Neurobiochemistry: A New Paradigm for Managing Brain Biochemical Disturbances

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More than 40 years ago, Abram Hoffer, M.D., Ph.D., and Humphry Osmond, M.D., introduced a concept of how the brain works at the molecular level and how defects in this complex system relate to schizophrenia.. This early work opened up the field which was later called biological psychiatry, or Orthomolecular medicine.[1,2]

Because the traditional psychiatric medical model is not working for many people, interest has increased in the Hoffer/Osmond concepts. The present psychiatric model provides therapeutic benefit for a number of crisis disorders, but for many chronic metabolic conditions of the brain, in which a complex milieu of interlocking biochemical and physiological processes are at work, this approach has significant limitations. An expanded therapeutic model, derived from the pioneering brain biochemistry work of Drs. Hoffer and Osmond is now being tested in clinical and laboratory research. This expanded model is based upon an understanding of the duration, intensity and frequency of mental health symptoms and their relationship to brain biochemical patterns. For the past four years my colleagues and I have employed a questionnaire which evaluates symptomatologies on a patient-specific basis. Leo Galland, M.D., developed the term "patient-centered diagnosis" to describe this method of assessment, using the patient as his or her own internal control, examining the individual's functional physiological ability without the limitation of disease attribution.[3]

The three page Metabolic Screening Questionnaire asks the patient to rank organ-specific intensity, duration and frequency of symptoms on a scale of 0 to +4. This questionnaire, which was developed from the Cornell Medical Index, has been used to evaluate several thousand people during the past four years. We have found the data from this questionnaire correlate very well with the Medical Outcome Survey Short Form 36 developed by the New England Medical Center, which has been validated by extensive research defining it as an effective quality-of-life assessment tool.[4] We have found the Metabolic Screening Questionnaire to be much less time-consuming to fill out and that there is a correlation of approximately 0.8 between the two questionnaires.

The relationship between the information derived from this questionnaire and nervous, immune, endocrine and gastrointestinal system dysfunctions, led to the hypothesis that many chronic mental and physical health problems are related to the accumulation of metabolic toxins. Examples of these metabolic toxins include the neurotoxins adrenoleutin and adrenochrome, which are derived from epinephrine. There are literally thousands of molecules, both native to human physiology and of exogenous origin, that could impair neurobiochemical function at some concentration.

The Relationship between Toxins and Nervous System Function

There is a very complex relationship between the concentration of various substances within the neuron and the function of the nervous system. The concentration of these substances changes throughout the day, with one's circadian rhythms and age, experiences, stress level, environment, drugs and alcohol consumption, the functional status of his or her gastrointestinal and hepatobiliary systems, and the diet. The analysis of the metabolite/toxin patterns can be accomplished using pattern recognition, sophisticated mathematical methods and computer technology. What is emerging is the recognition that a number of brain disturbances result from the accumulation of various patterns of neuro-active substances of both endogenous and exogenous origin.

