Oxidation-Reduction and the Brain

A. Hoffer, M.D. Ph.D.[1]

Introduction

In 1954, Hoffer, Osmond and Smythies suggested that the increased oxidation of adrenalin to adrenochrome was involved in the causation of schizophrenia. Adrenochrome has some of the properties of a free radical, i.e. it is highly reactive and rapidly is changed into a number of similar substances including adrenolutin, 5,6 dehydroxy N methyl indole, and others. These are more stable but in turn form complex polymers such as the pigment in the red areas of the brain and rheomelanins found in blood (Hegedus, Kuttab, Altschule and Nayak, 1981; Houlihan et al., 1970). Other sympathomimetic amines such as dihydroxyphenylalanine (dopa), dopamine, and noradrenalin are converted via similar pathways to chrome indole derivatives. Our hypothesis was the first comprehensive attempt to relate what was then known about schizophrenia, to schizophrenia. We demonstrated that adrenochrome and adrenolutin were hallucinogenic for men (Hoffer, 1962; Hoffer and Osmond, 1967). We studied its properties (Heacock 1959, 1965) and reviewed the powerful evidence it was made in the body. But only within the past few years have research physicians overcome the massive criticisms of scientists and have shown it does exist in substantial quantities in the body (Graham, 1978, 1979; Graham, Tiffany, Bell and Gutknecht, 1978; Hegedus et al., 1981). What has not been proven is that schizophrenics contain much more adrenochrome substances than when they are well. Now that the opposition has died down, newer research scientists will be able to examine our hypothesis again, but free of the remarkable passion which prevented these studies many years ago.

Our adrenochrome hypothesis was the first free radical hypothesis of schizophrenia. It also led to the first use of antioxidants. We began our vitamin B3 and ascorbic acid studies in 1952. We planned on trying thiamin and riboflavin but did not get around to it (Hoffer, Osmond, Callbeck and Kahan, 1957). Vitamin B3 as part of NAD (nicotinamide adenine dinucleotide) regenerates adrenalin from oxidized adrenalin. Oxidized adrenalin is adrenalin which has lost one electron. In the presence of NAD and reduced NAD the free adrenalin is regenerated. According to Walaas and coworkers (1961, 1965, 1963, 1966) this occurs in the synapse. If the reversible NAD<=>NAD H_2 cycle is deficient, oxidized adrenalin will lose one more electron

1. 3A - 2727 Quadra Street Victoria, B.C. V8T 4E5

and become adrenochrome; this is no longer reversible. Because adrenochrome is so toxic it must be deactivated very quickly; it is a synaptic poison as are other hallucinogens. Nicotinamide decreases oxidation in guinea pig lung and in rat peritoneal mast cells (Bekier, Wyczolkowska, Szyc and Maslinski, 1974; Moussatche and Prouvost-Danon, 1961). Ascorbic acid is a moderately strong antioxidant and when used in adequate doses inhibits the oxidation of adrenalin. Adrenalin will oxidize in solution containing ascorbic acid, but the vitamin quenches the red colour of adrenochrome, accelerating its conversion to adrenolutin, which is a yellow fluorescent molecule, and dihydroxy indole. Adrenolutin is an hallucinogen, but the dihydroxy indole is an anti anxiety molecule. About equal parts of each are formed. In the presence of penicillamine nearly 90 percent of the adrenochrome is converted to the non toxic 5,6 dihydroxy indole. This was why we added penicillamine to our program.

Over the past twenty years free radicals have been invoked more and more to account for a large number of pathological changes. There are free radical theories for senility, for arteriosclerosis, for disorders of the immune system, for cancer. Within the past ten years free radical antagonists, better known as antioxidants, are being used more and more to reverse and prevent the free radical induced pathological changes. Since the brain is almost always involved, it is useful to review the role of free radicals and antioxidants as they apply to diseases of the brain.

