The Adrenochrome Hypothesis and Psychiatry

A. Hoffer, M.D. Ph.D. and H. Osmond, M.D.

First published in Journal of Orthomolecular Medicine, Vol. 5, No.1, 1990

Introduction

The adrenochrome hypothesis of schizophrenia (Hoffer, Osmond and Smythies, 1954), was stimulated by the work of Osmond and Smythies (1952) which focused on methylated derivatives of adrenalin as possible endogenous schizophrenogens. They showed that the experience which followed the ingestion of mescaline was in many ways similar to the experience induced in normal people by schizophrenia. This drew attention to derivatives of adrenalin (and of all the sympathomimetic amines and their precursors) as etiological factors. However, in 1952 very few of these compounds had been studied. With our resources we were forced to limit our studies to one derivative, adrenochrome, an oxidized, coloured derivative of adrenalin. So little was known about its chemistry it was not surprising chemists had concluded, incorrectly, it was inherently unstable and difficult to study. We allocated much of our chemical researches to this interesting substance. As a result, under the direction of Dr. R. Heacock (1959, 1965), an enormous body of data was gathered and published detailing the chemistry of adrenochrome, its synthesis, metabolism, conversion to other products and its reactions with substances like ascorbic acid.

Adrenochrome is a member of a class of chemicals known as aminochromes, each one derived by the oxidation of its precursor amine. Thus, 1-dihydroxy phenylalanine (L-dopa) is oxidized to dopachrome; tyrosine to a series of coloured indoles; noradrenalin to noradrenochrome and adrenalin to adrenochrome. The chemistry of these oxidation reactions is very complex for these compounds are very reactive. They are formed via free radicals and rapidly break down to several classes of trihydroxy and dihydroxy N methyl indoles. Adrenolutin is the best known example of trihydroxy N methyl indole, and leukoadrenochrome is the best known of the dihydroxy N methyl indoles. Both are derived from adrenochrome. Adrenolutin is coloured yellow and is toxic, as is adrenochrome. It is psychotomimetic. Leukoadrenochrome is colourless and non-toxic. On the contrary, even in small doses given sublingually, it has antitension and anti-anxiety properties. Adrenolutin is more stable than adrenochrome.

The aminochromes polymerize readily, forming a complex system of melanins. Recently the melanins have been considered among the most important organizing systems in the body.

We also published a large series of clinical studies showing adrenochrome and andrenolutin were hallucinogens. These studies are described in our book, *The Hallucinogens* (Hoffer, Osmond, 1967). That review is still pertinent for the whole area of adrenochrome investigation went into hibernation for a number of reasons, especially in psychiatry. In 1981 Hoffer wrote, "Interest in the amino-chromes is returning because some of the properties of the centrally active amines can not be understood unless their degradation into these oxidized derivatives is considered."

The dopamine hypothesis of schizophrenia is widely known and accepted, even though it is a simple "too much or too little" idea, i.e. in schizophrenics there may be too much dopamine, or too little. Major support was provided by the finding that tranquilizers block dopamine receptors. Ascorbic acid also blocks dopamine receptors but so far this finding has been ignored–it is embarrassing to have a vitamin have the same effect as a tranquilizer.

Hoffer (1981) concluded, "The adrenochrome hypothesis accounts for the syndrome of schizophrenia more accurately than do any of the competing hypotheses. The two main hypotheses are superfluous since they are accommodated by the adrenochrome or, more accurately, the aminochrome hypothesis."

Recently Cadet and Lohr (1987) came to the same conclusion. They summarized their report as follows: "The dopamine hypothesis has been criticized because it fails to explain many clinical facts and biochemical findings in schizophrenic patients. 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."

We find this hypothesis very interesting for it is exactly what we have been proposing since we first publicly discussed our adrenochrome hypothesis in 1952 before the Dementia Praecox Committee of the Scottish Rites Masons in New York.

Hoffer (1981) wrote, "Unfortunately the many leads developed by the adrenochrome hypothesis have been neglected by research institutions for a number of reasons. The critical and hostile attitude of the professional associations and granting agencies discouraged scientists from entering this difficult but challenging field. Fortunately the climate of opinion is changing. I expect that for the next decade the aminochrome hypothesis will receive more careful attention."

