and I listen to your story, I'm reminded of so many interesting things. We could call them fortuitous or serendipitous or directed. Here is a person, in your case, that gets a PhD in a chemical field and understands about pellagra and niacin, as it relates to an entirely different field and discipline from that of psychiatry. Then goes to medicine and focuses on psychiatry. And then, because of a creative mind, makes the connection. As I recall, in your paper, you were maybe the first group to talk about the similarity between pellagrous dementia being schizophreniform with schizophrenia.

AH: Correct.

JB: So that connection is a brilliant leap of abstraction for most people, but for you it was clearly obvious.

Early Work Results in Criticism from Colleagues

AH: It was so clearly obvious that I didn't think people ever would object. I thought I would be looked upon as a hero. I said, "Oh my God. The psychiatrists are going to love me now." By that time I was very popular, anyway, because I was doing a lot of nonsense research that didn't mean anything. And as long as I published papers that had no meaning-you know what I'm talking about-I was popular. But after we published that first paper that you read, guess what? They said, "Oh my God. That guy's a heretic!" And at that time, of course, as you know, the tranquilizers came in (in '55, '56, '57), and they were financially so rewarding to the big drug companies that they overwhelmed the whole field. And today psychiatry is owned by the Big Pharma; that's what has happened to psychiatry today.

JB: As you made this discovery, I find it extraordinarily interesting, from an intellectual development perspective, that you took the pre-pellagrous dementia connection to schizophrenia, and then you asked

questions about what other genetic metabolism disorders associated with nutrition can we think about that could have central nervous system effects (like hyperhomocysteinemia). And then you talked about B6 and B12 and folate, so your model got extended and seemed to be able to be mapped against many of these conditions.

Establishing the American Schizophrenia Association

AH: That's true, and that wasn't just by my doing. We were able to assemble...we organized the American Schizophrenia Association many years ago, and we were able to enlist the interest of a bunch of very good American psychiatrists (Dr. Ted Robie from New Jersey, Alan Koch from New York), a whole bunch of very brilliant psychiatrists. And we were wide open at that time. Since I was the Director of Research I had lots of time. I made myself everything-I was Chairman, I was this, I was that. We would meet twice a year as a committee on research of the American Schizophrenia Association. We were wide open. Alan Koch would say, "Hey guys, I had a patient that wasn't talking. He was mute." And he says, "I put him on vitamin B6 and it was an amazing change." So we all said, "Hey, isn't that amazing?" instead of saying, "Forget that nonsense. You can't do that." We said, "Isn't that interesting?" So at the next meeting we would someone would come [and say], "I tried out what Koch said, and hey guys, it works." We had these informal meetings and this was a fantastic amount of information, and that's when we brought Linus Pauling in. I remember we had our meeting in Vancouver at the home of Dr. Ross McLean. There I am Chairman of the meeting, and as the Chairman you're not supposed to do anything (you are supposed to just sit there and be quiet and make sure things are running properly). So I'm listening to all my colleagues (there were 10 of us) reading their fantastic papers. They are talking about folic acid, they are talking about B6, talking about zinc. Carl Pfeiffer-everyone-they are all giving us some amazing information. So I said to myself, "Isn't it fantastic? Here is this very important information and no one hears about it. We have to publish it." So David Hawkins is sitting on my right, and he's a good friend of mine. "David," I said (to the group), "we have to publish a book." So they stop and since I'm the chairman they have to listen to me (that's the power of the chair). I said, "David, you are going to be the editor." And he gulped. He said, "What?!" I said, "Don't worry, we'll help you. Each one of us will submit a chapter." So eventually David said, "Okay, he thought he would do it." So after awhile we were starting to organize this book. It occurred to one of us (I don't know who it was-it might have been David) that maybe we could ask Linus Pauling to become an editor. I am talking about the book *Orthomolecular Psychiatry*.²³ So David-not I-I think David wrote to Pauling and asked him. And Pauling said yes, he would, on one condition. The condition was that he would have to approve of every paper that appeared in it. So we, of course, said, "Fantastic!" And that's how that book came out. Because we had that spirit of cooperation, we were able to examine new ideas so quickly we didn't have to wait for these terribly slow university-sponsored....If you have an idea today in psychiatry forget it. By the time you're ready to go forward two years later you will have lost interest in it. We didn't have those handicaps in those days towards doing research because we knew the basic rule of medicine: First, do no harm. And you cannot harm your patients by giving them vitamins. It was fantastic.

Collaborating with Dr. Linus Pauling

JB: Now you have talked an epic chapter that I think propelled this whole model that you birthed forward, and that was the 1968 publication in *Science* magazine authored by Pauling of the article "Orthomolecular Psychiatry." That seemed to put the discipline up on the big board. Did that change the visibility for you or what you had been doing?

AH: Yes, it did. It gave it prestige. It also gave us a lot of work. I remember what happened. I had not met

Linus Pauling before then. Apparently he had been getting letters from a large number of Americans who had heard about the vitamin approach and were putting themselves on it and were getting some response. So he was getting more interested. And it fitted in with his own basic concept of molecular medicine. I think this had been gestating in his mind for some time. So one day I get a letter from Linus Pauling. "Dear Dr. Hoffer," he said, "I am enclosing a manuscript which I propose to send to Science. Would you please go over it to make sure you are properly quoted?" Now isn't that amazing?

JB: Fantastic.

