Schizophrenia: An Evolutionary Defense Against Severe Stress

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The adrenochrome investigations into schizophrenia which I have pursued since 1952 and the recent important investigations into the relationship between heart function and (adrenalin —> adrenochrome) points to a connection between brain and cardiac disorder. I suggest there is a link between schizophrenia and some types of heart dysfunction. My hypothesis is that the biochemistry of schizophrenia has evolved as a protection against death from cardiac fibrillation during severe stress, but for one to two percent of the population that life saving mechanism has gone too far, it leads to schizophrenia. The evidence for this idea has been forming slowly over the past 40 years, and is an outcome of the adrenochrome hypothesis of schizophrenia proposed by my colleague, Dr. H. Osmond, and me.

The hypothesis can be presented as a series of equations:

A) Under normal conditions there is a balance between release of catechol amines and their conversion to their oxidized derivatives and neither sets of compounds are produced to excess.

B) Severe stress —> too much adrenalin and other sympathomimetic amines. Excessive concentration of adrenalin in heart muscle. Oxidation of adrenalin in myocardium to adrenochrome, and to adrenolutin. Adrenochrome causes fibrillation and other cardiac pathology and dysfunction.[2]

C) Leakage of adrenochrome and its derivatives such as adrenolutin into the blood and into the brain causing a toxic psychosis called schizophrenia.

D) Schizophrenia - perceptual illusions and hallucinations combined with thought disorder. This was the definition used by Conolly.' Psychiatry has recently started to use the same definition;[3] they wrote "a break with reality usually manifested as hallucinations, delusions, or a disruption in thought processes".

This reaction is accelerated by increasing the oxidative potential, i.e. by increasing the availability of factors which increase oxygenation or which increase oxidative enzymes or auto catalysts, and by decreasing the availability of factors which inhibit the reaction, i.e. the antioxidants. It will also be driven to excessive oxidation by inhibiting the enzymes which destroy adrenalin via non phenolic pathways.

A) Severe stress and excessive secretion of adrenalin.

The flight or fight mechanism deduced by Dr. Walter Cannon many years ago has served us well in understanding why the body suddenly secretes or releases copious amounts of adrenalin when we are threatened. Animals with the quickest and most aggressive response to threats would be most apt to survive and pass on their genes to their offspring. The flight-fight mechanism remains intact today, even though the nature of the threat has been completely altered. Our bodies have not been changed very much over the past 50,000 years. Dr. Robert M. Sapolsky[2] provides an excellent popular description of the effects of stress upon the various body systems and hormones. But there is very little discussion of the connection between these effects and the sympathomimetic amines and their derivatives.

Adrenalin is a very powerful toxic natural chemical which has important positive actions and many potentially toxic effects. One of the toxic effects is upon the heart. This has been known since 1905 when the first results were recorded that intravenous adrenalin caused carditis. The literature on the toxicity of adrenalin on the heart is well documented by Dhalla, Yates, Naimark, Dhalla, Beamish and Ostadal.[3] In their summary they write, "It is well known that massive amounts of catecholamines are released

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from the sympathetic nerve endings and adrenal medulla under stressful situations. Initially, these hormones produce beneficial effects on the cardiovascular system to meet energy demands of various organs in the body and their actions on the heart are primarily mediated through the stimulation of the beta-adrenergic receptors-cyclic AMP system in the myocardium. However, prolonged exposure of the heart to high levels of catecholamines results in coronary spasm, arrhythmias, contractile dysfunction, cell damage and myocardial necrosis."

It is clear that no animal could have evolved unless it developed measures for moderating the effects of adrenalin and other sympathomimetic amines, and quenching them once the stressful event was over.

B) Excessive concentration of adrenalin in heart muscle

Adrednalin undergoes oxidation in the myocardium to adrenochrome, and to adrenolutin. Adrenochrome causes fibrillation and other cardiac pathology and dysfunction. Adrenochrome is less toxic than adrenalin. It is removed by conversion into two main chrome indoles, adrenolutin which is toxic, causing psychotic changes similar to those caused by adrenochrome and 5,6 dihydroxy indole which is not.[9] This requires the presence of anti oxidants.

I will refer to adrenalin only but include all the other catecholamines such as noradrenalin and dopamine. In the same way when I discuss adrenochrome I refer also to the other oxidized derivatives of the other catecholamines such as noradreno-chrome and dopachrome.

Any animal that cannot eliminate adrenalin will quickly die from overdose of the adrenalin. There are two factors which will lead to an over accumulation of adrenalin: (1) excessive release of adrenalin and too rapid absorption into myocardium; (2) slow removal of the adrenalin from the heart muscle and other tissues. But both factors may be operating simultaneously. The sudden death of cocaine users in a stressful situation could be an example of both factors in operation. The stress of the reaction induces excessive secretion of adrenalin and the cocaine itself blocks the activity of two of the four enzymes which remove adrenalin. Two systems which do not lead to adrenochrome are blocked thus throwing too much of the burden on the phenolase pathway and increasing adrenochrome production.

Evolution has created four main enzyme pathways for degrading adrenalin with an additional auto oxidation pathway. Auto oxidation occurs in the presence of known oxidizers such as iron or copper and in the absence of anti oxidants such as vitamin C, vitamin E and coenzyme Q10. The five pathways for dealing with adrenalin are the culmination of millions of years of evolution. The best example of the auto oxidation is the spontaneous conversion of adrenalin to the red colored adrenochrome when it is allowed to stand in solution in contact with oxygen. The first preparations of adrenochrome that were made for us in 1952 contained silver ions. It was impossible to keep it stable even at 40 degrees below zero. The red powder slowly turned black. However, when we removed all the silver ions from the preparation it became quite stable and could be stored at room temperature.

The first pathway requires phenolases, i.e. enzymes which oxidize catecholamines to adrenochrome (chrome indoles or colored indoles). Adrenochrome is almost a free radical and is rapidly changed to adrenolutin and other indoles in the blood. It must have a very short half-life in blood.[4] The phenolase pathway is the major one in the heart. Up to 80% of the adrenalin absorbed by myocardial tissue is converted into adrenochrome. It is also the major pathway in polymorphonuclear leucocytes[5] and is therefore a factor in inflammations. In the rest of the body it may comprise a minor pathway, but other tissues of the body have not been examined very thoroughly. The controversy over the formation of adrenochrome in the body is reviewed by Hoffer and Osmond,[6] Hoffer.[7]

Two pathways (the second and third) require the enzymes amine oxidase and catechol-O-methyl transferase. The new products formed are aldehydes, not indoles such as adrenochrome. This is the pathway which has been studied very intensively in psychiatry, but this research has been largely of little value both in determining the cause or aiding in the treatment of schizophrenia. The fourth pathway requires the minor enzyme phenolsulfotransferase. Other enzymes

which oxidize adrenalin are xanthine oxidase, heart muscle cytochrome C oxidase, cytochrome C and methamyoglobin.