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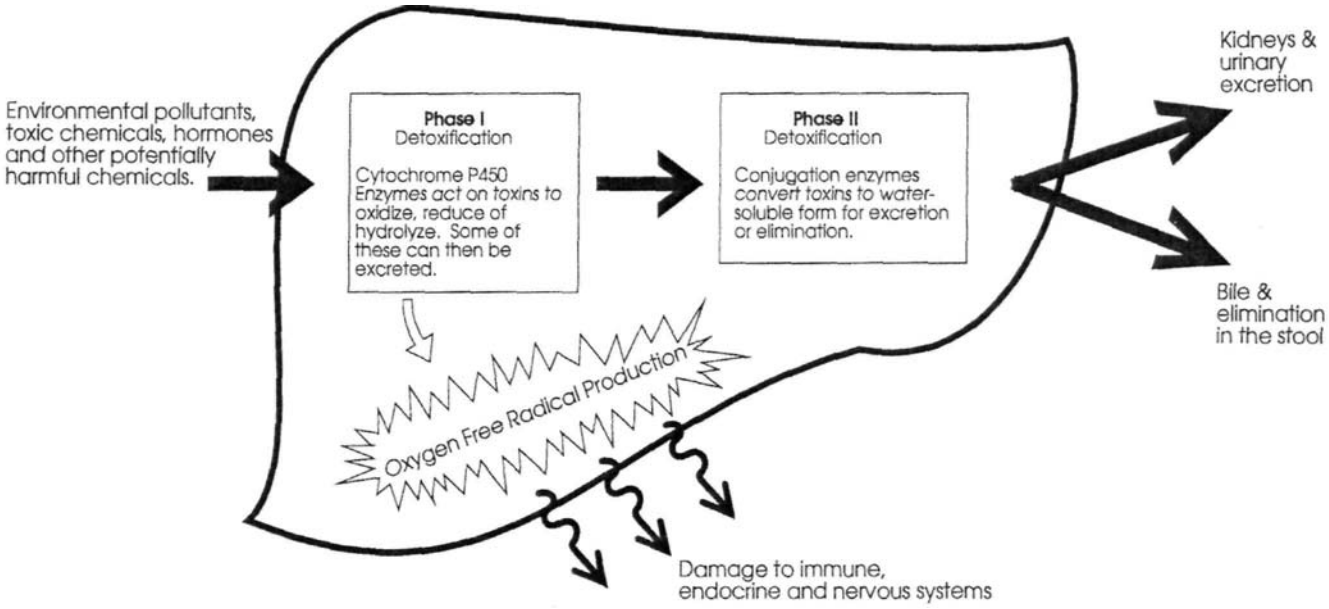
Figure 1. Detoxification in the Liver

The body's ability to rid itself of toxic substances from the environment is dependent upon proper function of the liver. In the liver, detoxification occurs in two general phases. Each of these phases may be reduced or enhanced in activity, depending upon availability of critical nutrients.



Many neurotoxins in systemic circulation are detoxified by the liver. There are two metabolic steps by which the liver transforms most of these toxic "foreign" substances into nontoxic derivatives which are excreted with the bile (in the feces) and in the urine. These steps are shown in Figure 1. These substances may be of exogenous origin, originating in the external world, or they may be endogenously produced, having built up in the brain or other tissues due to an error of metabolism.[5]

The first step in hepatic detoxification involves the cytochrome P450 mixed-function oxidase super-family of enzymes. There are many different types (isozymes) of cytochrome P450 with abilities to remove different chemicals from the bloodstream by an oxidative process. The cytochrome P450 family of enzymes produces in the liver an intermediate series of compounds called oxygenated metabolites, or biotransformed intermediates, which can be even more toxic than the original substances. Fasting as a method of detoxification can increase the level of biotransformed intermediates in the body. Some individuals continue to get more severe symptoms as they fast, because their liver's Phase II enzyme systems cannot keep up with the load of biotransformed intermediates with which they are presented.

In Phase II of detoxification, the oxygenated or biotransformed intermediates are converted to nontoxic byproducts that can be excreted. They go into the bile if they are higher molecular weight toxins, or into the urine if they are of lower molecular weight. This second stage is called the conjugation stage of detoxification. The liver has six separate pathways for converting these transformed intermediates to nontoxic derivatives. They include amino acid conjugation, glucuronidation, acetylation, sulfation, sulfoxidation and glutathione conjugation. The ability of the liver to detoxify toxic substances, therefore, depends upon the activity and balance of both the Phase I and Phase II enzyme systems. If they are not working in balance, toxins which can alter brain chemistry and behavior can accumulate.[6]

In our research, we have found that both Phase I and Phase II detoxification systems can be modified through specific nutritional intervention. If a person is undernourished, then he or she is less able to detoxify various toxins. If you give inadequately nourished individuals the right balance of nutrients (at

required doses that may be higher than the Recommended Dietary Allowance), their detoxification ability and symptoms of many functional neurological disorders improve.[7]

The origin of many toxic substances with which the liver must cope is the gastrointestinal tract. Hundreds of substances which originate from bacterial action in the gut cross the GI mucosal border in apparently healthy people, and all of these substances must be detoxified by the liver. Therefore, an individual's ability to protect against brain-active substances depends upon the status of the intestinal flora, GI mucosal function and hepatic detoxification ability.[8] *A* permeable GI mucosa is known as a leaky gut. When the gut becomes leaky, more substances are delivered to the liver, and if the liver's functional ability to detoxify is impaired, more metabolically active substances are delivered through the bloodstream to other tissues, including the brain.[9]

In a study of brain-injured children at the Institutes for the Achievement of Human Potential in Philadelphia, Pennsylvania, we have found that many of these children have an impaired gut/liver detoxification system. They are, therefore, exposed to more toxins originating in their gut, potentially overloading their liver detoxification system, resulting in an adverse impact on their brain chemistry.