AH: Can you think of any other scientist that would do that? He was so honest. And so I read it, and of course Linus Pauling never made any mistakes. I read it carefully. He quoted us. He was very fair and very honest (what he wrote about this). I wrote back and said, "It's absolutely great." Then he came along with the word. At that time, we had been playing with the word "Megavitamin Therapy," which I didn't really like that much because there is no such thing as a megavitamin; it just doesn't exist. When he published this paper I said, "That's the answer. This term of Linus Pauling's covers almost everything that we are going to do." Since then I haven't thought of anything better than the term "orthomolecular." But even amongst my colleagues they became very upset because they were getting used to the term "megavitamin therapy." We had our own conservatives, as well as liberals, in our own group. So I took on a major role. I said, "I am going to defend the word 'orthomolecular' until it kills me. It is going to become 'the' word." And since, again, I was Chairman and I had some prestige, I was able to gradually force the word in. Even with the journal, Orthomolecular Medicine, for many years people wanted me to change the word because "orthomolecular" is very unpopular. I said, "So what? Of course it is unpopular, but we are going to change that." And thank God, Jeff, we are actually changing. The word is becoming well-known, popular in Europe, in Brazil, many other places. And recently (in the past few weeks) we have had people here from Portugal, people here from all over the place who are, in fact, so determined to go back home and start up with this word. Now it's a temporary word. It's a temporary word I think because one day when all of medicine is orthomolecular we won't need the term. We will drop the term "orthomolecular" and we'll say this is what modern medicine is and anyone who doesn't practice it will be subject to malpractice suits.

JB: You mentioned this book, and it strikes-for me-such an important chapter in my life, because as a young assistant professor in 1970 I was searching for models and mentors outside my own department and trying to carve out my identity as a young, new, emerging academic researcher, I happened on to that book in...I think it was probably '71 or '72 (in that early 1970s period) and it just was like finding the Rosetta Stone for me. When I opened that book, it was so powerful. Each chapter was like a treasure. You had assembled such a remarkable group of authors and thinkers.

AH: But don't forget, we also had the master read each paper, and he was so kind. I remember, in one paper I sent to him-a manuscript...I like to write content. I think a paper (its content) is important. I'm a bit more sloppy when it comes it comes to punctuation and style. I just don't have enough energy to do that. In one of my papers I think I left out a comma. And Linus is too polite to tell me, "You forgot to put that comma in," so he sent me a letter and he said, "Dear Abram," he said, "I think your secretary forgot to put a common in (in this particular slot)." Isn't that amazing?

JB: That's so Dr. Pauling. The two of you share something very common that I think great people have, and that's humility and grace. I think you both have that.

AH: He had that. He was like a racehorse that never lost a race. And I knew that when Linus joined us, I said to all my friends, "The battle is over. We won." The world may not know it for a long time, but we knew we had won the battle because his theories, even today, are so sound. I'm sure you know. And the sad thing is that if the drug companies had accepted his view, they wouldn't have wasted billions and billions of dollars finding toxic drugs that do more harm than good. It has been a terrible waste. The drug industry has been a terrible waste. I was proud to be a psychiatrist. Very proud. I started as a standard psychiatrist; I got my specialty in psychiatry. I became well-known in that field. I was one of the five top directors of psychiatric research in the United States and Canada. We were the first to bring Haldol in; I remember I was one of that first study group to do Haldol. I knew drugs. I knew drugs. I was an MD. And I was proud of it. Now, guess what? Now, I have turned against it. I now have concluded (and since I am no longer practicing as a doctor I can talk freely because they can't take away my license if I don't practice anymore), if every psychiatrist were to go to Mars, they would be worse off and we would be better off. That's my opinion.

JB: When we look at the development of this whole wonderful rich model, the concept that Dr. Pauling proposes in that paper on orthomolecular psychiatry in Science magazine was a concept that was fairly sophisticated for the average doctor because it talks about mass action and kinetic rate constants, and it talked about enzyme binding to coenzymes. These are things that the average doc doesn't think that much about, but some (now) 30 years later, Dr. Bruce Ames at Berkeley comes back with this marvelous paper that kind of says, "Guys, relook at this. This is all right."

AH: That's right. In his last paper he maintains that most of the conditions, in fact, are a result of some metabolic fault of this type. Now, Harry Foster and I wrote that book, and I stole Linus Pauling's title (I hope he forgives me for a bit of plagiarism, but I thought it was such a nice title I would honor him by using it). In this book we maintain, as a result of very careful studies, that half the population of North America would benefit by taking B3, either niacin or niacinamide.²⁴ It is a very, very important nutrient. They are all important, but this one is of particular import. Linus Pauling suggested that we lost the ability to convert sugar into vitamin C-what is it...²⁵ or 50 billion years ago-that this was advantageous as long as our diet contained enough vitamin C. I think the same thing is happening with B3 and tryptophan. There was a major change in 1800. The first description clinically of schizophrenia was around 1800. Before then it was rare. Around 1800 it was a major change in that the millers learned how to make white flour. On my PhD I was a flour chemist; I did analyses on flour. So they learned how to make white flour, which had lost all of its B vitamins, and I think it was after that that we gradually began to see an increase in the incidence of schizophrenia. It keeps on going up.

David Horrobin, a good friend of mine, in his book Adam and Eve (or something), maintains that the genes for schizophrenia (I think there is more than one-I think there are a whole bunch of them) are gradually sweeping into the population.²⁵ And my prediction is that if we all are still here a million years from today, we will all have the genes and no one will be sick. Because if we are intelligent enough we will make sure that every human gets the right quantities of B vitamins (not just niacin-all the B vitamins). My prediction is that almost half of all the human illnesses will vanish; they will vanish within 10 years.

JB: This sounds very consistent, also, with Dr. Roger Williams' concept of genetotrophic disease.

AH: Absolutely.

JB: You were all birthed in the same period of time-you, Dr. Pauling, and Dr. Williams-in the 40s and coming into the 50s was when this concept really emerged beautifully.

AH: Yes. I knew Roger Williams. He was a great guy. Unfortunately he was deaf and blind (almost) at the end of his life, but he was great. I loved his work. In fact, I refer to his concept frequently. I have a friend who was the world's greatest pianist, Anton Kuerti. He is a Canadian. Beautiful pianist. You remember Roger Williams made the comparison of an orchestra. In other words, each member of the orchestra plays a vital role, otherwise you don't have a symphony if you don't have everyone playing from the same book with the same conductor and the same music-you have a cacophony, you don't have a symphony. I tell this story, which is true. In Boston, a few months ago, Anton Kuerti, who is the world's greatest pianist, was at a concert where his son was the conductor. That evening they were having a show and the pianist who was supposed to perform couldn't make it. So without any notice he called upon his dad to come forward and play and they had a fantastic concert. So this was reported in The Economist. I thought that was absolutely great.