Oxidation and Reduction

Oxidation is defined as the loss of electrons from one atom or molecule to another. Reduction is thus the gain of electrons. The best known oxidizing atom is oxygen (0_2), but it does not have to be involved. The best known reducing atom is hydrogen. Oxygen can add two electrons to the six it already has to complete the set. By withdrawing these electrons the molecule which has lost them is said to be oxidized. Oxygen first adds one electron. If another is not added we have an activated molecule or free radical which has a much greater tendency to extract another electron from any electron donor. In living tissue almost every molecule can be a donor, but in giving up an electron to the 0_2 it will be altered and may become pathological. Thus lipids in membranes lose their essential properties by being oxidized.

But if other molecules are freely available which have a greater avidity for these free radicals, there will be a reaction between the two. The antioxidant and the free radical destroy each other. The antioxidant is destroyed, but in doing so protects other molecules from harm. Thus one vitamin E molecule will defend 1000 lipid molecules in a membrane against excessive oxidation (peroxidation). Antioxidants have two beneficial effects by destroying the free radical: (1) they prevent a chain reaction whereby one free radical induces more than one new free radical, (2) they protect membranes, protein and other easily oxidized substances such as vitamins, from damage; thus selenium will spare vitamin E.

Both oxidizers and antioxidants can be classed into natural molecules such as hydrogen peroxide (H2O2), or xenobiotic molecules. A xenobiotic molecule is one naturally not found in the body. Phenothiazines are xenobiotic. Vitamins are naturally present. Psychiatrists have begun to practice orthomolecular therapy, i.e. they use optimum quantities of natural substances. We also use optimum amounts of xenobiotics such as tranquilizers and antidepressants. Psychiatrists generally are xenobiotic therapists. B. Rimland has called them "toximolecular" therapists, i.e. we use toxic drugs in optimum (sub lethal, sub toxic) doses. I believe the orthomolecular xenobiotic dichotomy is a more useful one.

Free radicals have a very transient existence in the presence of electron donor molecules. In a pure state some may be stable, but they may be trapped by electron traps. Melanin is such an electron trap. It can quickly soak up and deactivate free radicals. When one tans in the sun, the amount of melanin is increased to protect the skin against the free radicals induced by ultraviolet light.

Free radicals react with membranes, particularly lipid ones. They will be less able to carry on their function of protecting cell contents, transferring molecules and communicating with other cells. They also attack other protein-associated membranes. One can see the effect of peroxidation on human

skin by looking at those over-tanned people who do not know enough to come in from the sun. The skin is brown, almost black, dry, wrinkled and has lost its elasticity; one can visualize similar changes in internal membranes.

Polyunsaturated lipids can be peroxidized into lipid peroxides which cause constriction of blood vessels. Arachidonic acid is oxidized to prostaglandins, which constrict vessels and cause platelets to become sticky. Excessive oxidation of cholesterol can damage endothelial cells lining blood vessels which become carcinogenic.

DNA is damaged by the establishment of cross linkages. The free radical binds long chains to each other. When this is done to latex (liquid, fresh rubber) it is polymerized and becomes the rubber we are familiar with. It is difficult to repair these new cross linkages. Enzymes on protein receptors are damaged. Thus dopa given for Parkinsonism is oxidized to dopachrome at the receptors and increases their destruction (Graham, 1978, 1979).

Free radical damage increases the probability of cancer formation, increases risk of arteriosclerosis, and increases atrophy of organs. But in this report I will be concerned only with the relationship of free radicals to schizophrenia and senility.

Living in Air

Life originated in the absence of air, i.e. it was anaerobic, as it still is in a few regions. In the Pacific Ocean anaerobic organisms are found near hot water eruptions at the bottom of the ocean. Converting food into energy without oxygen is very wasteful. When 0_2 is used much more energy becomes available. This changeover occurred after enough 0_2 began to change the composition of our air. Just as green plants today release 0_2, so did primitive life forms. But as the amount increased to our present twenty percent, life had to adapt, become aerobic, or die. Today the air is in balance. Processes removing 0_2 for the creation of organic matter, trees, leaves, etc., are in balance with processes which release 0_2 back into air by photosynthesis.