One catecholamine, dopamine, has been studied quite intensively and enshrined in psychiatric research as the dopamine hypothesis.[8] But no attention has been given to one of the end products of dopamine metabolism, dopachrome, as if the molecule simply bounced back and forth unaltered within the synapse between receptor and the the nerve terminal from which it originated.

The presence of these potent, highly reactive substances has finally been firmly established by Dhalla, Ganguly, Rupp, Beamish & Dhalla,[9] Matthews, Henderson and Campbell.[5] Matthews et al write, "We have demonstrated the presence of an adrenalin oxidase in serum during the days following acute myocardial infarction. Furthermore we have extracted a compound which was precisely equivalent to adrenochrome on analysis from the synovial fluid of patients with rheumatoid arthritis". Dhalla et al published a method for measuring the amount of adrenolutin in plasma. Administration of different catecholamines as well as adrenochrome and adrenolutin in rats also increased the level of adrenolutin in plasma. Adrenolutin was found to be present in plasma in other species including dog, rabbit and pig. High levels of adrenolutin, which may represent total concentration of aminolutin in plasma, suggests the presence of an efficient mechanism for the oxidation of catecholamines under in vivo conditions. Another derivative of adrenochrome is 5.6 dihydroxy N methyl indole (leuco adrenochrome). This compound has anti tension or anti anxiety properties. See Hoffer and Osmond[10] (pages 48 to 74).

Matthews, Henderson & Campbell[5] found that the percentage conversion of adrenalin to adrenochrome markedly increased as the concentration of adrenalin decreased. This suggests that the ability to detoxify adrenalin by the adrenochrome pathway is restricted to conditions where the production of adrenalin is relatively low. As the amount of adrenalin increases the other pathways (mono amino oxidase and catechol-O-methyl transferase) come into play and help remove the adrenalin. But with excessive amounts the adrenalin is auto oxidized again leading to adrenochrome and other free radical molecules. It is probable the body has evolved a series of reactions for dealing with adrenalin and other catechol amines as follows:

1) Under resting conditions small amounts of adrenochrome are formed and circulate in the blood as adrenolutin since adrenochrome is too unstable to remain very long in the blood. This is a condition of little stress, e.g. when sleeping and when relaxing during the day free of unusual anxiety or depression. In the synapse adrenalin loses one electron and becomes oxidized adrenalin. In the presence of NAD it regains the electron to reconstitute the original adrenalin. If there is a deficiency of NAD the oxidized molecule loses another electron to become adrenochrome. This last reaction is irreversible. Oxidized adrenalin is a free radical and adrenochrome shares many of the properties of free radicals. This reaction is controlled by the oxidizing enzymes chiefly in heart and in leucocytes and in inflamed tissues but perhaps in other tissues not yet examined. The major antioxidants vitamin C, vitamin E and selenium probably play major roles, as does nicotinamide adenine dinucleotide (NAD). Another main derivative of adrenochrome is leuko adrenochrome which is not toxic.

2) Under conditions of increased secretion of adrenalin the adrenochrome enzyme pathway becomes saturated and the non adrenochrome pathways come into play, forming aldehydes and other non amino-chrome substances. This would be characteristic of moderate stress or of severe short lived stress that we have to endure most of our lives. There are many known pathways for changing adrenalin and removing its toxic properties on heart and on blood pressure, indicating how essential is the rapid detoxification of adrenalin. These are: (1) Mono amine oxidase - The end product is 3,4 dihydroxy phenylhydroxyacetaldehyde. Inhibitors of this enzyme include cocaine, histamine, ephedrin, adrenochrome, caffeine, amphetamine, nicotine, harmine, antabuse, LSD, hyperbaric oxygen. (2) O methyl transferase - The end product is 3 methoxy 4 hydroxy mandelic acid. (3) Phenol sulfotransferase - The end products are sulfates. Cocaine is an inhibitor of this reaction. (4) Other enzyme systems and mol-

ecules. Most of the adrenalin released into the synapses is rapidly reabsorbed. The rest must be metabolized quickly.

3) Under severe and prolonged stress none of the enzymatic pathways would be adequate to deal with the huge amount of adrenalin and the final mechanism would come into play - auto oxidation in the cell compartments where the concentration rose the most. Auto oxidation might be the major pathway under these conditions. This would give rise to many other free radicals such as orthoquinones and indolic catechols.[11] Ferritin and copper catalyze the auto oxidation of the catechol amines.

Anything which increases the production of adrenochrome will increase cardiac pathology. This will result from major and prolonged stress. It will also come about when the mechanisms for removing adrenalin are distorted by drugs or other conditions and from a deficiency of antioxidants. Thus pyrogallol, a catechol-O-methyl transferase inhibitor, increased the severity of heart lesions.

Antioxidants protect against the effect of free radicals. Free radicals are formed with adrenochrome when catecholamines are oxidized. Vitamin E protected rat hearts against damage while, on the contrary, vitamin E deficiency made them more sensitive. Other antioxidants are vitamin C, and coenzyme Q10. Vitamin B_3 is also involved since the nicotinamide-adenine-dinucleotide system, of which vitamin B_3 is component, plays a role in the oxidation of adrenalin first to oxidized adrenalin and then to adrenochrome.[12] Cocaine abuse, according to Beasley,[13] is associated with mycardial infarction arrhythmias, transient severe hypertension, stroke and seizures. Cocaine abusers also suffer from nutritional deficiencies including vitamin B_6, vitamin B_1, and ascorbic acid.

C) Leakage of adrenochrome and its derivatives into the blood and brain.

The oxidized products of adrenalin metabolism are circulating in the blood. It is likely the major source is from the heart which is the largest organ in the body which can make adrenochrome and its derivatives. The largest organ which detoxifies catecholamines is the skin. The end product is melanin derived from tyrosine. Melanin is a polymerized complicated molecule made from chrome indoles.