Pattern Recognition Analysis and Gut/Liver Function

Wayne Matson, Ph.D., vice-president of ESA, Inc., in Massachusetts, has developed a technology which makes it possible, using a very small volume of plasma, urine or cerebral spinal fluid, to analyze simultaneously more than 5,000 metabolites. Through cluster analysis of these metabolites, certain patterns have been identified, making it possible to design specific nutritional therapies to improve gut and liver detoxification function. This technology has been used as part of the program at the Institutes for the Achievement of Human Potential to differentiate the metabolite clustering of individuals with midbrain or cortical brain injuries from that of individuals who have autism or epilepsy.[10]

From these observations we have been exploring how various brain metabolite patterns relate to the gut/liver connection. We have confirmed that various factors, such as medications, alcohol, allergies, autoimmune disorders, dysbiosis, environmental toxins and substance abuse all impact the barrier of defense called the gut mucosa." When the gut mucosa is disturbed, permeability increases, facilitating the passage of various substances to the liver. Ten percent of the liver by weight is composed of cells called Kupffer cells, which are imbedded lymphocytes; therefore, the liver is in part an immune system organ. When the Kupffer cells of the liver are activated by antigens passing across the permeable GI mucosa, they trigger the release of chemical messengers, lymphokines and cytokines, represented by interleukins 1, 2, 6, 12, tumor necrosis factor and gamma interferon. [12] These substances travel to target tissues, including the blood/brain barrier, altering cellular function. This altered function results in modification of biological response in the immune, endocrine and nervous systems. Many chronic symptomatologies may be a manifestation of the continued chronic release of cytokines which, in a sense, represent the cellular messengers, resulting from a continued "toxic" insult.

Oxidative Stress and Neurobiochemistry

Secondarily, when the liver is engaged in trying to detoxify nervous system-active toxins and drugs, it also produces oxidant stress byproducts, such as superoxide, hydroxyl radical, hydrogen peroxide and singlet oxygen, which are very reactive molecules. These molecules react rapidly with structural protein, enzymes, DNA or membrane lipids, resulting in nonspecific tissue damage. Therefore, an overly active detoxification system, due to an abundance of substances the liver has to detoxify, enhances oxidative stress, which requires more antioxidant protection. The principal damaging effects of oxidative stress are manifest in oxygen-sensitive tissues, such as the brain, kidneys, heart, blood and lungs.[13]

In our research with brain-injured children, when we examined whole blood reduced glutathione levels, we found that many of them had very low levels of this important antioxidant which circulates in the blood. Whole blood reduced glutathione is reflective of the redox (reduction/oxidation) potential of the whole body, and a low level of blood glutathione indicates the body is under con-

siderable oxidative stress. In other words, many of these brain-injured children either were not able to synthesize glutathione, or they were under high oxidative stress that was causing depletion. Therefore, we concluded, children who had sustained brain stem, cortical or midbrain injuries in general had very high levels of oxidative stress, which meant that toxins (oxidants) were affecting their brain chemistry. Protection against these oxidant stress reactions is provided by antioxidants. The need for these protective substances, which include vitamins C and E, bioflavonoids, and the enzyme-activating minerals zinc, copper, manganese and selenium, may be much higher in an oxidatively stressed individual.

Another condition which is associated with very low levels of whole blood reduced glutathione and high levels of oxidative stress is AIDS encephalopathy. It is believed that the condition that damages the brains of terminal AIDS patients is, once again, the depletion of antioxidant protection, such as glutathione, due to high oxidant stress load.[14] When examining data from studying the brain-injured children, we concluded there might be something significant about oxygen toxicity, or free radical toxicity, in these children. Paradoxically, the time when the brain is most subject to oxidative stress is the time when it has the least oxygen available. Children who suffer from various neurological problems generally exhibit shallow breathing, little activity, compressed chest, poor posture and low oxygen tension. If they have had some kind of brain injury, they might also have suffered vascular damage that prevents proper oxygen delivery.