As life evolved in the presence of ever greater concentrations of 0_2 in air, it had to protect itself against uncontrolled and excessive combination with 0_2/A fire is the most violent example of destruction by oxidation. Equal damage can result at the cellular level with slow but steady peroxidation. In order to extract energy from oxidation of food stuff, without burning up, nature evolved a complex system of energy transfer chains. With each step a small amount of energy is released. A few of the vitamins are members of such a respiratory chain. They are thiamin, riboflavin and nicotinamide. With an intact, optimally active respiratory chain, energy is made available with minimal peroxidation.

Apparently peroxidation is unavoidable to a small degree; living tissue, plant and animal, developed antioxidants to trap and destroy those which do form. They are water soluble including ascorbic acid, bioflavonoids, glutathione, selenium, or fat soluble including vitamin E and vitamin A. Thus, life evolved an efficient system for using 0_2 safely with antioxidants ready to mop up any spillover into free radicals.

Peroxidation may cause anoxia in some tissues. If free radicals excite the production of prostaglandins which reduce the size of vessels and increase platelet stickiness less blood and less oxygen will be delivered to these tissues. Sludging of red blood cells due to excessive stickiness of these cells for each other will prevent these clumped cells from passing through capillaries, leaving those tissues anoxic, i.e. lacking 0_2. Anoxia, according to Warburg (Hoffer and Walker, 1980) is a factor in causing cancer. So we have an anomalous situation where peroxidation in some tissues can cause anoxia in others.

Warburg suggests that cells developed a second function as they became anaerobic. The first function is to divide and increase in numbers. In the earth's primitive air only anaerobic respiration and growth were possible. As cells developed aerobic respiration the increase in efficiency in releasing energy allowed cells to adhere, to form tissues and to develop specific functions. Thus, muscle cells contract, liver cells process a remarkable number of molecules, kidney cells allow water and solutes to leave and reabsorb water and essential solutes, neurons communicate with other neurons and other cells. This process whereby cells which could only grow develop other functions Warburg called differentiation.

This required aerobic respiration.

But according to Warburg, the reverse process can occur. Cells can lose their specific activity or function and fall back on their growth function; this is dedifferentiation and is caused when too little 0_2 is available. This, he suggested, was a cause of cancer. He found that cells grown in pure culture in too little 0_2, below 70 percent of their requirement, would switch from aerobic to anaerobic and become cancer. Once this occurred, restoring 0_2 did not renew these cells back to aerobic respiration. He also found that the most rapidly growing tumors had the least 0_2 in their tissues. It followed, he reasoned, that cancer can be prevented and treated by preventing anaerobic respiration, and he gave a few examples, using vitamin B3 for leukoplakia, a precancerous lesion.

Hoffer and Walker (1980) took this idea one step further. What would happen to tissues which had lost their original function — growth, if made anaerobic? Perhaps neurons are the only cells which have forever lost their ability to divide and reproduce. The neurons we have at age ninety were present at birth. Obviously a neuron is so complicated with its millions of interconnections it would be impossible for such a cell to divide. Axons, the extensions from the body of the neuron, if cut can regenerate in some cases. Perhaps we will one day have factors which stimulate all axons to regenerate. Hoffer and Walker suggested that anoxia may induce cancer formation only in tissues which still have the ability to grow. Liver cells become cancerous, etc. But when the cells can no longer grow anaerobic respiration will not cause cancer; neurons will not form neuron tumors. We suggested that these cells merely become quiescent and that this may be the final reason why neurons no longer function. The result is senility. This will be discussed more fully. I will show how excessive oxidation will cause a paradoxical anoxia in the brain and lead to senile dementia.