Adrenochrome can be transferred across the blood-brain barrier. In our early experiments with adrenochrome we were able to show the psychological effects of adrenochrome given parenterally, (see Hoffer and Osmond[6]). It is highly probable it is transferred. In addition it can be made in the brain at the synapses from the catecholamines. The pigment in the red nucleus is an adrenalin-derived melanin which must have gone through the adrenochrome pathway. It cannot come from tyrosine since it is also present in albinos who lack tyrosinase, the enzyme which converts tyrosine into black melanin.

D) Schizophrenia.

The adrenochrome hypothesis of schizophrenia has been reviewed many times.[6] We suggested that an increased conversion of adrenalin to adrenochrome was one of the causes of schizophrenia, basing this conclusion on our findings that adrenochrome and adrenolutin are hallucinogens, that they could be made in the body and that reversing or preventing the reaction was therapeutic for schizophrenia. We used large doses of vitamin B_3 and ascorbic acid. Over the past five years it has been reinforced by the final proof that adrenochrome is formed in the body. The major criticism of our hypothesis was the objection to the view that this could occur in vivo. The evidence was very powerful when we first published the hypothesis in 1954, but our critics refused to look at the evidence. Since then evidence that the aminochromes are made in the body has been accumulating.

Mark D. Altschule[14] compared the aminochrome blood levels in 52 normal subjects with 12 schizophrenic patients. The normal subjects had between 0.2 and 1.1 ng/ 100 ml of blood while the amount in the blood of the patients ranged from 1.5 to 3.2. Altschule was not happy with the accuracy of the methods which he was then developing but he concluded that all the methods he used, "showed that patients with mental diseases actually have a condition that is more properly called hyperaminochromia." He thought the substance was adrenolutin, not

adrenochrome. The final proof by Dhalla, Ganguly, Rupp, Beamish & Dhalla[8] has resolved this problem. What still remains is to show the relation between adrenochrome (or adrenolutin) levels and the schizophrenias using the accurate methods developed by this group.

Another psychiatric disease which may be related to increased production of amino-chromes is Parkinson's Disease. L-dopa, the main treatment for this disease, is readily oxidized to dopachrome. Not surprisingly, with prolonged use of l-dopa there is an increase in the rate of destruction of the neurons. When higher doses were used there was up to a 25% incidence of psychosis attributable to l-dopa.'[5]

The first recent tentative moves to look at the adrenochrome hypothesis by psychiatrists appeared in a report by Cadet and Lohr[16] who concluded, "After a review of the possible neurotoxic effects of free radicals formed during states of high dopamine turnover, we postulate that the neuronal damage caused during these episodes might form the substrate of a comprehensive hypothesis that could potentially explain the protean findings in the group of schizophrenias and the progression of the syndrome, in some patients, to the so-called schizophrenic defect state." Dopamine is one of the catecholamines and the free radicals are either adrenochrome or other free radicals formed during its synthesis. Since these two authors were totally unaware of our adrenochrome hypothesis originally reported in 1954,1 wrote and told them that I thought their hypotheses was a very good one. I added I had also considered it was a very good one when we first published it many years before. I received no reply. The word adrenochrome does not appear in their paper, as if it were poison.

The Role of Antioxidants

Antioxidants protect both heart and brain against the toxic effects of adrenochrome and similar chrome indoles by decreasing their formation.

A) Niacin

Niacin is not in itself an anti oxidant but nicotinamide adenine dinucletoide exists in both oxidized and in reduced forms and is an important respiratory oxidation-reduction enzyme. Niacin has many therapeutic properties in the body including decreasing total cholesterol levels, and elevating high density cholesterol. Its hypocholesterolemic effect has given niacin the greatest prominence as a safe and effective substance.[17] It also decreased mortality by 10 percent and increased longevity by 2 years.[18] The use of niacin to change cholesterol levels initiated the new paradigm in medicine, i.e. the use of vitamins for treatment, not only for prevention. Niacin was included in this long trial because it lowered cholesterol. I doubt this is the only factor which decreased mortality since other substances lowered cholesterol as well and had no effect on mortality. I suspect that niacin worked because it protected the heart against the effects of stress, particularly against the adrenochrome and other chrome indoles. It also decreases the release of fatty acids which occurs under stress. There is some evidence that xeno-biotics, which also lower cholesterol levels, increase deaths due to accidents, suicide and homicides but niacin does not do so.[1819] Since increased stress is associated with these deaths, this is more evidence that the vitamin does protect against stress.

In combination with folic acid niacin has been therapeutic against atrial fibrillation in six of my patients. The first case was a physician, age 70, who had been on nicotinic acid for many years, three to six grams daily. On this dose he developed lymphedema in the left leg. In order to deal with this he discontinued the nicotinic acid. The edema cleared but after many months he began to suffer a number of disturbing symptoms. These included a very low pulse rate unresponsive to demand. It remained slow even when he walked or tried to walk fast, and would speed up only after a few minutes. He became very short of breath and he also suffered episodes of tachycardia which was controlled by pressure on the carotids in his neck or changes in body position. The episodes lasted up to 20 minutes and were accompanied by shortness of breath and sometimes with dizziness. On physical examination he was normal, as was the electrocardiogram. He had a normal sinus rhythm. He therefore resumed taking the nicotinic acid, starting with a low dose and gradually

working it up to 4.5 G daily. At the same time he increased his folic acid from the five mg per day he had been taking for several years to 40 mg daily. He continued to take vitamin B_{12}, 1 mg sublingually daily. By the time these dosage levels were reached, over a couple of months, all the heart rate symptoms vanished. He can now walk any distance with no shortness of breath.

The second case is a physician age 76. She had consulted me for advice in helping a young patient. This patient was a schizophrenic who had schizophrenia and recovered on vitamin B_3 and vitamin C. The physician was so impressed with this recovery she had decided to place herself on a vitamin program. The vitamin regimen included niacin one gram bid and folic acid 15 mg bid. During one of her visits she described how she had suffered atrial fibrillation for as long as three hours before starting on the vitamins. It had not recurred as long as she remained on the program. When she went off it for several months it recurred.

The third patient, age 72, consulted me for severe depression. In 1981 she had a coronary. She was advised she would suffer pain after this and she did. In 1988 she was admitted to hospital for severe chest pain. Thereafter she had recurrent episodes every three weeks, unrelated to activity or exertion. In 1989 she was in hospital for one week for depression. She then started on niacin 500 mg tid plus small doses of antidepressants. She recovered and remained well until April 1993. She was then admitted to hospital with atrial fibrillation. In June 1993 her pulse rate was around 100.1 added folic acid 5 mg tid to her program. She remained on digoxin. By March 1994 she was well. She had very few brief episodes of pain, no fibrillation and was able to walk 1.5 miles and to garden with no difficulty.