We think it is appropriate to review the aminochrome hypothesis of schizophrenia, for in our opinion it is a powerful hypothesis. Hypotheses are needed to direct research. They are not forever, for with new information they must inevitably change. But the aminochrome (adrenochrome) hypothesis has not yet run its course. It should lead to even better treatment for all diseases in which oxidation (by enzymes or by auto-oxidation) plays a role

The Original Adrenochrome Hypothesis

This was developed between 1952 and 1954 when little was known about the chemistry and physiology of adrenochrome. All we did know was that it was readily formed by oxidation of adrenalin to a red compound in solution. It was "known" that it was inherently unstable and therefore could not form stable crystals. But very little was known about enzymes which could oxidize adrenalin, about pathways, and whether it was made in the body. Nothing was known about its effect on the brain. it was known to be an enzyme inhibitor and had antimitotic properties. But we suspected it might be an hallucinogen because pink or deteriorated adrenalin was, and it resembled the few known hallucinogens like d-lysergic acid diethylamide (LSD), and ibogaine. Mescaline is not an indole but resembles adrenalin and could be indolized in the body. It is now known that methylated derivatives of sympathomimetic amines do form aminochrome derivatives. Aminochrome is a term applied to all chrome indoles; derived from catecholamines (sympathomimetic amines).

Our hypothesis was prepared as a series of simple equations:

1. Noradrenalin ⟶ Adrenalin
2. Adrenalin ⟶ Adrenochrome

i.e. schizophrenia arose in an individual when too much adrenochrome was formed, that adrenochrome then interfered with brain function as would LSD, and that created the essential stage for the formation of schizophrenia.

To test this hypothesis we needed data in a minimum of three areas: (1) was adrenochrome made in the body, where, how much, by which enzymes? (2) was

adrenochrome an hallucinogen? (3) would reversing or preventing the formation of adrenochrome be therapeutic for schizophrenia. If these were all found to be true, it would provide strong support for the adrenochrome hypothesis. If any one were negative it would be very difficult to sustain. We believe our adrenochrome hypothesis is a good one and will now show why we think so.

Is Adrenochrome Made in the Body?

As soon as scientists discovered adrenalin turned pink in solution it appeared likely that what happened *in vitro* could also occur in the body. Adrenalin is a member of a class of catecholamines which polymerize very readily. The melanins are these polymerized, oxidized and indolized catechol-amines. All the conditions required for the oxidation of adrenalin to adrenochrome in vivo are present. These are: (1) the substrate - noradrenalin, adrenalin; (2) the enzymes and metallic oxidizers which convert adrenalin to adrenochrome, or accelerate its auto-oxidation. Auto-oxidation does not require an enzyme. The oxidation of adrenalin to adrenochrome in water is an example. It requires oxygen and is accelerated by traces of metal such as copper ions. We have discussed the theoretical argument for the formation of adrenochrome in several previous reports (Hoffer, 1981, 1983, 1985; Hoffer and Osmond, 1967).

Ideally, final proof would have been gained when adrenochrome crystals extracted from the body are in one's hand. But because adrenochrome in solution is so reactive it is highly unlikely it can be extracted. It will have to be stabilized first by combining it with another molecule. Adrenochrome semicarbazide is a stable derivative. Perhaps this could be made in blood or other fluids and then extracted.

However, any stable derivative will do. Nature has already made a number of stable derivatives of the catecholamines. Thus, tyrosine forms the melanins in skin and other tissues. Albinos are without melanin pigment because their bodies do not have the enzyme needed to oxidize the tyrosine to melanin. Albinos do have a reddish pigment in the pigmented areas of their brains. They can form pigmented indoles, most likely from noradrenalin and adrenalin. Tyrosine melanin is more in the brown/black/red area compared to neuromelanin which is usually red. Adrenochrome and noradrenochrome are red. (Hegedus and Altschule, 1968, 1970, 1970a; Hegedus, Kuttab, Altschule and Nayak, 1981).

Adrenolutin is another derivative of adrenochrome and more stable in blood. Hoffer and Kenyon (1957) showed that the compound made in blood from adrenaline (Leach and Heath, 1956), was adrenolutin. Leach and Heath found that the rate of conversion was greater in schizophrenic blood compared to normal blood. In our studies, adrenaline added to serum was gone within one hour and replaced by adrenolutin. There it is more stable due to the presence of reducing substances such as ascorbic acid, glutathione, and sulfhydryl groups in protein. Copper ions increase the oxidation of adrenaline to adrenochrome.

Recently Dhalla, Ganguilly, Rupp, Beamish and Dhalla (1989), measured adrenol u tin in plasma. They found surprisingly high concentrations. In rats, injection of adrenaline was followed by a several-fold increase in adrenolutin formation in plasma. The level came down at 15 minutes and increased thereafter. Large amounts of injected adrenaline released endogenous catecholamines. Injections of adrenochrome and adrenolutin yielded maximum blood levels at 15 minutes. Injections of noradrenaline and dopamine also increased adrenolutin levels. The natural levels in blood were many times greater than concentrations of adrenaline.