I talk about this and I say that according to Linus Pauling, no nutrient can be substituted by any xenobiotic-if you need niacin, no drug is going to replace it; you have to give that. So I say it is like suppose in a concert the first violinist dies (or faints, or something) and the conductor decides the show much go on so he invites the drummer to play in his place. I think you aren't going to have a symphony. Unfortunately every nutrient is like Anton Kuerti: every nutrient has to play its own role and you cannot replace it. And that is my major complaint about the drug: they are trying hard-because they can't patent vitamins-to find a drug that will replace niacin. My friends and I discovered it lowered cholesterol levels in 1954. You can't patent niacin. If I could have taken a patent on it I'd be a billionaire today, because drug companies have spent billions trying to find a compound that has the same good beneficial properties of niacin without any of the terrible side effects that the statins have. It's not available. It is the combination of Roger Williams and Linus Pauling that I think were two of the main contributors to this whole field, and I have depended upon them really hugely.

JB: What you are teaching all of us, as we are hearing your story, is that all great new paradigms start with observation.

AH: Absolutely.

JB: And that being a good observer and being not afraid of your observation, and saying, "This is something really remarkable that I need to follow-up on." Not just discounting it as an aberration.

Strong Opinions about Double-Blind Trials

AH: Jeff, you're totally right. I absolutely agree with you. The only honest scientists are good observers and thinkers. The double-blinds don't tell you anything. Double-blinds are a fraud. I think they should be totally made illegal. They shouldn't permit them at all. You have to have good, honest (I should have said honest) [people] who don't have any conflict of interest with the drug companies. Because once you are working for a drug company, honesty flies out the window. That's harsh, but I am absolutely convinced that it is true. And so does the literature.

JB: Let's start back at the turn of the last century for a moment, because I would like to trace the impact of your intellectual development on medicine from talking, first, about Sir Archibald Garrod, who was credited as the founding person for the field of genetic metabolism diseases of infancy.

AH: Great work. Fantastic work.

JB: That, then, was kind of leading people to the belief that we had these inborn errors of metabolism that created Wilson's, Gaucher's, Fabry's, this whole constellation...methylmalonic acidurias and Hartnup's disease, and so forth. And then along comes Abram Hoffer and Humphry Osmond and for the first time a model of biological psychiatry is born, which takes these constructs that there are these molecular processes going on in the body that have genetic relationships that are one-size-not-fitting all. That there is a differentiation.

AH: That's right.

JB: What you birthed, it seems to me, is the biological psychiatric revolution from the observations you made. But then it appears to me (and this is my question) that biological psychiatry, as you birthed it, got perverted into becoming a new form of pharmacology with new-to-nature molecules.

AH: That's right.

JB: How did that happen? How did a good idea get transmuted?

AH: The idea that Sir Archibald Garrod developed...that was a fantastic idea. And the early pioneers in the use of vitamins were of that type. In fact, almost all the papers dealing with vitamins published until 1950 were positive. It is amazing the amount of literature that describes the many virtues of these vitamins. But they were tied down to what I call the "vitamins-as-prevention" paradigm, which meant that you only needed vitamins for a very few classical deficiency diseases like scurvy and pellagra and so on. And they couldn't break this concept into saying, "Maybe we should try higher dosages." The early pioneers-the early pellagrologists-who did such great classical work in the United States, they were using all sorts of doses of vitamins and tried getting good results. So this was the beginning of breaking down the concept of the old paradigm. I've known some of my friends who lost their license to practice because they gave their patients vitamin C. It sounds unbelievable. It is laughable. It has happened. So we try to move into the new paradigm, which says, "Look upon vitamins as treatment potential, they way you would a drug. If a patient has a severe type of pneumonia, you're not going to give him 10,000 units of penicillin a day when he needs 10 million." What's happening today in the literature is that all these negative papers, if you read them carefully, they'll make a claim that no one ever made before: they'll claim, "Vitamin E prevents heart disease." Well, whoever claimed that? I don't know of any who have said that. What they have said is that if you do have heart disease you can get a lot of help by taking enough vitamin E. So having made a spurious claim, they then go ahead and do a study, giving their patients 50 units of vitamin E a day. They spend millions on this stupid study, and then they come up with the right conclusion: "We were right. It doesn't help." This is what has been happening in the whole field of nutrition. The whole nutritional literature is unbelievable. There is a very famous Greek professor of philosophy and mathematics, and he is very blunt, like I am, and he says 80 percent of the stuff published in medical journals is wrong. Eighty percent of the stuff in medical journals is wrong. I think he's underestimating it. I think the most interesting parts of today's medical journals are the ads because they have beautiful pictures and they are well written and they are full of lies...You know, the medical ads are superb for fooling the public. The content-not that interesting because it is written by the drug companies, mostly.

JB: So we have talked now about extraordinary successes and contributions and things you are very proud of. Are there things that you look back and you say, "These are things I wish I would have done differently?"

AH: I wish they would have believed me. The main thing I wondered is, "Why didn't they believe me? Why didn't they?"

JB: Why do you think they didn't?

AH: Oh, I know now why. You have just gone through a very exciting, interesting election campaign in the United States. You have a president elect who, for the first time, is black. He spent 600 million dollars (at least) on the campaign. He apparently had one of the most promising campaigns ever run in the United States. And all he had to do is to persuade a few people that they could elect him if he was black. Now if it takes that much money to change the attitude, you can imagine how much money it is going to take to change the medical attitude of those who are already firmly convinced they have the answers. The answer the medical profession has is more drugs, more drugs. They are still looking for the Holy Grail that they will never, ever find. That's the answer. The only way we can deal with that is to do what you are doing: education, education, and education. We have to demand more and more. Teach the doctors. If you can teach 30,000 doctors, and if 10 percent of them are convinced, you have made a major contribution. And it is happening.