Niacin is an antidote against d-lysergic acid diethylamide[20] (LSD) and against adrenochrome. It reverses the effect of adrenochrome on the electroencephalogram in human subjects,[21] and reverses the psychotomimetic effects of adrenochrome when injected intravenously into human subjects.[6] It is also a safe and effective therapeutic agent in the treatment of the schizophrenias and several other psychiatric diseases. It is one of the main elements of Orthomolecular psychiatric treatment. Every physician who has duplicated the niacin schizophrenic studies has corroborated our earlier findings. However the treatment is not accepted because it was introduced during the wrong paradigm, the paradigm of vitamins as prevention only. For a full discussion see the reports.[22]

B) Ascorbic Acid

Vitamin C is nature's most effective water soluble antioxidant. We began to treat our schizophrenic patients with it in 1952 because we thought its antioxidant properties would decrease the conversion of adrenalin to adrenochrome. We did not include it in our double blind controlled experiments as we had been advised this would make the interpretation of the results too complicated. But we used it routinely in the clinically controlled studies. In one case a psychotic woman was to be given ECT in three days. I started her on ascorbic acid one gram each hour on Saturday. By Monday morning, after receiving 45 grams she was mentally normal and did not need any ECT. Her ulcerated breast which had failed to heal after mastectomy began to heal. She died 6 months later from her cancer but did so mentally normal. Since then, based on observations on thousands of patients, I have no doubt it does help promote schizophrenic recoveries.

C) Vitamin E

Vitamin E is now established as an effective nutrient for protecting against heart disease.[23] Coronary deaths were decreased 40 percent over 8 years in over 87,000 women and over 51,000 men by taking vitamin E, over 100 iu daily. But there is no reference to the pioneer work of Drs. Evan and Wilfred Shute in these two reports. In the The Summary,[24] The December 1973 issue, volume 25, Evan V. Shute, presented letters, abstracts and striking colored photographs of the response of wounds caused by freezing, by diabetes and by burns to the administration of vitamin E. In this issue he described six properties of vitamin E. The first two are most relevant: (1) It is both an antioxidant and improves the ability of tissue to use oxygen. (2) It prevents the formation of emboli from clots and extension of the clot.

It must do so by decreasing the formation of too much adrenochrome and similar chrome indoles. Antioxidant is a term more politically correct than the word vitamin.[26] Being an antioxidant has helped vitamin E gain a lot more popularity. (An excellent history of vitamin E and its controversy is provided by Di Cyan.[25])

The oxidation of the catechol amines to their chrome indoles is inhibited or decreased by the presence of ample supplies of the main anti oxidants of the body and the toxicity of normal amounts of adrenochrome —> adrenolutin is prevented by nicotinamide adenine dinucleotide. Thus the three main defence mechanisms against excessive formation of these indoles are vitamin C, the major water soluble antioxidant, vitamin E, the major surface or fat soluble oxidant, and vitamin B_3. There are probably other antioxidant defense mechanisms including coenzyme Q10 and selenium.

The first defense mechanism was eroded after we lost the ability to synthesize vitamin C in our body and we moved from a diet rich in this vitamin to the usual sub clinical scorbutic diet of most of the human population. The ascorbic acid-rich diet which we left was also rich in vitamin E compared to our modern diets. This has eroded the second major defense against excessive oxidation. The third defense mechanism, ample amounts of vitamin B_3, was removed with the major deterioration of modern food which has occurred within the past 200 years. Pellagra is one of the best examples of this. At one time a quarter of the admissions to southern mental hospitals were pellagrins. Schizophrenia was rarely described before 1800 A.D. Over the past two hundred years it has become one of the major disease problems in all industrialized countries. To sum up this argument, the genetic disease hypoascorbemia, and the gradual change of our food supply to a diet low in vitamin C, vitamin E and vitamin B_3 has made it impossible for the schizophrenic patients to take advantage of the beneficial defense mechanism against overproduction of adrenochrome and its derivatives.

D) Stress

Huxley, Mayr, Osmond and Hoffer[27] presented the hypothesis that schizophrenia involves a genetic morphism. Sir Julian and Professor E. Mayr had independently arrived at the same conclusion. We wrote, "The high frequency of schizophrenia cannot be maintained by mutation alone, and is evidence of a balanced morphism. The fertility (reproductive fitness) of schizophrenics is only about 70 percent of that found in socio-economically comparable normals. The incidence of the disease would therefore be rapidly reduced to the level where it is maintained by mutation alone, unless its selective disadvantages of lower viability and fertility were compensated by some selective advantage. The physiological advantages are high resistance to surgical and wound shock, to otherwise dangerous concentrations of insulin and other hormones, histamine etc., and to various allergies and infections." Hoffer and Osmond discussed this further.[14]

An excellent example of this occurred many years ago. I had admitted a chronic female schizophrenic from the back wards of the mental hospital in Maryland where she had been neglected as a patient for many years. When she arrived at our hospital she was found to be very ill physically. Her teeth were so bad a dentist who had examined her stated there was nothing that could be done except to remove them all. He planned to do that in two sessions. She was given a general anesthetic and half of her teeth were removed. The next day I saw her eating her meal with out any evidence of pain. She had no complaint whatever about her teeth. About two weeks later the remainder were removed. In the meantime she had been given Orthomolecular treatment and she was already much better. After this operation she complained frequently about the pain and now reacted as would most normal people to the pain. This was a dramatic example of the ability of the disease to act as an anesthetic in controlling pain. She flew back to Maryland. I drove her to the airport and there we met a friend. After the conversation when he did not guess she was schizophrenic I told him something about her history. However the family could not find a psychiatrist nor physician in Baltimore who were willing to supervise her treatment and eventually she went back to the same mental hospital, this time to a better ward than the one she had

been in before.

There is no overall advantage in having schizophrenia, in being sick. The advantage arises from having some of the genes of schizophrenia which do not express themselves, i.e. in the first order relatives of the patients. Parents, children and siblings of schizophrenics will have the advantages as will the recovered patients. I have observed that these advantages are in both physical and intellectual areas. When other psychiatrists begin to examine the patients and their relatives for these positive attributes, I have no doubt they will come to the same conclusion.

Physical - More youthful in appearance, especially as they age with much less grey hair, fewer attacks of auto immune diseases, more ability to tolerate pain, more resistance against bacterial infections. There is evidence they get cancer less frequently.