Causes of Excess Free Radical Formation (Peroxidation)

Basically this is due to the presence of too much oxygen and the absence of adequate antioxidants. I will not discuss xenobiotics which induce free radical formation; these include all the synthetic chemicals present in our air, water, soil and food. They include pesticides, herbicides, petrochemicals and so on. Only natural systems will be considered, as if we lived in a world before the first chemist arose.

1. Hyperbaric Oxygen. Man has exposed himself to excessive amounts of 0_2 in chambers where the pressure of 0_2 can be doubled or tripled, in deep sea diving and at one time in space vehicles. Red blood cells can increase the amount of 0_2 they carry a little, probably not enough to do much damage, but plasma can carry much more 0_2 in solution. The greater the pressure of 0_2 the more is dissolved and the more harm is done. The effect of excessive 0_2 in premature babies is well documented. Less well-known is the effect of excessive 0_2 on astronauts, divers and racing drivers who inhaled pure 0_2 from masks. These dangers are described in Hoffer and Osmond (1967) in the section on adrenochrome.

Russian scientists found during the last war that rabbits placed in hyperbaric 0_2 eventually had grand mal seizures. At autopsy their brains were free of noradrenalin and adrenalin but were coloured red. The oxidized derivatives of these amines are red. In other words, excessive 0_2 oxidized all the noradrenalin and adrenalin to noradreno-chrome and adrenochrome. That is why their rabbits convulsed. Adrenochrome is very toxic, it prevents cell respiration. Is this an additional reason the first Russian astronauts went up in air, not in pure 0_2 as did the American astronauts?

Divers are also at risk, not only from nitrogen narcosis but from 0_2 toxicity. I would expect that professional divers would have a higher incidence of psychiatric diseases. One of my patients, a diver, is schizophrenic, recovering on antioxidant therapy. Vitamin E was used later by astronauts to prevent red cell lysis by too much 0_2.

2. Too much ozone. Ozone is a much more active form of oxygen. It will be more toxic in the body.

3. Exertion increases the need for more oxygen. Trauma also is a factor. A person requiring a greatly increased transfer of 0_2 across lung tissue increases the risk of peroxidation.

4. Sluggish circulation. When this occurs any free radicals formed are not swept away as quickly.

5. Allergies and infections increase free radical formation; leukocytes kill bacteria by releasing H_20_2 which releases free hydroxy! radicals.

6. Deficiency of respiratory enzymes. This will cause 0_2 tension to build up as it is not removed quickly enough.

7. Deficiency of antioxidants, particularly vitamins A, C, E, B3, bioflavonoids and antioxidant minerals, selenium and manganese.

8. Excess of oxidizing enzymes due to too much copper, or iron.

Living tissue must have a balance between the tendency or pressure to oxidize and the countervailing pressure to prevent oxidation, i.e. to reduce. It might be very valuable to have a measure of this balance. In chemical reactions this can be measured as a redox potential. We need a biological redox potential for then corrective measures could be taken. If the pressure for oxidation is too great, we could reduce this pressure by changes in lifestyle, for example stopping smoking, and we can increase our antioxidant consumption until our redox index is once again normal.

Biological Redox State

I do not think we can place an electric probe into the body and measure its redox potential. The chemistry of our body is much too complex for that. We can, however, measure systems which are reversible. One of these is the system ascorbic acid and dehydro ascorbic acid.

Lewin (1976) provides a careful analysis of the various ascorbates which are present in the body. There is an equilibrium between ascorbic acid and dehydro ascorbic acid; the latter is the oxidized form and is usually present in very small amounts. Dehydroascorbates have a transient life; when ascorbic acid and dehydro ascorbic acid are mixed an ascorbic free radical is formed. Excess oxygen, other oxidants, light and some enzymes reactions will also cause the formation of this free radical. It plays a special role in reacting with adrenochrome.