JB: That's a very optimistic note. Now, with your very senior perspective and seeing how things travel through time and space in the evolution of the profession, what's your view of medicine as we look forward to the future?

Dr. Hoffer, Age 90, Discusses the Future of Medicine

AH: I don't complain about all of medicine. I think surgery is superb. If I were in a car accident I would want to go to a modern surgeon; they do a beautiful job. I think that neurology is just about the same as psychiatry. The worst branches of medicine are neurology, internal medicine, pediatrics, and some of the others. I think that the surgeons are the ones who are really the tops in the field. Maybe that's because they get paid the most, I don't know. I'm hopeful that this will change. Also, we have to widen the people who are allowed to treat. We have to bring in the naturopaths. We have to bring in all sorts of therapists. We have to allow psychologists to practice orthomolecular. And also we have to give patients freedom. We don't have enough freedom-you in the states and we in Canada. We don't have enough freedom to select our doctors. For example, in Canada I had a young schizophrenic male, who was both on drugs, which he got free from the government, and he was on niacin that he would have to buy himself. He was doing well. And then he came to me and he said, "Dr. Hoffer, I can't afford to buy the niacin." It was five dollars a month. Can't afford it. He smoked. I said, "Why don't you quit smoking?" "No. I couldn't quit smoking." He could afford that. Because the government wouldn't pay for the five dollars a month, he had to stop taking the niacin, and he remained sick forever. That's what is happening to our reasoning.

JB: I believe that what you are speaking to is more than a medical paradigm. It is a thought process as to how we, as individuals, take responsibility, understand something about our bodies, and then elect to do something as advocates for our own health, and taking charge of that. And medicine is there to help educate and support patients, but in the end, there has to be some responsibility, doesn't there, with the patient taking charge?

AH: I'm absolutely convinced of that. I think that the Americans made a major mistake when they changed the FDA Act under Jack Kennedy. You may remember that before that, the only policy was to check on the toxicity, and if they could prove that the drug was non-toxic they said, "That's your problem hereafter." I think that wasn't a bad policy. But when they gave the FDA the role of ruling on the efficacy of drugs, it developed an enormous problem.

Imagine yourself: you are the head of the FDA and a drug company and says, "We have this application" and they'll send you a boxcar full of data that you have to go over. And you have to decide, "Shall I release it or not?" And if you release it and three years later it turns out you have killed 100,000 people, you are not going to be very happy about that. So they developed a system which took away all guilt. They began to use the double-blind controlled study as the arbiter of whether anything is good or not, and if the p value is at .05, "Okay, well it's not our fault. That's what the P value said." There is a drug that is now used and it's very common for Alzheimer's. I understand that the company that produced that, the first 11 or 12 studies they submitted to the FDA were all negative. The 13th or 14th were positive, and according to FDA rules, if you get one positive out of ten, they'll still approve it. So here we have this drug, which I know well doesn't do anything, except make the drug companies rich. We have too much of that. I don't know how we can do that. We have to change the patent system. If we had allowed vitamins to be patented, different situation.

JB: We are at a very interesting juncture, I think, in human history. There are these epic points in human history-inflection points. We have kind of assumed that cultural history grows kind of linearly, but it doesn't. It grows in fits and starts and we're now in one of those really interesting exponential change periods. As we see this change occur, the leverage of wisdom that comes from the past will become very important for determining our future. If a doctor was starting out today and you were to meet with them, what guidance would you give them?

AH: Before I would accept them into medicine, I would want them to take a course in the history of medicine. The history of medicine and the history of conflict. Most doctors don't know that. For example, anesthesia was opposed because the male doctors knew that women had to suffer pain. God said that when you had to have a baby you had to suffer pain. So therefore, you could not use it to relieve suffering. Except for Queen Victoria, who thought she was probably God in her own right, so she accepted ether, and that broke the log jam. Once she used ether for having one of her babies, pretty soon doctors were clamoring to claim they had discovered it first. She broke the log jam. Did you know that the stethoscope was opposed for a long time? You knew about that. And the reason was that it was indecent to listen to a female chest. You were not allowed to put your ear up against a female chest. Why not? Male doctors weren't allowed to do that, so they used rolled up paper. And then they started the stethoscope and that took a long time to bring in.

So the history of medicine tells us that it takes anywhere between 40 and 60 years for a new paradigm to get established. So I would want them all to take a course in the history of medicine-a really good course in the history of medicine. I would want them to take a course in the doctor-patient relationship-how important it is that you be a human dealing with a human of equal value. You are not talking down to a servant or to a slave. In the medical profession, they think they are gods and sitting in front of them are their poor slaves. The slave says, "Doc, I have a headache." "Great. Take this pill. Out you go. Don't bother me anymore." How are we going to change that?

I would insist they take courses in sexuality, which they don't do now. Most doctors know nothing about sex except that of their own experiences. We'd have to prepare them by actually spending a year or two in preparation for what they would take as medicine. And then I would like to see two streams into medicine. Medicine, after all, is a technology. It is not a science; it is a technology. We need it. We need superb technologists. That's why the surgeons are so great. Surgeons aren't scientists, but they are excellent technologists. They know exactly what to do and how fast to do it. They know what to do. So we need to have two streams: one stream goes into a technical school, which gives you an MD but you don't do any basic research (or if you do, you switch), then we would have the second one where you would go on to a university to take a PhD in medicine, which would then teach you the elements of honest research and train you to look into new ideas whenever they develop.

We have to completely change the whole system of medicine. We have to take from the drug companies any influence they have. We have to prevent them from giving any money to the universities (that's going to be a problem). We have to force the governments to become more responsible and to take over the burden that they really should be caring (because they'll save so much money if they do it properly). These are the things I think we'd have to do. We have to reorganize the whole system of medical education. Won't happen in my time.