If the brain is deprived of oxygen, the mitochondria in the neurons cannot produce energy properly, and oxygen becomes a limiting nutrient. When oxygen becomes a limiting nutrient to the brain, the brain cannot build its energy-carrying intermediates, such as adenosine triphosphate (ATP). If the brain can't build ATP, that substance is quickly broken down into a number of other substances. An enzyme in the nervous system, xanthine oxidase, becomes activated, as shown in Figure 2. The xanthine oxidase enzyme tries to clear xanthine from the body to produce uric acid, and in doing so it creates superoxide as a byproduct. In the presence of iron or hemoglobin, superoxide is converted into hydroxyl radical, which quickly contributes to further damage of the brain. Therefore, the time of lowest oxygen tension, when oxygen is the limiting nutrient in the brain, is when the brain is under highest oxidative stress and incurs the most damage.[15]

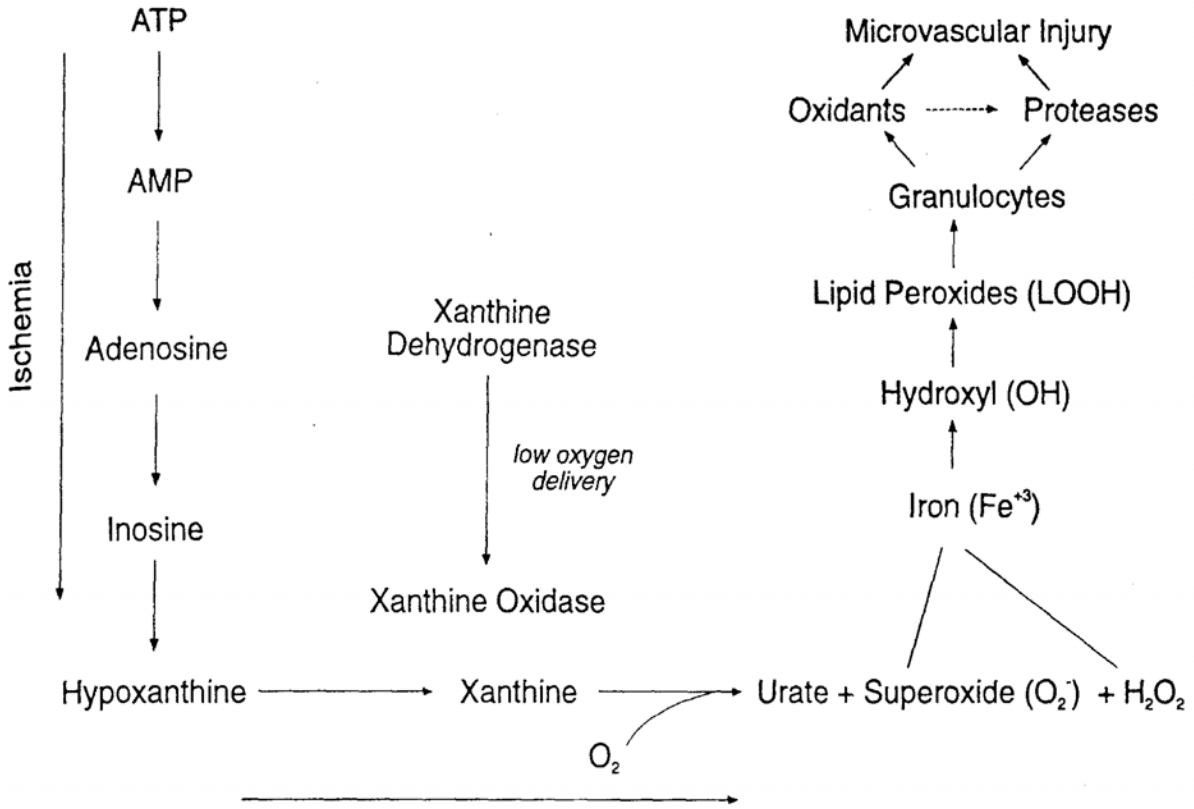
Oxygen-Antioxidant Therapy for Brain-Injured Kids