Intellectual - They are not more intelligent, but I have found them to more creative in their thinking and many have become top scientists, artists, writers, and poets.

Patients who are ill will regain these advantages when they recover. If every potential schizophrenic were to be given adequate amounts of vitamin B_3 before they became ill they would have much less probability of becoming sick and would then enjoy the same advantages. I have suggested that one of the genetic mechanisms is the loss of the ability to convert tryptophan into vitamin B_3 thus making the person more dependent upon external sources of this vitamin. In other words it is a vitamin B_3 dependency disorder. People who can make adequate amounts of vitamin B_3 would have less tendency to become schizophrenic. In the same way the need to make ascorbic acid while living on food very high in ascorbic acid became redundant many millions of years ago,[28] I suggest that the need to convert tryptophan to nicotinamide-adenine-dinucleotide (NAD) became redundant as long as the food contained adequate amounts of vitamin B_3.

Stress is a factor in precipitating the illness in people who have the genetic apparatus for making them sick. This is the conclusion of Yatkin and Labban.[29] They write, "The results of this study demonstrate that traumatic war events can be regarded as of primary importance for risk factors in triggering the onset of schizophrenia." The individual is not able to deal with the increased stress because he is not able to make enough vitamin B_3 from tryptophan, or from a deficiency of this amino acid as in pellagra.

The production of the oxidized derivatives of adrenalin such as adrenochrome and their rapid conversion into adrenolutin and 5,6 dihydroxy N-methyl indole is a defense mechanism against the toxic effects of adrenalin which is secreted in large amounts during severe and prolonged stress. It protects the heart against fibrillation and sudden death. Excessive amounts of these chrome indoles from the adrenolutin pathway leaks into the blood and then crosses the blood brain barrier. This interferes with synaptic transmission and creates the typical perceptual and thought changes found in these patients. The discussion of these ideas is presented in Hoffer and Osmond.[30] The price of having this increased ability to protect against stress on the heart is the schizophrenia.

If this hypothesis is correct, it follows that the two main components of biochemical treatment of the schizophrenias must be to decrease the biochemical effects of stress, i.e. decrease the secretion of sympathomimetic amines, and to use ample quantities of the antioxidants. Niacin and ascorbic acid have been examined most thoroughly. Vitamin E has received a little attention. The other natural antioxidants have not been investigated for their potential therapeutic properties. It would be very interesting to examine beta carotene and selenium.

The final common chemical pathway

This hypothesis represents the final common pathway in the production of the schizophrenias. Orthomolecular psychiatrists were the first to recognize that a large number of conditions will lead to one or more of the schizophrenic syndromes. Regardless of the precipitating factor, the final clinical pictures are similar. They include the perceptual and thought disorder symptoms combined with mood and behavioral changes. But the different syndromes will have different clinical courses and will requires specific treatment to deal with the inciting causes as well as dealing with the

final common pathway, the disorder of amine metabolism. These precipitating factors impinge upon the adrenalin —> adrenochrome transformation by driving the reaction from adrenalin to adrenochrome and on. For a detailed discussion of these and many other factors see Hoffer and Osmond.[6]

1) Factors which drive the adrenalin —> adrenochrome reaction.

a) Deficiency of nicotinamide adenine dinucleotide (NAD). Adrenalin loses one electron becoming an unstable oxidized adrenalin. In the presence of adequate concentrations of NAD and NADH it is reduced to adrenalin, the original molecule. But in the absence of NAD it loses a second electron to become adrenochrome which is no longer reducible to adrenalin. Thus a deficiency of NAD leads to an increase in the production of adrenochrome and its derivatives. The most common reason for the deficiency of NAD is a deficiency of vitamin B_3 as in pellagra or a dependency where for reasons unknown much more vitamin B_3 is required.[22] Pyridoxine is required for the conversion of some of the tryptophan to NAD. With a deficiency of Pyridoxine pellagra symptoms will also appear.

Walaas[32] showed how in the presence of NAD and NADH catecholamines lose one electron to form the unstable oxidized adrenalin. This in turn is reduced by the gain of one electron from the NAD system to reform the adrenalin. If NAD is lacking the oxidized adrenalin will oxidize further to form an aminochrome. Ceruloplasmin, a copper containing enzyme, is one of the oxidizing enzymes. This was a model of what can occur in the synapses. Dopamine is oxidized most rapidly followed by noradre-nalin and adrenalin.

Horrobin[33] in his review of the relationship between schizophrenia and essential fatty acids (EFA) pointed out that EFAs and in particular the PGE1 metabolite of dihommogamma-linolenic acid (DGLA) antagonize dopaminergic effects in many tissues. He suggests, "An EFA or PGE1 deficit could therefore lead to an apparent dopaminergic excess and produce many of the features of schizophrenia. In a study of five groups of schizophrenics from different countries there was a consistent lowering of linolenic acid. The amount of fat in the diet also altered the clinical severity of the disease and its outcome. There was a poor outcome with a diet high in animal (saturated) fats and a good outcome with diets high in vegetable and fish fats. Efamol improved memory and decreased symptoms compared to placebo. When four co-factors known to be important in EFA metabolism were added there was a further clinically significant improvement. The four factors were zinc, Pyridoxine, niacin and vitamin C."

Rudin[34] suggested that schizophrenia might be considered a form of substrate pellagra. The EFAs are converted in the body into the prostaglandin series of compounds. It is the deficiency of these substances which he thinks is a main factor. This can be produced by a deficiency of the substrate, i.e. the EFAs or by a deficiency of the essential nutrients which are required to catalyse the conversion. Pellagra is an example of a deficiency of niacin and of Pyridoxine. But according to his view a deficiency of other co-factors such as zinc could also lead to the same condition. In fact it does. Vitamin C is also a co-factor. Scurvy was considered one of the causes of psychosis when it was described around 100 years ago. At that time the differential diagnosis of dementia praecox (now called schizophrenia) was dementia praecox, tertiary syphilis, pellagra and scurvy.