JB: It is fascinating. In the United States, now, less than ten percent of the incoming students are interesting in doing any what is traditionally called family practice. They are all being pulled into specialty medicine because that's where the money is to be made.

AH: That's right.

JB: And so we're losing a lot of the things that you're talking about: the skill of listening to patients, the skill of being there (present) to understand a patient's complex etiology of their condition. Some of the things that are the most profound in medicine, you're saying, are the simplest things if they are properly applied.

AH: That's right. I can't stop talking about the things I've seen. I remember one patient that I had to admit to hospital. She was on 5 or 6 or 12 medications. I said, "Hey, nothing. Withdraw everything. Take her off everything." A week later she's feeling great. I had a woman come here with a printout list of 28 drugs she was taking. She's 75. She's on 28 different drugs, and she says to me (seriously), "Doctor Hoffer, I have to take every one of them." It puts me in a terrible position. She's already taking 28, are you going to add 3 or 4 more to this big list? We are overmedicating. We are killing. Take it from me, Jeff, this is a prediction. We are heading for a major catastrophe. Imagine all of the hundreds of thousands of schizophrenic patients who have been on drugs 10, 15, 20 years. It's the same as the HIV virus (they've been on these retroviral drugs). Everyone claims, "Isn't that fantastic? They don't die." Well, they don't die as fast. Many wish they would. They are not healthy. They are very, very sick people. They cannot perform, they are mostly sick, they have to take huge amounts of drugs. They get all sorts of illnesses, like tuberculosis, lesions, cancer, everything.

We are heading into a very sick century. If China really wants to beat the Americans, they should forbid any Chinese from taking any American drugs. They will remain as healthy or sick as they are now, which Linus Pauling called "a moderate state of ill health," and the Americans and Canadians...we'll go downhill. Down, down, down. We're going to run out of people who can work because there will be too

many sick. Our major industry is going to be nursing and doctors. We are creating a society where we need more doctors, more nurses, more caretakers, more this, more that. We will spend all of our money just simply looking after ourselves. Who is going to build our highways? Who is going to make our equipment? Maybe that's why we're sending everything offshore, because we don't have enough people left behind to do these things. We are creating a very sick society.

In Closing: Dr. Bland's Tribute to Dr. Pauling and Dr. Hoffer and his Thoughts on the Future

I hope that you were as moved as I was to hear Dr. Hoffer, and also to put it into the context of a 20-year previous interview with Dr. Linus Pauling. Just to have those voices resonating in our ears and influencing our nervous systems and patterning our thinking is like putting a virus of hope and goodness into our system of learning. What an amazing two contributors they are to the paradigm of what we have been talking about. You know, I reminded myself as I listened to these interviews that I was very fortunate, also, to interview Dr. Roger Williams. I think it is really fascinating to think through how these three individuals, who were all living at the same time, gave birth to not only an industry, but to a field of medicine that will gain traction as we move into the 21st century further and becomes a systems biology functional approach towards health care. Really epic kinds of landmark discussions.

Let me, if I can, say a few things about Dr. Hoffer's contributions, for those of you who might want a little additional information. Dr. Hoffer has two sons, one of whom is a research professor of medicine at McGill University, at the Lady Davis Institute for Medical Research and the Jewish General Hospital in Montreal, Quebec, Canada. He is also an MD, PhD; this is Leonard John Hoffer. I was very intrigued to learn, showing coincidence in life, that Dr. John Hoffer was a doctoral student at the same time that our own Dr. Bob Lerman was getting his PhD in nutrition at MIT and so they shared the same department and the same research professor as medical doctors going through their PhD programs in nutrition. Dr. Lerman is one of our chief investigators and our clinical directors in our functional medicine clinical research center. It is kind of, again, showing the consanguinity of knowledge and interaction in kind of how ideas spread from individuals who share intellectual domains and sometimes even physical domains and how these contacts can create spreading effects in terms of the stickiness of new ideas.

Dr. Hoffer, who obviously grew up in the environment with his father (you can only imagine what was talked about around the dinner table), ultimately moved on to become a psychiatrist on his own and also a PhD in sciences. He has been studying many, many things from a basic and clinical science perspective, one of which is to revisit these vitamin therapy and schizophrenia discoveries that his father had made. In a recent review paper that he authored in the *Journal of Psychiatry and Related Sciences* (this is in 2008), he talks about the fact that "it is dismaying that well into the 21st century, schizophrenia remains a highly prevalent, devastating, and poorly understood disease for which the only accepted therapy is non-specific antipsychotic and antiseizure medication."²⁶ He goes on to say that, "Fresh approaches, even unconventional ones, should be welcomed for study by the psychiatric community if they are biologically plausible and non-toxic." In a review article-this article in 2008-he summarizes the evidence that certain vitamin insufficiencies can worsen the symptoms of schizophrenia, and the evidence that at doses of certain vitamins could improve the core metabolic abnormalities that predispose some people to develop it. It rounds the history, in this article, of the controversial vitamin-based therapy that his father and Humphry Osmond discovered for schizophrenia, called orthomolecular psychiatry, and the collaborative work with Dr. Linus Pauling that you heard Dr. Abram Hoffer talk about in his interview. He ultimately concludes, in this review article, advocating a process for discovering promising new schizophrenia therapies that involve small, carefully conducted clinical trials of nutrient combinations in appropriately

selected patients. This is, again, part of the evolving frontier of this paradigm that we have been describing to look at nutrient insufficiencies from an orthomolecular genetotropic disease perspective, and to modulate them in the individual needs (personalized nutrition or personalized medicine, in this case) to improve their function.

It is currently popular to regard schizophrenia as a multiple hit, neurodevelopmental disorder, but equally plausible is the older hypothesis of a toxic psychosis triggered by an abnormal endogenous metabolite. Organic brain disorders, including indistinguishable forms of schizophrenia, may be induced by certain drugs and by neurological, metabolic, and inflammatory and infectious diseases. Such disorders account for approximately five percent of cases initially diagnosed as first episode schizophrenia by expert psychiatrists. We start thinking that maybe not all forms of schizophrenia come from nutrient insufficiencies because it is a heterogeneous diagnosis, but if we could pick out those that are responsive to nutrient insufficiencies we might be able to get very marked clinical improvement in some percentage. Who knows if that percentage is 5, 10, or 20 percent or whatever it might be based upon a more personalized approach that is dependent upon proper assessment, so this has to go back to proper biochemical assessment: asking the right questions to get the right answers. If you don't ask the right questions, you never get the answers.