Ascorbic acid is the reduced form of vitamin C and is non toxic. Dehydro ascorbic acid is the oxidized form and is toxic. It will produce a type of diabetes in animals. Fortunately, very little of the vitamin C is in the oxidized state. In living tissue ascorbic acid is associated with bioflavonoids. These are essential vitamins according to Szent-Gyorgyi (1972). They keep vitamin C in a safe, reduced state. Ascorbic acid is readily oxidized by air, 0_2, copper ions.

It is therefore prudent to use pure ascorbic acid. When dissolved in water it should be drunk immediately. If it must be stored it should be dissolved in juices such as tomato juice or fruit juice which contain bioflavonoids. Clemetson (personal communication, Clemetson and Andersen, 1966) recommends only freshly recrystallized ascorbic acid should be used, but this is impossible for most.

In 1963, Hoffer and Osmond discussed the therapeutic role of vitamin C for schizophrenias. We calculated the ratio of ascorbic acid over dehydro ascorbic acid for a number of diseases. Clemetson and Andersen (1964) examined this ratio in nineteen normal pregnant women and eleven with pre-eclampsia. The sick group had a lower ratio. Four women after abruptio placentae were even worse.

Stone (1972) called this a morbidity index. His examination of the literature showed there was a high degree of correlation between the index and the seriousness of the disease. A summary from his book, page 181, follows on page 297.

Patients close to death have hardly any ascorbic acid; most is in the oxidized state. Convalescent patients have higher indices. The more life threatening the disease, the lower the ratio. With adequate vitamin C supplementation, the ratio may be much higher.

These early studies must be repeated to determine if this morbidity index will be a good measure of health. If so, it would be a useful clinical index of the redox state and would be used to measure severity of illness and the type and dose of anti oxidant treatment. It would also indicate outcome. A rising index would indicate recovery, a falling index would indicate the disease was getting worse. An index below 0.5 would indicate death was imminent.

$$\text{Morbidity Index} = \frac{\text{Ascorbic acid}}{\text{Dehydro ascorbic acid}}$$

1. Normal ratio = 14 (6½% of Vitamin C is dehydroascorbate.)

2. Diseases	**Died**	**Survived**	**Convalescent**
a. Meningitis	**0.3**	**0.7**	**2.8**
b. Tetanus	**0.5**	**1.3**	**5.0**
c. Pneumonia	**0.5**	**1.3**	**4.0**
d. Typhoid	**0.4**	**1.1**	**4.5**
Means	**0.4**	**1.1**	**4.1**
Percent dehydro AA	**70**	**47**	**20**

More data from Stone:

Diseases	**Number of Subjects**	**Index**
Normals	16	14.8
Cholera	21	1.7(1)
Smallpox	16	0.9(1)
Meningitis		
Pyogenic	16	0.7(1)
Tuberculosis	16	4.2(2)
Gonococcus	16	2.0(1)
Lues	16	4.2(2)

(1) Acute — more life threatening.

(2) Chronic — less life threatening. Ratio for acute group =1.3 (42% oxidized). Radio for chronic group is 4.2 (19% oxidized).

Senility

Free radical theories of senility are gaining favor (Hoffer and Walker 1980). We suggested that in senile brains the neurons had become quiescent due to anoxia in certain parts of the brain. How can one reconcile what appear to be two conflicting views? How can anoxia exist in a body suffering peroxidation? There are several explanations. Peroxidation may occur even though overall there is no increase in 0_2 load. Oxidation is defined as loss of electrons, not as a superabundance of 0_2. They may not coexist. But I do not believe this is the explanation.

When the body is in a peroxidized state (low morbidity index) due to a variety of factors, the brain probably senses this by sensors either in the body or in the brain. When signals indicating too much oxidation are received, the brain can reduce oxidation by decreasing the amount of 0_2 coming into the brain. This it can do by shutting down circulation in those parts where a shutdown will not kill. The part of the brain monitoring life must not be touched. During sleep there is a decrease in circulation in the frontal lobes. The total blood flow is unchanged. Each night we readjust our brain pattern of circulation, but we can dream, have fragmentary erratic memories, be aware and so on. A senile person is remarkably like a person asleep. They can not learn, cannot remember new information. A decrease in frontal lobe circulation on a permanent basis would result in frontal anoxia, quiescent neurons and senility.