In conditions of high oxidative stress, anything one can do to increase oxygen tension to the brain and reduce the deleterious effects of oxygen free radicals might be considered beneficial. This includes administering ascorbate (vitamin C), tocopherol (vitamin E), Carotenoids, bioflavonoids and coenzyme Q10, all of which are nervous system-protective nutrients. (Incidentally, they also protect other oxygen-rich tissues, such as those in the heart, blood and liver.) It is important to increase oxygenation of the tissue which, in the case of these brain-injured children, means getting them to breathe deeply and start moving and participating in physical therapy. When the nutritional intake includes an enhanced intake of antioxidants, and they are exposed to exercise through a graded program of physical therapy, their depressed glutathione levels begin to rise to normal. Many of the altered brain neurochemicals, such as metabolites of epinephrine, dopamine and serotonin, start to improve or normalize with such a program, because the metabolism of dopamine and serotonin families of neurochemicals is controlled in part by the redox potential of the nervous system.

Methods of evaluating the redox potential of the nervous system in neurobiochemistry have only recently begun to be utilized. In doing so we have seen that altered neurochemicals often relate to the inefficient use of oxygen or the unavailability of redox agents like vitamin C, vitamin E, carotene, bioflavonoids and coenzyme Q10. This new method of evaluation may provide a whole new fundamental methodology for modifying nervous system function in individuals who have altered neuronal oxidation-reduction function.

In the nervous system, the power of the neuron is generated by the same type of metabolic process that generates energy for the rest of the tissues of the body, through the metabolic activity of the mitochondria. In the

Figure 2. Proposed role for xanthine oxidase, reactive oxygen metabolites and granulocytes (neutrophils) in ischemia/reperfusion-induced injury.



mitochondria, oxygen is combined with nutrient-derived substrates to give rise to metabolic energy. The neurons use that metabolic energy for the synthesis and release of neurotransmitters and neurochemicals which are transmitted through the body where they affect the modification of organ system functions. In other words, activation of the nervous system stimulates the process of oxidative phosphorylation in the production of neurotransmitters and neuromodulators such as serotonin, dopamine and noradrenaline and their metabolites, which subsequently must also be detoxified. In fact, through their metabolic activity, the neurons are responsible for the production and metabolism of a complex array of intermediary metabolites. If the neurons have been subjected to chemical, oxidative or traumatic stress (from injury or accident), altered concentrations of these metabolites develop, and physiological process is modified. There is a relationship, therefore, between neuronal biochemistry, detoxification mechanisms, the overall toxic load on the body, and cognitive and emotional function. If a child has sustained a brain injury resulting in an ischemic event (a state of low oxygen tension in the nervous system), that event increases the toxins produced as byproducts of altered neuronal biochemistry. This may be further complicated by chronic gastrointestinal infection (e.g., dysbiosis) and the associated leaky gut. The liver then is exposed to other toxins it has to process, producing increased oxidative stress reactions. The cumulative effects of all these factors can be expressed as altered function of the nervous, immune and endocrine systems.

Nutritional Modulation of Neuronal Biochemistry

Although the brain represents only 6 percent of body weight, it consumes between a quarter and a third of the body's oxygen and blood sugar. A very metabolically hungry organ, the brain is fueled by blood sugar, glucose. It converts sugar into energy through the Krebs cycle in the mitochondria, then through the electron transport chain, eventually producing high energy-carrying interme-

diates such as ADP and NADPH. These are potential energy sources the brain uses to manufacture neurotransmitters and neuroregulators and to power nerve depolarization which transmits electrical impulses down the nerves. This process requires the proper use of oxygen by the neuron in its metabolism. If oxygen is used improperly in the neuron, however, it can produce intermediate compounds (such as superoxide or hydroxyl radical), which are highly toxic to the nervous system.

An example of this process has recently been reported by a team of scientists in Amsterdam who deal with molecular diseases.[16] The case concerned a nine-year-old boy with neuropathy of unknown origin. When this boy was born he appeared to be normal, but as he developed he was unable to walk. He had very poor muscle tone, and since age two he had been confined to a wheelchair. He had undergone extensive neurological evaluation, but the origin of the condition was not known. Finally, he was evaluated using Phosphorus 31 Nuclear Magnetic Resonance Spectroscopy, which noninvasively measures the metabolic energy in tissue.