What kind of assessment do we do for looking at general nutritional status and biochemical individual needs and this whole genetotropic origin in the soil that Archibald Garrod talked about at the turn of the 19th to the 20th century? With that in mind, it leads us into this concept that, as Dr. Abram Hoffer pointed out, the signs of schizophrenia look very similar in presentation to part of the triad of presenting symptoms of pellagra: dermatitis, diarrhea, and dementia. These dementia-like affects resemble very closely some of the things that are associated with schizophreniform presentations.

As we get into this whole metabolite question and we start looking at genetic metabolism diseases associated with nutrient need, like cystemia or pellagrous dementia or things that are related to beriberi, or things that are related to issues of various megaloblastic anemias, we see that they all have kind of the schizophreniform affects that are presented in the individuals, suggesting metabolite toxicity, to use a term loosely, that has been seen as a consequence of insufficiency of specific nutrients needed by the genetic uniqueness of that individual. So we not only have niacin (vitamin B3), but pyridoxine (B6), and evidence on folic acid, and evidence on ascorbic acid. There's good data on all of these having influences on metabolic function in genetically unique individuals that can lower the load of secondary toxic metabolites.

So I think we are starting to witness maybe a revisiting of this now 50-year-old model that was presented by Dr. Hoffer. He talked about it in his interview, and I find it very, very interesting, because if you look at Dr. Hoffer's original papers, what you will find that these papers that appeared in *The Lancet* really discussed this metabolite hypothesis in a very, very, what I would consider precise way, given the knowledge we had about physiological chemistry in the middle 20th century. We have kind of dismissed these out of hand for reasons that are not easily understandable, and we've kind of from that, then, just said, "Well, we need to find drugs to block the function or to arrest a certain outcome and to treat a symptom without looking deeper at where the cause of these conditions that we call schizophrenia might originate." I think this paper that appeared in *The Lancet*, again, in the same period of time (in the early 50s and 1960s)-this actually was titled "Massive Niacin Treatment in Schizophrenia: Review of a 9-Year Study."²⁷ This was Abram Hoffer and Humphry Osmond in *The Lancet*, 1962. It's a classic. They go on

to say (as Dr. Hoffer in his interview pointed out), their interest in niacin began at the end of 1951 when exploring ideas developed with Dr. John Smythies. By the way, that's the same John Smythies that you probably know is credited with having the observation that neural tube defects are found in babies born by mothers who are suffering from folic acid insufficiency. It took some 50 years from the discovery of Smythies of this association between B vitamin deficiencies and encephalopathy and neural tube defects (the most common birth defects) before that was generally accepted.

In these discussions among Humphry Osmond, Abram Hoffer, and John Smythies was born this niacin concept. He goes on to say, "We thought that schizophrenia might be caused by a disorder of adrenaline metabolism in which the body produced a substance with metabolic toxicity that induced psychological effects that were similar to that of, say, some of the psychotropic drugs, like mescaline or D-lysergic acid diethylamide (LSD). These ideas have since been called the adrenaline or adrenochrome metabolite theory of schizophrenia and it is a special example of that particular theory. I think that these conceptual frameworks, which maybe were dismissed early on when they were first presented and published are now being revisited in the age of metabolic medicine and the age of network and systems biology.

That takes us to a further reflection on Dr. Pauling's work because what we really said is that maybe there is something about general function that is related to immune defense, and to cell repair, and cell replication that has to do with individual nutritional status. This has its roots in the concept of orthomolecular medicine. I found a very interesting kind of example of this that appeared in the journal *Neurology* in 2008 in which the investigators-this is a group from the VA Medical Center in Oklahoma City-reported that intervening, post-stroke, in patients with an intensive nutritional supplement program significantly improved their outcomes.²⁸ They wrote that intensive nutritional supplementation using readily available commercial preparations was found to improve motor recovery in previously undernourished patients receiving intensive in-patient rehabilitation after stroke, and therefore an induced effect (in this case, a stroke event) may enhance the level of need of specific nutrients for improving outcome in a post-stroke situation. Again, it's a whole series of variables: genetic uniqueness coupled with environmental factors give rise to the individual need for specific nutrients, and one size doesn't fit all, and it's not just on the back of a cereal box that you learn about what the level of nutrients are for optimal function of that individual. I think that's a very interesting kind conceptual framework as it pertains to this emerging theme that both Dr. Pauling and Dr. Hoffer talked about.

The vitamin C and cancer story was a fully engaged discussion when I was at the Pauling Institute as a Research Scientist back in the early 1980s (at the time I interviewed Dr. Pauling). There was very strong criticism of the concept of vitamin C and cancer (the Ewan Cameron and Linus Pauling concept). In fact, Dr. Moertel, who was one of the principals in oncology at the Mayo Clinic, made a very big story about debunking (supposedly) the vitamin C/cancer connection, but now we come to the more recent period of the 21st century and we see this magnificent bit of work and paper that was authored by Dr. Baltz Frye and Steve Lawson, from the Linus Pauling Institute at Oregon State University that appeared in the *Proceedings of the National Academy of Sciences* in 2008.²⁹ In this paper they write about vitamin C and cancer being revisited in light of the more recent work that has been published on vitamin C and cancer by Chen, et al, titled "Pharmacological Doses of Ascorbate Act as a Pro-oxidant and Decrease Growth of Aggressive Tumor Xenographs in Animals."³⁰ This was another *Proceedings of the National Academies of Science* paper from 2008.