Doubt about the ability of the body to make adrenochrome and its derivatives has been replaced by interest. This is especially

true in three areas: (1) neurology (Graham, 1978, 1979; Graham, Tiffany, Bell and Gutknecht, 1978); (2) cardiology (Beamish, Dhillon, Sinsal and Dhalla, 1981; Karmazym, Beamish, Fliesel and Dhalla, 1981; Sinsal, Yates, Beamish and Dhalla, 1981): and more recently, (3) psychiatry (Jeste, Lohr and Mani, 1985; Cadet and Lohr, 1987).

The research in cardiology shows that adrenalin is very readily oxidized into adrenochrome. Adrenochrome is toxic to myocardial tissue and may be responsible for fibrillation and sudden death under stress. Myocardial tissue is very high in the enzyme which oxidizes adrenalin to adrenochrome.

Cocaine blocks two of the enzyme systems the body normally uses to destroy adrenalin, thus forcing more of it into the adrenochrome pathway. Is this the explanation for sudden death associated with cocaine abuse?

The neurological studies suggest that dopachrome, the oxidized derivative of L-dopa, is responsible for some of (lie degenerative changes in the brain. Jeste et al (1985) point out that the cerebral cortical areas rich in catecholamines are prone to age related neuronal loss. Brain stem areas containing high concentrations of dopamine and noradrenalin exhibit significant neuron loss with aging. These patients also risk developing psychotic symptoms since dopachrome is like adrenochrome

Vitamin B_3, niacin or niacinamide, protects brain tissue against some of the toxic effects of adrenochrome such as EEG changes and schizophrenic-like symptoms (Szatmari, Hoffer and Schneider, 1955). In our opinion all patients with Parkinsonism should be taking vitamin B_3. It will not protect them from the ataxia and tremor, but will prevent psychiatric changes (or reverse them if they have already occurred), and may prevent further loss of neurons,

Are the Aminochromes Hallucinogens?

The two classic hallucinogens are mescalin, derived from the cactus, peyote, and d-lysergic acid diethylamide (d LSD-25) which is extracted from ergot. LSD is the most active of the hallucinogens, i.e, 100-200 mcg will cause a reaction lasting six or more hours. Much more mescalin is required to produce a similar reaction. These compounds do not cause schizophrenia, but do cause a reaction in normal people which mimics schizophrenia. They produce what is usually written as "model psychosis."

Only three of the aminochromes have been tested for hallucinogenic properties: adrenochrome, adrenolutin and leukoadrenochrome (5.6 dihydroxy N Methyl indole). The first two are hallucinogens but the third is not. On the contrary, it is a very effective anti-anxiety compound when given sublingually for some very tense individuals, producing an effect within five to ten minutes. The evidence for these conclusions is available in *The Hallucinogens* (Hoffer, Osmond, 1967; Hoffer, 1962). The reactions induced by adrenochrome and by adrenolutin are somewhat different. Adrenolutin causes changes which are more subtle, with fewer perceptual illusions. It tends to flatten mood more and its effect lasts longer. Adrenochrome causes more perceptual changes but they are rarely as pronounced as those caused by LSD or mescalin. Its effect may last a long time. It produced a two-week paranoid depression in one of us (A.H.) and a one-week paranoid depressive reaction with visual illusions in a distinguished colleague of ours.

Adrenochrome potentiated the activity of LSD in a few alcoholics. Between 1954 and 1962 we treated several thousand alcoholics with psychedelic therapy using LSD, usually 200 to 400 mcg. In the usual reaction the first changes would occur in about one hour. Increased anxiety was usually the first reaction. Within two hours they would experience the usual reaction. Anxiety would fluctuate but was seldom high or a problem. However, many alcoholics did not have the usual reaction even with 400 mcg. They

remained very tense and uncomfortable all the time. This group did not profit from their experience. In a few patients an injection of adrenochrome after two hours would, within a few minutes, bring on the typical LSD reaction. We concluded that LSD did not act as an hallucinogen per se but that it induced an increase in the production of adrenochrome which was the hallucinogen. An individual who could not make enough adrenochrome would not be able to have the typical LSD reaction. This conclusion was supported by our earlier finding that vitamin B_3 markedly reduced the intensity of LSD reactions whether given before or during the LSD reaction. By blocking the adrenochrome effect it would also block the effect of LSD. It would also explain why Brom LSD, a very potent antiserotonin, would not be an hallucinogen. Brom LSD probably has no effect on adrenalin oxidation and would not increase the formation of adrenochrome. These are interesting speculations. Perhaps now with increasing interest in free radical hypotheses and in oxidized derivatives of the catecholamines, scientists will direct their interest back into these areas.