With the aid of this instrument, it was determined that the boy was suffering from a breakdown in mitochondrial energy production in the neuron as a consequence of the genetic impairment of a single enzyme, pyruvate dehydrogenase complex IV, which represents a major metabolic control point in the neuron. The impairment of this enzyme resulted in the production of oxygen free radicals which were damaging the boy's nervous and muscular systems. It was as though a metabolic wire, which we call the electron transport chain, had lost its insulation and was shorting out.

The doctors who were treating the boy concluded that the only way to "detoxify" the free radicals and "put the insulation back" on the electron transport chain was to give him very high doses of antioxidants. They administered what they had concluded was a saturation level of vitamin E at 2000 IU per day. (The RDA is 15-30 IU.) After several weeks of supplementation the ATP ratio in his resting muscle had improved considerably. Although it was still not totally normal, it was much more nearly normal. He was producing fewer damaging free radicals to cause alteration of his mitochondrial energy production. Most important of all, after vitamin E therapy he was able to walk for the first time.

Neurotoxicity and Alterations in Brain Chemistry

There may be a relationship between this model and the expression of various forms of neurological disorders as well. Several recently published papers have described the buildup of benzodiazepine-like substances in the blood of some individuals at concentrations high enough to alter brain chemistry.[17] Benzodiazepine is the active ingredient in diazepam (Valium). The patients described in these articles never consumed any diazepam-containing drugs, but their blood contained pharmacologically active concentrations of these benzodiazepine-like substances. Where they came from is still unknown, but it has been suggested that they may have come from the synthesis of bacteria in the gut, alterations of the metabolism of nitrogenous compounds in the liver, neuronal biosynthesis, or even from certain foods. Potatoes and wheat both naturally contain very small amounts of benzodiazepines.[18] The levels in these foods, however, are too low to account for the pharmacological concentrations of benzodiazepines found in these patients, unless the individuals' detoxification processes for diazepines were impaired, preventing the elimination of these substances they consumed in wheat and potatoes.

When we examined apparently healthy people's ability to detoxify these substances, we were surprised to find individuals may differ from one another by as much as 30-fold in their detoxification ability. People with environmental sensitivities, who are traumatized by exposure to chemicals in their environment, may be much more sensitive to various substances because they can't detoxify them efficiently. These differences in detoxification ability from one person to another may account for alterations in brain biochemistry and behavior seen in some chemically sensitive people.

It has recently been reported that there are individuals who typically lead what seems like a normal life and then suddenly fall into a stupor.[14] When they revive they carry on normally again until they are overtaken by the next bout of what has been described as "idiopathic recurring stupor." Literally, this

diagnosis simply means they pass out on a recurring basis for no known reason. When a group of researchers in England took samples of cerebral spinal fluid from a group of these patients and analyzed them by high-pressure liquid chromatography, they found that at the time these individuals passed out their cerebral spinal fluid contained extraordinarily high levels of benzodiazepine-like substances. Once again, these were patients who had never taken diazepam, but these substances built up in their nervous system until they eventually reached a pharmacological threshold, as if the individuals were suffering from a drug overdose. After the crisis passed, they revived and got along fine until the substances built back up again, and then they would have another episode. These substances were termed "endozepines," meaning they were diazepines manufactured by the physiological process.

All of these examples illustrate that a lot of what we may have considered to be abnormal brain chemistry could be related to the buildup of toxic molecules due to alterations in the body's metabolic detoxification processes or excessive accumulation of specific substances due to impaired metabolism.

The Relationship of Neurotoxicity to Alzheimer's and Parkinson's Diseases

Many years ago, Dr. Hoffer started asking different questions about schizophrenia. He investigated many biochemical intermediary metabolites in brain chemistry, how they modify, alter and affect the receptor sites and activation pathways within the brain, and how this relates to schizophrenia. This model has now been extended into asking questions about other nervous system disorders, such as Alzheimer's and Parkinson's diseases.

A recent report explained that Alzheimer's patients also have mitochondrial defects that produce more free radicals that can damage neurons.[20] The formation of the neurofibrillary tangles characteristic of Alzheimer's disease may have a genetic linkage, but not every person with this genetic propensity develops Alzheimer's disease, which indicates that other factors are involved as well. It has been proposed that other mitigating circumstances which create more oxygen free radicals in specific regions of the brain contribute to the disease. Perhaps we should be measuring individual susceptibility factors, looking at these intermediary substances and then tailoring nutrition to the needs of the individual, to prevent oxidative stress of the nervous system.