There is also some extraordinary work that's been done at the NIH looking at the graded doses of vitamin

C in humans as it pertains to individual needs, showing the diversity of need using in situ kinetics. This is Mark Levine's work. He is an endocrinologist at NIH who has found that the level of need of vitamin C from person to person is far greater than we thought. And then we get into therapeutic doses of vitamin C, where we are actually using vitamin C intravenously as a potential selective pro-oxidant to induce, in cells that have been transformed that have poor antioxidant defense mechanism, selective alteration in their reactive oxygen species production, causing internal cell suicide to occur (apoptosis). What we are starting to see is that millimolar concentrations of extracellular vitamin C kill cancer cells in these xenographed animals but not normal cells, once again reopening what Dr. Pauling had talked about with Dr. Cameron back in the 1970s and 1980s.

Today, new methods for understanding of the role that particular augmented levels of certain nutrients (in this case, vitamin C) might have as therapeutic agents-safe, non-toxic therapeutic agents-are being explored. I think the story is not over. It is continuing to be revisited, and what Dr. Pauling talked about in this interview in 1982 is still emerging to be seen today. A very nice paper authored by Dr. Leonard John Hoffer and Dr. Mark Levine-this was a Phase I clinical trial of IV ascorbic acid in advanced malignancy (a human intervention trial)-was published in the *Annals of Oncology* in 2008.³¹ This group of investigators reported that high doses of intravenous vitamin C was well tolerated. They were unable to demonstrate, in this phase I study, anti-cancer activity when administered to patients with previously treated advanced malignancies, however what they say is that there might be benefit synergistic administration of vitamin C, intravenously, with other cytotoxic or redox-active molecules to enhance the cytotoxicity in a selective way.

Work is still ongoing. We are still learning more about this story. We are still learning about the different nutritional needs of the individual as determined by their genetics and therapeutic nutrition-what we call nutritional pharmacology (enhanced levels of specific nutrients beyond that that you would use for normal maintenance for therapeutic application in disease states or environmentally altered physiology). We still have a lot of confusion in the epidemiological literature about how important some of these antioxidant vitamins are in helping to protect function and enhance health over the long term and reduce the risk of disease. We have papers like one that appeared in the *Journal of the American Medical Association* in 2008 titled "Vitamin E and C in the Prevention of Cardiovascular Disease in Men."³² In this large, long-term trial of male physicians, it was reported that neither vitamin E or C supplementation reduced the risk of major cardiovascular events and the data do provide not support for the use of these supplements for the prevention of cardiovascular disease. However, again, we have to kind of ask the question: Is there data lost in the mass? Should we be stratifying the data? Should we be looking at those cohorts that are most genetically unique and susceptible? Should we be screening for biomarkers that are more likely to be responsive so we don't lose them in the mass of the non-responders because we didn't tease out those that are most uniquely at risk? The same thing can hold true for sodium restriction and hypertension, or cholesterol/dietary restrictions and hypercholesterolemia. There are a myriad of examples of individuals who have specifically higher risk to certain things as a consequence of their environmental choices versus the body politic.

One can even use gluten as an example. Not everybody has gluten sensitivity, but for those individuals who do have gluten intolerance, the food which may be good for one becomes the poison for another. They may be lost in the mass of a large study, but this is very real for those people who end up with celiac sprue and who may be, statistically, an aberration in a large study. For them, eating wheat is very dangerous.

By the same token, we might say that concept could be applied to things like the roles various vitamin supplements and nutrient supplements have on modulation of relative risk in individuals with unique susceptibility. Their data points get lost in the mass of those that are non-responders because not everybody needs the same thing, and we make decisions from the law of averages. Dr. Roger Williams said something very powerful about this. He said, "Nutrition is for real people. Statistical humans are of little interest." Yet as we look at the history of the way we learn about therapeutic applications of various agents, we recognize that we often apply them to 70 kilogram mythical humans (the statistical average). We regress to the mean. Sometimes you can regress to the mean and lose all your value of specificity. I believe that in this age of personalization and genomics, what we are going to recognize is that we lost a lot of very important data by just throwing them out as the law of the averages, losing them in the noise. This might even be true for autism and the relationship of autistic disorders to MMR vaccination. It may be that in the gross level of children there is very low penetrance of the susceptibility to MMR being the etiological trigger for autism, but in a small percentage of individual children, this may be a real trigger for immunological activation, and as a consequence for them, they end up with a neurological risk that is lost in the average of means.

I suggest that we are moving from this "massification" concept of medicine to a personalization concept of medicine. The individual has primacy. The statistical human is of lower interest. It's much easier to do statistical studies and to group everybody together. That makes it fairly simple. It is much more complicated when you start stratifying and looking at differential effects, and individualization, and biochemical individuality, and orthomolecular and systems biology. That's certainly a more complicated situation.

If we have squeezed out all of the value-the low-hanging fruit, so to speak-of the single agent against single outcome, maybe it is time (if we are really going to rectangularize the survival curve for compressed morbidity and increase the health span) that we start to look at this new model-this systems biology model, this differential biochemically stratified model-looking at individuality that is really born out of the discoveries of Archibald Garrod and geneticists of the transition of the 19th to the 20th century and moving in to the transition of genomics, as a paradigm, in the 21st century. This is ultimately leading into systems biology, which is the future of where functional medicine and functional nutrition is going.

I hope that you appreciate that what you have just witnessed (by listening to the interviews with Dr. Pauling and Dr. Hoffer) is really the birthing of what has taken more than a hundred years to evolve and to mature. This is a paradigm shift in thinking-a frame shift in the way we see the origin of disease, this new lens of filtering information through. It's not just an individual therapy that we're talking about, it's a conceptual shift in the framework of how we understand and manage chronic age-related diseases at the individual level, at the patient-specific level, at that moment that we are in the exam room with that patient at that senescent, humanistic level of discourse about how to manifest the appropriate program for them. It is not the program for the average, but the program for that individual patient as they present with their antecedents and triggers, exposing them to their mediators, which ultimately creates their signs and symptoms.