The brain is an excellent organ for studying free radical pathology (Demopoulos, 1982), as it is for measuring accelerated senescence, using irradiation of the whole human brain. At

several centers brain tumors are given radiation postoperatively to control growth. Survival time is doubled from seven months after surgery alone to fourteen months. They die from the tumor or from radiation damage. At autopsy irradiated brains show typical senescent changes; clinically they are very similar to Alzheimer's, where personality changes progress to incoordination, to inability to do personal care, finally to semi stupor, coma and death.

Chronic malnutrition also accelerates aging (Hoffer, 1974). Canadian soldiers kept in Japanese prison of war camps forty-four months suffered severe stress from multiple vitamin deficiencies, starvation, infection and brutality. About one-quarter died. The remainder have suffered five years of premature aging for every year in camp. Thus veterans at age 50 were about as aged as they would have been at age 70. However, this premature senility was reversible by adequate dosages of niacin. It was a vitamin B3 dependency, induced by severe and prolonged malnutrition combined with severe stress.

Other changes such as chronic dehydration and shrinkage of the brain may be damaging in the same way, or simply by changing the three-dimensional relationships of the brain.

There is some evidence senility does arise from anoxia. First, anoxia produces senile confusional states; secondly, increasing oxygenation temporarily restores memory in some senile people.

Anoxia is caused by excessive altitude or too little 0_2 in air. It may arise from defective transfer of 0_2 from air in alveoli of the lungs to the cells. Lung pathology, pneumonia, congestion, bronchiectasis, all limit diffusion of 0_2 to the red blood cells. Defective circulation due to sludging of red cells, arteriosclerosis, stroke, tumor, trauma, will limit transfer of 0_2 as will anemia or leukemia or polycythemia vera. Poisons such as carbon monoxide or cyanide will prevent oxygen transfer and release, and respiratory poisons and deficiency of respiratory enzymes will do the same. All these factors cause toxic confusional states as will anesthetics and narcotics.

Removal of these factors and restoration of normal delivery of 0_2 to brain cells cures the induced senility. Even more, Dr. E. Boyle (1972, 1973) reviewed evidence which confirmed that hyperbaric oxygen treatment, thirty minutes per day week days for two weeks temporarily restored memory in a number of his patients. But after a few weeks the senility gradually settled in again.

Hyperbaric oxygen would force oxygen into the brain via the plasma, overwhelming the ability of the brain to shut down circulation. Enough oxygen would get into the frontal lobes to awaken the quiescent neurons until they became anoxic again.

Had Prof. Boyle not been killed in a car accident, he would have been able to combine hyperbaric treatment with vigorous antioxidant therapy. I have little doubt we could have used hyperbaric oxygen to awaken quiescent cells in a rehydrated brain and maintain restored memory by orthomolecular antioxidant therapy.

The anoxic/quiescent hypothesis is just that, an hypothesis. It is based upon evidence already available but by no means is it an established fact. However, treatment based upon this hypothesis has been helpful in preventing and reversing senile changes; I therefore consider it a useful hypothesis. It is not the objective of an hypothesis to be right; its only function is to direct research. If it leads to a better understanding of a disease and to improved treatment, it has served its purpose. For every hypothesis must one day be proven wrong in one way or another. Hypotheses are ephemeral; observations endure.