Will Blocking the Production of Aminochromes be Therapeutic for Schizophrenia?

Our two basic equations immediately directed our attention in 1952 to the need for compounds which would decrease the formation of adrenochrome. We needed compounds that were safe, could be taken over a lifetime and which had no side effects. We realized that any treatment for schizophrenia must be life long. It is impossible to give ECT or insulin for life, which explains why these treatments were successful for short periods. We wanted to decrease the formation of adrenalin, not stop it, by pulling methyl groups away from noradrenalin. We also knew that adrenochrome was a respiratory enzyme inhibitor and that the respiratory enzymes were made in the body from thiamin, riboflavin and vitamin B_3. Increasing the amount of respiratory enzyme is one way of overcoming an inhibition. Only one compound, vitamin B_3, met all these requirements. It is a vitamin (more accurately, an amino acid), water soluble, safe (an LD 50 of 5 grams per kilogram in animals), has few side effects and fewer dangerous side effects, and is a methyl acceptor. Furthermore. it was then known to be the antipellagra vitamin, i.e. a vitamin B_3 deficiency caused pellagra. The most prominent effect of pellagra is the schizophrenic syndrome which in its early stages is not distinguishable from schizophrenia. We decided to test vitamin B_3.

We also wanted to decrease the oxidation of adrenalin to adrenochrome, and for this we needed a reducing substance which met the same criteria for safety. The only compound which fit these criteria was ascorbic acid. Thus our first pilot trials were done using a combination of vitamin B_3 and ascorbic acid. We also planned on studying thiamin and riboflavin but were not able to do so. By this time we were planning our double blind controlled experiments. In a double blind experiment, testing one compound against placebo is difficult. To add two more compounds would make it impossible. We had no resources, few research personnel and very little money. When our double blind design forced us to select one compound only, it was obvious it would have to be vitamin B_3. However, it also forced us not to use ascorbic acid

The first patient treated with large dose of vitamins was Mr. K.C., a catatonic young man who had not responded to insulin coma or ECT and was dying. He was given both vitamin B_3 and ascorbic acid and was well in thirty days. We believe our results have always been better when both vitamins were used, but we can not point to any controlled experiment to prove this. We routinely now use both,

By 1952 when we needed 500 mg tablets, none were available. The largest tablets available were 100 mg and contained

mostly filler in order to make a decent sized pill. Giving three grams per day, or thirty of these pills, would make most people ill from the filler. In fact, nearly twenty years later, a mental hospital in southern California wanted to repeat our work, but their pharmacy would only supply them with 100 mg tablets, Most of their patients developed nausea and vomiting and the study was destroyed. I believe they blamed the niacin. We therefore obtained a barrelful of pure vitamin B_3 crystals, niacin and niacinamide, and these were placed into capsules. A few years later drug companies prepared 500 mg tablets for us. Kirkman Laboratories in Portland, Oregon, was the first company to prepare 500 mg tablets in the USA.

We will not again review the many clinical studies, double blind and open, which prove that schizophrenic patients treated with vitamin B_3 have a much better prognosis. We reported the first double blind controlled experiments in psychiatry cloney Hoffer, Lucy, Osmond, Smythies and Stepamuch (1954). Before tranquilizers were introduced it was the only effective treatment. Tranquilizers rapidly control symptoms but patients on tranquilizers will not recover if this is the only treatment. Tranquilizers replace one psychosis by another. However, they are essential for many patients if we are to keep patients out of mental hospitals. The evidence that vitamin B_3 is effective is available in a very large orthomolecular literature. From our early studies (four double blind) we concluded:
1. That vitamin B_3 doubled the recovery rate of acute schizophrenics compared to placebo.
2. That chronic schizophrenic patients did not respond.

Modern orthomolecular therapy is more sophisticated, wide-ranging and effective. Treatment includes an optimum combination of nutrition, vitamins in optimum doses, drugs and psychotherapy. The prognosis for chronic patients is much better today. Our work established one vitamin B_3, as a useful adjunct to treatment. This opened up the field, which now involves a large number of nutrients. When tranquilizers are used they are decreased gradually as patients respond to the nutritional treatment. A combination of drugs and vitamins takes advantage of the rapidity of action of the tranquilizers and the efficiency of the orthomolecular treatment in bringing about recovery.