It has also been suggested that Parkinson's disease may be a result of oxidative damage to the nigrostriatal neurons. The release of excessive concentrations of oxidant free radicals in the nervous systems of Parkinson's patients may be related not only to the genetic uniqueness of the individual, but also to the exposure to neurotoxins from both the external and internal environments.[21] The neurotoxic events which damage neurons in specific regions of the brain over many decades result in the loss of neurons which finally triggers the diagnosis. Steventon in England has shown that the ability of the hepatic detoxification systems of both Parkinson's and Alzheimer's patients to undergo proper Phase II sulfoxidation of toxins is impaired.[22,23] As a result, both endo- and exotoxins become potentially more neurotoxic for these genetically sensitive individuals. Over many decades of life, the effect of exposure to toxins in these individuals who are at risk is to reduce the "reserve" of specific neurons in the brain, resulting first in functional neurological disorders and later in diagnosable neurodegenerative disease. Each specific toxin may have an affinity for different types of neurons, producing a specific molecular lesion. Based upon the individual's unique genetic makeup and the translation of that makeup into neurobiochemical function, different sensitivities to neurotoxicological exposures can result. The association of xenobiotic exposure with Parkinson's disease has been called the "environmental toxin theory" related to the risk for the disease.[24]

A number of clinical reports indicate that exposure of the brain to neurotoxins can contribute to oxidative stress reactions in the central nervous system, resulting in premature neuronal death.[25] This work clearly indicates that protection against neurodegenerative diseases involves identifying susceptible individuals who are poor detoxifiers. reducing exposure to endo- and exotoxins in the susceptible individual, and then providing antioxidant support to prevent damage by oxidative stress and nutrient intake consistent with proper support of the hepatic detoxifica-

tion systems.[7]

Subtle alteration in neuronal biochemistry may be overlooked by conventional medical assessment. Once an individual has been defined as suffering from a neurological disorder, an assumption is made that the progression of the condition is inevitable. This assumption overlooks the importance of asking questions about neuronal biochemistry and toxic metabolite patterns which might be altered by selective intervention. By asking a different question about the functional status of neuronal biochemistry, we have found that the clinical course of many individuals may be improved.

We have been exploring a variety of Orthomolecular agents to try to modify specific metabolic patterns associated with neurotoxicity to see if neurological function can be improved. The early results of this research are encouraging.

Functional Neurobiochemistry: A New Approach

The research we are doing, and the new technology that makes it possible, leaves us with the question as to what insults to the nervous system might be responsible for altered neurobiochemical function which is observed symptomatically but which is not yet serious enough to result in a well-defined diagnosis.

Traditional neurology has presumed that without a diagnosis an illness doesn't exist. But our research suggests there could be a myriad of metabolic events which give rise to functional alterations in the nervous system of the individual. Even an apparently healthy individual who "gets the blues," experiences mood swings or just has a "bad day" might be suffering from transient alterations in neuroactive metabolites. Everyone has a toxic experience at some time in his or her life — a toxic headache, for example, or a "hangover" after an overindulgence in alcohol. Until recently, we have gone through life not knowing that biochemical derangement, due to overproduction and underdetoxification, may be responsible for these toxicity symptoms. Our research has begun to define reproducible metabolic patterns associated with altered brain function, and we propose that many other mental/behavioral problems may be related to neurobiochemical disturbances which cluster in specific patterns. Understanding these patterns will open the door for specific therapies based upon detoxification, reducing oxidative stress and normalizing brain biochemistry.

Asking these different questions and thinking about the brain and its relationship to function in a very different way may lead to the development of these new effective therapies. The practitioner of functional medicine identifies the molecular uniqueness of the individual and then intervenes with a specific therapy to help normalize neuronal biochemistry in that unique individual.

These emerging technologies, newly published research studies and fearlessness on the part of clinician/researchers like Dr. Hoffer, who demonstrate a willingness to open their minds to these new opportunities, are paving the way toward the more effective management of neurochemical disorders that have traditionally been outside the scope of successful therapy.

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