Increased adrenochrome formation in the synapse would play havoc with the transmission of signals by binding with receptor cites on the neuron. It is a synaptic inhibitor, as are LSD and other hallucinogens.[35] Bindoli et al[10] speculated that noradrenochrome formed in the synapse by auto oxidation could combine with acetylcholine thus establishing a short circuit between the adrenergic and cholinergic pathways. Galzigna[36] had suggested this could cause the mental symptoms.

b) Allergic reactions - Somatic allergy symptoms such as eczema, rashes, and others are not as common in schizophrenic patients. They can also tolerate large quantities of histamine.[5] Both adrenalin and adrenochrome are anti histamines. Adrenalin is used to protect against anaphylactic shock. Adrenochrome has 4% of the anti histaminic activity of pyrilamine.[6] Adrenolutin present

in the blood in normal amounts could be another protective mechanism against allergic reactions. I have studied several patients where there was a clear relationship. When they were very ill they had no somatic allergic reactions but when they had recovered they suffered a recurrence of allergic reactions they had had before. A female patient recovered with the use of nicotinamide three grams daily. But her eczema came back so strong she stated she preferred to have some of the schizophrenia rather than the eczema and itching. I decreased the nicotinamide to 500 mg, three times daily. Her eczema vanished and her paranoid ideas came back to a small degree. She was content with the trade off.

But foods and other chemicals can induce the schizophrenic reaction. I have fasted (water only) over 200 patients for four days or more to determine whether they were allergic. These were patients whose response to megadoses of vitamin B_3 was not adequate. They were all better after the fast and most were normal. When they then ate the foods that they were allergic to they promptly became psychotic.[22] It can be turned off and on as simply as by giving volunteers LSD. I suggest the allergic reaction calls for the continued secretion of adrenalin, a higher level of aminochromes in the blood and the perpetuation of the psychosis. After the offending foods are removed this mechanism is not needed as much, there is a decrease in the aminochrome levels and the psychosis is no longer present.

c) The hallucinogens - Many of the hallucinogens are indoles thus resembling adrenochrome in structure and many are similar to adrenalin in structure. An example of the first is d-lysergic acid diethylamide (LSD), and of the latter is amphetamine and the methylene dioxy amphetamines (MDA). LSD does not always cause the typical hallucinogenic reaction. During our research with psychedelic therapy for alcoholics using LSD[37] we had many patients whose only response to 200 mcg of LSD was severe anxiety and tension. We would then double the dose to 400 mcg but even then a few did not react. This means that LSD in itself is not an hallucinogen but it must create the reactions in the body which do produce the typical psychiatric reaction. A few patients were given adrenochrome intravenously three hours after they had been given the LSD and had not reacted. Within a few minutes after the injection they went into the usual type of reaction with perceptual changes and thought disorder. Hoagland, Rinkel & Hyde[38] suggested that LSD might owe its psychotomimetic properties to a disturbance of adrenalin metabolism.[7]

It is likely that LSD increases the formation of adrenochrome and that the usual reaction results from the activity of both LSD and adrenochrome. When the body can not make enough adrenochrome the LSD by itself causes a lot of anxiety and tension. Injecting adrenochrome allows the full experience to develop. Perhaps it does so by inhibiting amine oxidase and catechol-O-methyl transferase. The excess adrenalin would than be changed into adrenochrome by auto oxidation in the synapse.

Amphetamines are similar in structure to adrenalin. But it may also act by increasing adrenochrome levels. It has been reported that amphetamines displace dopamine from its vesicular stores into the cell where auto oxidation can occur forming dopachrome.[39]

d) Increasing oxidation by fever, hyperbaric oxygen and copper. Fever increases the rate of the chemical reactions in the body. Every ten degrees rise in temperature doubles the rate. Thus a fever of 104°F can have an appreciable effect. The association between high fever and delirium is not rare. While a delirium is not schizophrenia it is sometimes difficult to distinguish them. Hyperbaric oxygen is also known to increase perceptual problems.[6] Hyperbaric oxygen is much less toxic for animals after the adrenal glands were removed while injecting adrenalin increased toxicity.[6]

Copper increases the rate of auto catalytic reactions. The association between increased blood copper (and decreased zinc levels) is not strong but several studies have linked them. Penicillamine, a powerful copper chelator, has been used to assist in the treatment of schizophrenia. In 1954 I saw an unusual response of a schizophrenic patient to penicillin. She had not responded to any treatment including ECT. I gave her penicillin for an infection of her wrist. Within five days there was a substantial improvement. Shortly after that penicillamine, a derivative

of penicillin, became available and I incorporated that into the treatment program I was then developing. I gave it to my treatment failures. In 1960 in *The Chemical Basis of Clinical Psychiatry*[9] I described four treatment failures who responded when penicillamine was added. They were given ECT, niacin, three grams daily, ascorbic acid three grams daily and penicillamine two grams daily for up to two weeks. They had not responded to the same treatment without the penicillamine. Of the four, three became normal and one much improved.

Another childhood schizophrenic was treated by his father against the wishes of his psychiatrist.[40] His father, a physician, called me in 1960. He told me his son age 12, had just been declared hopelessly ill by a professor of psychiatry and he had been advised to commit him to a mental hospital and to forget about him. He immediately began a search of the local medical library and ran across our first 1957 publication. I suggested he start him on niacin three grams daily. These large dose tablets were not commercially available then. However he was able to persuade a company in Oregon to make him a batch containing 500 mg. But the psychiatrist in charge refused to give the pills to his patient claiming that he had tried them before and it had not worked and secondly that it would "fry his brains".[41] Both statements were lies. The physician then began to feed his son jam sandwiches every day containing the niacin. He did this while they were walking in the grounds of the university Hospital. After about six weeks the boy told his father he wanted to go home. He was discharged, remained well for 18 months. He was able to complete grade 12 in the top USA five percentile.

His father had asked me how long he should remain on the vitamin. I suggested that one year might be adequate. To be on the safe side he was on 18 months. But after the vitamin was stopped he relapsed. When the vitamin was resumed he did not respond. I then suggested he add penicillamine two grams daily until he had some side effect. He was on for several weeks. He became well and has remained normal. He became a research psychiatrist.