This is the functional medicine model. This is what we have been talking about for more than 20 years. I believe that it is starting to gain traction, gain an understanding, gain fundamental science that supports the paradigm, and now the challenge is finding ways to really apply this effectively in the clinic. I hope what you have learned from the discussions with Dr. Pauling and Dr. Hoffer is that we are on this journey together. It is one step at a time. It is an evolving paradigm. But truth is its own victory. It wills out in the

end, and there is a fundamental truth to this model that is emerging that will ultimately deliver a more effective patient-centered medicine that results in better patient outcome and ultimately achieves what Dr. Pauling and his wife, Ava Helen, talked about with me years ago when I asked them why the Pauling Institute of Science and Medicine was born, and he said, very simply, "It was to find ways to reduce human suffering." I think this model that we are describing can deliver that outcome in a humanistic, cost-effective way.

Thanks so much for listening to this epic version of Functional Medicine Update. I think this will stand, timeless, when we go back and re-listen, in years to come, to Dr. Pauling and Dr. Hoffer and their prescient view of the future of medicine.

Bibliography

- 1 Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. *Yale J Biol Med.* 2002;75(4):221-231. (Originally published in *The Lancet*, pp. 1616-1620, 1902.)
- 2 Neel JV. The inheritance of sickle cell anemia. *Science.* 1949;110:64-66.
- 3 Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. *Science.* 1949;110:543-548.
- 4 Williams RJ, Beerstecher E, Berry LJ. The concept of genetotrophic disease. *Lancet.* 1950(6599):287-289.
- 5 Williams RJ. Concept of genetotrophic disease. *Nutr Rev.* 1950;8(9):257-260.
- 6 Pauling L. Orthomolecular psychiatry. Varying the concentrations of substances normally present in the human body may control mental disease. *Science.* 1968;160(825):265-271.
- 7 Ames BA, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K_m): relevance to genetic disease and polymorphisms. *Am J Clin Nutr.* 002;75:616-658.
- 8 Yamafuji K, Nakamura Y, Omura H, Soeda T, Gyotoku K. Antitumor potency of ascorbic, dehydroascorbic, or 2,3-diketogulonic acid and their action on deoxyribonucleic acid. *Z Krebsforsch Klin Onkol Cancer Res Clin Oncol.* 1971;76(1):1-7.
- 9 Vallance S. Leucocyte ascorbic acid and the leucocyte count. *Br J Nutr.* 1979;41(3):409-411.
- 10 Enstrom JE, Pauling L. Mortality among health-conscious elderly Californians. *Proc Natl Acad Sci USA.* 1982;79(19):6023-6027.
- 11 Johnson GE, Obenshain SS. Nonresponsiveness of serum high-density lipoprotein-cholesterol to high dose ascorbic acid administration in normal men. *Am J Clin Nutr.* 1981;34:2088-2091.
- 12 Ginter E. Ascorbic acid in cholesterol and bile acid metabolism. *Ann N Y Acad Sci.*

1975;258:410-421.

13 Hornig D, Weiser H. Ascorbic acid and cholesterol: effect of graded oral intakes on cholesterol conversion to bile acids in guinea-pigs. *Experientia*. 1976;32(6):687-689.

14 Sestili MA. Possible adverse health effects of vitamin C and ascorbic acid. *Semin Oncol*. 1983;10(3):299-304

15 Herbert V, Jacob E, Wong KT. Destruction of vitamin B12 by vitamin C. *Am J Clin Nutr*. 1977;30(3):297-299.

16 Finley EB, Cerklewski FL. Influence of ascorbic acid supplementation on copper status in young adult men. *Am J Clin Nutr*. 1983;37(4):553-556.

17 Pauling L. *Vitamin C and the Common Cold*. WH Freeman & Company. San Francisco: 1970.

18 Anderson TW. Large scale studies with vitamin C. *Acta Vitaminol Enzymol*. 1977;31(1-5):43-50.

19 Cathcart RF. Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy. *Med Hypotheses*. 1981;7(11):1359-1376.

20 Pauling L. Vitamin C and longevity. *Agressologie*. 1983;24(7):317-319.

21 Osmond H, Smythies J. Schizophrenia: a new approach. *J Mental Sci*. 1952;98:309-315.

22 Hoffer A, Osmond H, Callbeck MJ, Kahan I. Treatment of schizophrenia with nicotinic acid and nicotinamide. *J Clin Exp Psychopathol*. 1957;18(2):131-158.

23 Hawkins DR and Linus Pauling. *Orthomolecular Psychiatry*. WH Freeman & Co. San Francisco: 1973.

24 Hoffer A and Harry Foster. *Feel Better, Live Longer with Vitamin B-3: Nutrient Deficiency and Dependency*. CCNM Press. Toronto: 2007.

25 Horrobin DF. *The Madness of Adam and Eve: How Schizophrenia Shaped Humanity*. Bantam Press. New York: 2002.

26 Hoffer LJ. Vitamin therapy in schizophrenia. *Isr J Psychiatry Relat Sci*. 2008;45(1):3-10.

27 Osmond H, Hoffer A. Massive niacin treatment in schizophrenia. *Lancet*. 1962;1(7724):316-319.

28 Rabadi MH, Coar PL, Lukin M, Lesser M, Blass JP. Intensive nutritional supplements can improve outcomes in stroke rehabilitation. *Neurology*. 2008;71(23):1856-1861.

29 Frei B, Lawson S. Vitamin C and cancer revisited. *Proc Natl Acad Sci USA*. 2008;105(32):11037-11038.

30 Chen Q, Espey MG, Sun AY, Pooput C, Kirk KL, et al. Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenographs in mice. *Proc Natl Acad Sci USA*. 2008;105(32):11105-11109.

31 Hoffer LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, et al. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. *Ann Oncol*. 2008;19:1969-1974.

32 Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C. Vitamins E and C in the prevention of cardiovascular disease in men. The physicians' health study II randomized controlled trial. *JAMA*. 2008;300(18):2123-2133.p>