Treatment for senility was described by Hoffer and Walker (1980). When we wrote this book we were unaware of the importance of dehydration as a cause of senility. Recently Galambos (1983) opened up an entirely new area of research and treatment when he reported that most of the senile, age 65 and over, men and women admitted to his geriatric hospital were chronically dehydrated. When they were started on a careful, steady hydration program they recovered or were greatly improved in six to nine months. He also used a multivitamin preparation (Mega-vits made by ICN) three times each day containing thiamin 100 milligrams, riboflavin 5 milligrams, pyridoxine 100 milligrams, niacinamide 200 milligrams and ascorbic acid 500 milligrams. This is a preparation I suggested to the vitamin company about twenty

years ago.

Galambos reported that the majority of senile patients were not Alzheimer's disease; this has become a fad, facile diagnosis. The original Alzheimer's disease was a pathological diagnosis; if at autopsy typical lesions were found, then that patient had Alzheimer's. True Alzheimer's comes early; it is a premature senility, and kills quickly. Few survive to age 65. With modern scanning devices it is easy to screen every person and to diagnose every case with frontal air space a case of Alzheimer's. When only x-rays were used not as high a proportion of elderly people were found to have air spaces, and fewer were called Alzheimer's.

According to Dr. Galambos a shrunken brain due to dehydration pulls away from the bony skull leaving an air space, i.e. air spaces are pathognomonic for Alzheimer's disease. In 1954, a patient at Munro Wing, General Hospital, was typically Alzheimer's, diagnosed by a competent neurologist. He was young, had electrical changes, air spaces and showed the typical confusional state of senile psychosis. Later on his behavior became more typically schizophrenic. He was one of the first eight schizophrenics placed on niacin, three grams per day, and recovered. An Alzheimer's lesion would not have responded.

Dehydration can be caused by a number of factors. Many elderly people develop a defective sense of thirst. All their lives they have depended upon this, believing one drinks water only when thirsty. Other people hate to go to the bathroom at night so cut down their fluid intake. Others think drinks such as coffee or alcoholic beverages supply fluid; they do not because they are diuretic and cause a greater loss of fluid than they provide. Still others are on diuretics which are used too commonly. Dehydration is not a recent problem; in the early 1950's I recall Dr. H. Osmond telling me that about one-quarter of the seniles committed to his mental hospital, Saskatchewan Hospital at Weyburn, were dehydrated, and quickly responded to rehydration. The major difference today is that most of Galambos' patients rehydrate slowly. They are given eight glasses of fluid per day, not counting alcoholic drinks or coffee. When rehydrated the air spaces are no longer seen. Adequate fluid intake should be part of every program to prevent senility.

Schizophrenia

Senility and schizophrenia are different even though peroxidation is involved in both. The difference is that the adrenochrome - adrenolutin pathway does not operate in everyone. It is under genetic control. When the brain senses peroxidation due to too much adrenochrome at the synapse it will shut down circulation to the frontal lobes. Schizophrenics have a circulatory pattern similar to the normal sleeping pattern. The synaptic interference leads to the perceptual changes and thought disorder. They are induced in normal subjects by the hallucinogens such as LSD. Senile patients do not have perceptual changes and their thought disorder is in memory, learning and recall.

There are a number of schizophrenias, which is a syndrome. But as I have shown (Hoffer, 1981), there is probably a common final pathway, the peroxidized state of central amines.

Anti Oxidant Therapy

Both senility and schizophrenia should and do respond to anti oxidant therapy. I will not review the extensive evidence based upon double blind experiments, comprehensive clinical trials and the wide clinical experience of many orthomolecular physicians. Much of this has been published in this journal.

An anti oxidant program should include:

1. ample fluid intake,
2. orthomolecular nutrition (Hoffer and Walker, 1978).

Demopoulos' (1982) anti oxidant nutrition is very similar. He recommends fresh fruit, fresh vegetables, legumes, poultry (no skin), fresh fish, low fat dairy products and grains. He recommends we avoid all processed foods, i.e. all visible fats or oils, beef, pork, all fried foods, all shellfish, avocados, olives and soybeans, all nuts except chestnuts, all sugar, salt, alcoholic and caffeinated beverages and canned fruits and juices. He states, "The emphasis in this diet is to put fresh fruits and vegetables in "center stage" because of their content of anti oxidants and fibers." This is in striking contrast to western diets which traditionally emphasize meat as the center-

piece of any meal.