In 1965 in a Nato Advanced Study Institute held at Drammen, Norway, August 2-14, 1965, I reported, "We gave two grams of penicillamine per day for 10 to 20 days to patients who had not responded to any previous therapy including niacin, electroconvulsive therapy and tranquilizers. Since these studies began we have treated about 20 and of these one half have been salvaged and are well. This is a controlled study since each subject had not responded to a series of therapeutic efforts and natural remission occurring within the period of penicillamine therapy is much less likely. In half the cases a slight fever and faint rash occurred at six to seven days. It was usually followed by remarkable improvement within 24-48 hours. The slight temperature elevation was a signal to discontinue medication and the temperature was normal next morning. The follow up period is now seven to eight years." These patients remained on the vitamin therapy.[42] The use of penicillamine is described in *How To Live With Schizophrenia.*

Greiner[43] studied the melanosis caused by large doses of chlorpromazine in some schizophrenic patients. The drug might have accelerated the formation of excessive melanin but he also found it was present in schizophrenic patients who had not been given this drug. He checked autopsy material on 30 patients. In order to reverse the melanosis he placed his patients on a low copper diet and gave them penicillamine 1.5 g daily. The pigmentation began to clear. But he also observed clinical improvement in their mental state, "During the penicillamine therapy and the usage of the low copper diet an interesting observation was made by our psychiatrists: most of our schizophrenics showed some mental improvement, especially in the so called negative symptoms. Since our first observations we repeated this therapy and observed the same results, conducting a double blind pilot study..." (Nicolson et al, 1966).[44]

But penicillamine has another property. It changes adrenochrome into 5,6 dihydroxy N-methyl indole, also called leucoadreno-chrome. This is a non toxic indole which Osmond and I found had good anti tension properties.[9] This may be another explanation of its therapeutic properties. Decreasing copper levels will decrease the formation of adrenochrome by auto catalytic oxi-

dation and removal of the adrenochrome into an innocuous indole will further lessen the amount of this hallucinogen in the body. e) Monoamine Oxidase Inhibitors. The most commonly used monoamine oxidase inhibitors are three of the older anti depressants, tranylcypromine (Parnate), isocar-boxazid (Marplan) and phenelzine (Nardil). These compounds are euphorients, stimulants and hallucinogens. I have had most experience with parnate and have seen a major transient psychosis produced by large doses of this antidepressant. This is not surprising since it does block one of the main pathways of adrenalin metabolism and forces the auto oxidation of adrenalin into adrenochrome. It is also similar in structure to the catechol amines. The psychosis promptly vanished when the parnate was discontinued.

2) Factors which suppress the formation of adrenochrome or remove it from circulation.

Several well known antioxidants are being investigated for their therapeutic properties, vitamin E against cardiovascular disease, beta carotene and selenium for their anti cancer properties, and vitamin C for a large number of clinical uses. Only vitamin C has been studied intensively for the treatment of schizophrenia. These originated in our research in Saskatchewan in 1952. I have found vitamin C to be very helpful in controlling severe anxiety and tension in schizophrenic patients, and in decreasing the incidence of relapses which may occur after a virus episode such as the flu. We discussed the relationship between vitamin C deficiency and schizophrenia.[45] The beneficial effect of vitamin C was confirmed by Kanofsky and Lindenmayer.[46] They gave two to six grams per day of ascorbic acid to 21 long term neuroleptic refractory schizophrenic in patients along with the medication for one month. In several definite clinical improvement was noted by the treating staff and in most cases by the patients as well. One who had been floridly psychotic at the beginning of the treatment achieved full remission within two weeks. A response rate of 33 percent for this type of chronic refractory patient is very good. Perhaps if they had used even higher doses, up to the sub laxa-tive level, they might have seen additional responses. There have been a few studies using vitamin E to reverse the tardive dyskinesia induced by tranquilizers but the results are equivocal. These studies did not aim at any general improvement in the psychotic state. There is some evidence that selenium may have a therapeutic role.[47] All the anti oxidants should be examined to determine which ones have the greatest therapeutic usefulness. Coenzyme Q10 was found to enhance memory and attention in a small series of chronic schizophrenic patients.[48] The ten subjects were on clozapine or haldol. This may mean that the impairment of these cognitive functions by these drugs is partially reversed by Q10, 300 mg daily.

There is thus very robust evidence that driving the adrenalin adrenochrome reaction toward adrenochrome is a causal factor in producing schizophrenia and inhibiting or reversing the reaction is therapeutic.

Normal people will produce a more or less constant amount of adrenalin oxidized derivatives with slight increases during stress and decreases when relieved of stress. In schizophrenics I suggest that there is an increase in the amount of adrenochrome and its derivatives. This may cause paranoid or other psychotic ideas which can be suppressed for long periods of time. If they are exposed to severe prolonged stress either from psychosocial stresses (being fired, being rejected, etc.) there will be a major increase in adrenalin production overwhelming the ability of the enzymes to cope and the overload into auto oxidation will begin. The increased production of adrenochrome will then interfere with brain synaptic transfer of signals and cause schizophrenia. Schizophrenia may thus be considered a failure of the enzymatic degradation of adrenaline forcing the body to use auto oxidation to prevent death from the excess adrenalin.

The final common psychological pathway

The interference with the synaptic mediators caused by the adrenochrome and other chrome indoles produces the perceptual distortions and thought disorder as do the hallucinogens. This is described in our book *How To Live With Schizophrenia.*[19]

Conclusion

I have presented some of the biochemical and clinical evidence to support the adrenochrome schizophrenia hypothesis, i.e. that schizophrenia has evolved too successfully in dealing with chronic and severe stress mediated by the release of adrenalin. The increased production of adrenochrome and similar chrome indoles, the final common chemical pathway, leads to the characteristic perceptual and thought disorder changes. In 1965 I suggested, "The hypothesis that I now propose is that when the reaction is driven too far, causing excessive formation of aminochromes, there will be an inhibition of synaptic transmission that will be expressed psychologically as disturbances in perception, thought and mood, including hallucinations of one or more of the sensory modalities".[49]

The final working hypothesis for the schizophrenias is as follows:

A) Under normal conditions adrenaline and adrenochrome are in balance.

B) Severe stress —> too much adrenalin and other sympathomimetic amines. Excessive concentration of adrenalin in heart muscle. Oxidation of adrenalin in myocardium to adrenochrome, and to adrenolutin. Adrenochrome causes fibrillation and other cardiac pathology and dysfunction.

1) Normal stress - adrenalin (oxidase) —>adrenochrome
2) Increased stress
   a) mono amine oxidase
   b) O methyl transferase
   c) Phenolsulfotransferase
   d) Other enzymes

Increased alertness, anxiety, tension, etc.

3) Severe prolonged stress - auto oxidation —> adrenochrome

Common final pathway to the schizophrenias. When the antioxidants vitamin C, vitamin E (and others) and vitamin B_3, are lacking the oxidative reactions are facilitated and the protective action of vitamin B_3 is less effective.