I wonder whether warm country fruits might be richer in anti oxidants because at high temperatures more protection from peroxidation is required. Fruit such as papaya, pineapple and bananas might be healthier than northern fruit such as apples and berries. However, they are deficient in Omega-3 essential fatty acids (Rudin, 1981, 1982), and may be less healthy for northern climatic areas.

Anti Oxidant Micro Nutrients

1. Vitamin A and its precursor beta carotene are useful anti oxidants. They are rich in green vegetables and in some fruit.

2. Thiamin is an essential respiratory catalyst. It is especially needed by people who peroxidize themselves by alcohol and sugar.

3. Vitamin B3 is an essential component of a very important pyridine nucleotide redox system. In the brain it controls oxidation of amines to their oxidized derivatives. It is very important in treating many senile conditions including some degenerative changes such as arthritis.

4. Pyridoxine controls formation of NAD from tryptophan. It plays an important role in schizophrenia.

5. Ascorbic acid and bioflavonoids. These should be considered a vitamin C family of vitamins. The bioflavonoids are excellent anti oxidants, thus they inhibit oxidation of adrenalin to adrenochrome.

6. Vitamin E. This may be the most important fat soluble anti oxidant.

7. Selenium — in microgram quantities spares vitamin E. It has anti cancer properties.

8. Manganese is present in superoxide dismutase, an important free radical scavenger. Tranquilizers chelate manganese out of the body and cause tardive dyskinesia. Perhaps this is a form of induced senility. It is reversible by manganese salts.

An experienced orthomolecular therapist will use a number of these micronutrients in optimum dosages, which may have to be determined over a period of time. So far we have no laboratory tests which will help us decide which nutrients to use and how much. Our science is still empirical, but it is a beginning. Used skillfully and with determination both patients and physician will be happy with the result. Most orthomolecular physicians are happy with their practice, for after all, our primary responsibility as physicians is to help patients get well and to advise well people how to stay well.

Essential Fatty Acids

Essential fatty acids are precursors of two main families of prostaglandins derived from Omega-3 and Omega-6 essential fatty acids. They have to be in balance. Rudin (1982) has reviewed the medical literature and emphasized the importance especially of Omega-3 EFA. This is because they have been almost totally removed from our diets because of their high reactivity and their instability. There is an excess of Omega-6 EFA. The ratio can be improved by eating foods rich in Omega-3 EFA such as linseed oil, fish oils, evening primrose oil, wheat germ oil and other northern (cold climate) plants.

Structural lipids make the cell membrane and regulatory EFA consist of prostaglandins and derivatives, cholesterol esters. Their modulators are lipid soluble anti oxidants vitamin E and selenium in glutathione peroxidase and copper and zinc in superoxide dismutase.

Xenobiotic Anti Oxidants

Hydergine has been used as an anti senile anti oxidant. Psychiatrists have had much more experience with tranquilizers; pheno-thiazines are anti oxidant. They also maintain elevated levels of NAD when given with vitamin B3 compared to using vitamin B3 alone. They are thus synergistic with this vitamin. This is also seen clinically. Patients receiving vitamin B3 generally do not need as much phenothiazine medication.

Conclusion

Free radicals are undoubtedly involved in a number of degenerative diseases. They may play a major role in causing senility and schizophrenia. The body controls excessive oxidation and free radical formation by fat and water soluble anti oxidants. Fat soluble anti oxidants protect lipid membranes while water soluble anti oxidants protect against water soluble free radicals. Anti oxidant treatment, primarily micronutrients and Omega-3 essential fatty acids, will prevent and treat all free radical caused diseases, including senility and schizophrenia.

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