C) Leakage of adrenochrome and its de rivatives such as adrenolutin into the blood and into the brain

D) Schizophrenia - perceptual illusions and hallucinations combined with thought disorder. Treatment should cover two main areas: (1) the reduction in the secretion of catecholamines, i.e. decrease stress by medication, by removing the inciting factors such as hallucinogenic drugs, allergens, toxic elements such as copper and iron when present to excess and infections, and psychosocial intervention including, if necessary, treatment in hospital. (2) decrease the formation of adrenochrome and similar chrome indoles using anti oxidants such as ascorbic acid and vitamin E and others in optimum doses and using vitamin B_3 (niacin or niacinamide or in combination) in optimum doses to protect against the toxic effect of the chrome indoles on the brain.

Why do other diseases respond to the combination of vitamin B_3 and the antioxidants?

Over the past 40 years I have been surprised at the number of diseases which respond to the combination of vitamin B_3 and the antioxidants.[50] I am no longer surprised since the role these natural substances play in controlling the chemical effects of stress have become clear. Stress must play a role in nearly every disease with the production of excessive amounts of adrenalin and its oxidation products as main factors. Therefore any combination of nutrients which will protect the body against the excess of the catechol amines and their chrome indoles must also be therapeutic for these diseases and will permit the body to repair itself more effectively. I consider schizophrenia a special case of stress accompanied by severe auto oxidation of adrenalin to adrenochrome, whereas with the other non psychotic conditions there is no excess auto oxidation and therefore no excess production of adrenochrome.

Hypothesis Relating Cancer and Schizophrenia

Small amounts of adrenalin are produced all the time even when asleep, but during the day and when exposed to stress the amount is increased. The continual, even if fluctuating level of adrenalin will ensure a constant production of adrenochrome and its conversion to adrenolutin and other indoles. I sug-

gest that this is one of the mechanisms the body uses to deal with excess mitosis. The leukocytes probably destroy abnormal cells by releasing adrenochrome which has the properties of a free radical and will destroy the cell. It is recognized that pro oxidants are needed to destroy cancer cells. Adrenochrome is probably the best and safest natural pro oxidant in the body.

This hypothesis suggests a number of testable sub- hypotheses:

A) A deficiency in the production of adrenochrome will increase the incidence of cancer and decrease the incidence of schizophrenia. This can arise from: (1) inadequate production of adrenalin, (2) a deficiency of enzymes which convert adrenalin to adrenochrome, (3) a deficiency of oxygen, and (4) auto oxidizing systems such as copper or iron.

A deficiency of adrenalin can arise from a deficiency of tyrosine but this is highly unlikely. It can also arise from extirpation of the adrenal glands, one of the major sources of adrenalin. It could arise from a lack of stimulation of the sympathetic nervous system. Factors such as staying in bed all day would decrease the need for adrenalin to help control blood pressure. An absence of challenges to the body both psychological and physical could also produce a deficiency of adrenalin. It could also come about by the use of anti anxiety drugs and tranquilizers which effectively isolate the individual from stress. Infections are stressful and increase the activity of the immune system. The use of tranquilizers since 1950 has effectively removed this spur to the immune system for many people and may be another factor in decreasing adrenalin and therefore adrenochrome production. Helen Coley Nauts made the very sensible suggestion that the loss of repeated episodes of infection by bacteria since the introduction of antibiotics may be a major factor in the rising prevalence of cancer in the highly industrialized world.

B) Excessive formation of adrenochrome will decrease the prevalence of cancer and will increase the prevalence of schizophrenia. This can arise from the following factors: (1) an overproduction of adrenalin for prolonged periods of time due to excessive stress of various types, (2) an increase in the production of adrenochrome due to an increase in the conditions which favor this reaction such as more of the oxidizing enzymes, too little activity of the other enzymes which convert adrenalin to other non indolic substance, an increase in oxygen tension, an increase in oxidizing metals such as copper or iron, and finally too much inhibition of the reaction by any factor which would normally take adrenalin down the non adrenochrome pathway.

If cancer did develop in a schizophrenic person it would probably be less invasive and easier to treat with a better outcome. Patients with cancer would be less likely to become schizophrenic, and patients with schizophrenia would less likely get cancer. Both of these propositions are true. Since 1977 I have examined and treated 620 patients with cancer covering almost the entire spectrum of types of cancers and organs involved. Only two were schizophrenic with the schizophrenia predating the discovery of their cancer, both breast cancer. In both cases the response to treatment was excellent. The usual stated incidence of schizophrenia is said to be 1%. I think it is closer to 2%. Therefore one would expect that out of this series I would have seen between 6 and 12 cases.

Kanofsky[51] (1994) concluded that schizophrenic patients have a lower incidence of lung cancer compared to the general population even though they are much heavier smokers. He also found that smoking did not lower their ascorbic acid blood levels as much as it does in other people. This he thought lowered their risk on exposure to smoking but according to the adrenochrome hypothesis it might equally have arisen from the increased concentration of adrenochrome. Kanofsky pointed out on the basis of a literature search that in general schizophrenics have a higher death rate than do the general public. Some studies have shown they have a greater rate for non lung cancer and a lesser or greater rate for all other cancers. The only clear finding is the decrease in lung cancer. Perhaps if they were non smokers their lung cancer rate would be even lower.

I have seen many thousand schizophrenic patients since 1952. Currently I have at least 500 chronic patients under my care. The total incidence of cancer is very low. From

my current list only two have cancer, the same two that I referred to in the cancer series. I would expect a much higher incidence of cancer in the schizophrenic group unless there was this incompatibility between the two conditions.

A Natural Defence System Against Cancer

To control cancer one needs two sets of reactions: (1) Pro oxidants e.g. adrenochrome, which are used by the body to destroy the tumor cells. Leukocytes kill by discharging free radicals into the bacteria or cell they are attacking. Adrenochrome is a natural superb free radical. (2) Antioxidants to neutralize the free radicals as soon as their work is done to prevent injury to other cells and tissues. The adrenalin-adrenochrome system provides a very good method for controlling mitosis. The adrenalin is maintained by repeated exposure to stress. The adrenalin is converted to adrenochrome and is used by the body as needed, and the excess is neutralized by conversion into other indoles which are not as toxic. This is done by the natural antioxidants such as ascorbic acid, vitamin E, beta carotene and other anti oxidants found in food.

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*There was no reference to any of the basic adrenochrome papers dealing with its possible formation in the body and with its psychological properties. However even this paper was too radical for the National Institute of Health, Washington, DC. The authors in a footnote write, "This article was written by the authors in their private capacity and does not necessarily reflect the views of the

NIMH". The NIMH has been the leading critic and opponent to our adrenochrome hypothesis since 1954.

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