Tranquilizer Syndrome

Tranquilizers alone can produce remarkable improvement, but very few patients remain better when they are discontinued, and no patient can be normal while on tranquilizers. Airline companies understand this and will not permit their pilots to fly if they know they are taking tranquilizers. It is not difficult to understand why, one need only accept two propositions as true:
1. That tranquilizers are helpful when given to schizophrenic patients.
2. That normal people are made ill if they take tranquilizers. The tranquilizer syndrome includes apathy, disinterest, and diminished ability to think and reason normally.

Schizophrenics are prepared to put up with the tranquilizer syndrome, especially when they still remember the previous schizophrenic state. However, later on they are not, for they realize they can not function normally on tranquilizers unless the dose is very small, or unless their job or station in life requires very little; it is not difficult to sit and stare at a blaring TV, even when heavily tranquilized.

We have challenged many to show our error in the two basic statements. No one has. If, then, they are true, it follows that tranquilizers can never make a person normal, for as they begin to approach normality, i.e. lose perceptual symptoms, lose paranoid ideas, and become less depressed, they will respond to the tranquilizer as will any normal person, i.e. they will become sick with the tranquilizer syndrome. Orthomo-

lecular treatment works on sick people to get them well, but once they are well serves only to maintain that wellness. Vitamins do not make normal people ill. We doubt any airline company would ground their pilots who are taking vitamins.

Why the Adrenochrome Hypothesis has Been Neglected

The adrenochrome hypothesis has so far withstood the assault of critics and of research data on the three basic counts. These are:

1.Adrenochrome is formed in the body, but we do not know whether more is formed in schizophrenics or where it is made, or are schizophrenics more susceptible to the effects of the aminochromes because they lack antioxidants or other protective factors. Future research will settle these issues. We need to know where the transformation occurs, in what quantities, and why. We need to know the endproducts of catecholamine oxidation and their pathways. We need to know which enzymes are involved and/or damaged, and we need more effective blocking agents which are effective in smaller doses but have the safety, and efficacy of vitamins.

2. Adrenochrome and adrenolutin are hallucinogenic. We need more information about the other aminochromes. We need to know which synapses are inhibited, which receptors are involved.

3. Inhibiting the formulation of adrenochrome is therapeutic. We need to know why the orthomolecular approach works.

That the adrenochrome hypothesis is not destroyed does not prove it is correct. Time will tell. It does prove it is a good, testable hypothesis and will continue to direct research in future as it has in the past. Why, then, has it been ignored for nearly thirty years?

We may be too close to the subject to really understand the reasons why the adrenochrome hypothesis has been ignored for so long. It did receive a certain amount of notoriety at the beginning, but it was quickly shot down by American psychiatrists led by the National Institute of Mental Health. A medical historian may one day be able to examine the issues more capably. In our opinion, there were two main classes of opinion: scientific, and political. The political opposition prevented any serious examination of the consequences of the adrenochrome hypothesis. Inadequate as it then was, it was able to direct our research in Saskatchewan for 15 years, and could have been examined much more quickly and thoroughly by research institutes which grew very quickly in the U.S.A., beginning in 1955.

Scientific

A. The Climate of Opinion

No ideas spring forth from a vacuum. All new ideas must confront the establishment of ideas until a new paradigm is established. But the establishment of ideas maybe so pervasive and powerful it is able to swamp and overwhelm new ideas. The adrenochrome hypothesis of schizophrenia attacked, head-on, several establishments.

1. In 1954, psychiatrists and psychologists believed that if there was a disease called schizophrenia, and many doubted this, it was due to stresses generated by intrapsychic or interpersonal relationships. The psychoanalysts had just won the field, routing all the so-called organic psychiatrists. To be labelled organic was as demeaning as being called a quack. The few biological psychiatrists who survived the onslaught carried on very quietly, with an occasional show of life. Schizophrenic patients were sick because of what had happened to them, or what they thought had happened to them, or they fantasized this pressure from their parents (usually Mom). Kinder analysts did not condemn Mom, while still blaming her, for she had done so unwittingly because of unconscious problems of her own.

The first major assault on these psy-

chosocial hypotheses came with the introduction of the model psychosis. The fact that tiny amounts of LSD could produce a major psychosis suggested similar small quantities of an endogenous hallucinogen could be formed. Psychiatrists who were active in research and the academic field between 1951 and 1957 will remember the vigorous controversy this idea generated. The model psychosis idea suggested that schizophrenia was a biological disease. This was intolerable to most academics who had worked so hard to establish that it was a psychosocial phenomenon.

By itself the model psychosis idea would not have gone far, but it was soon reinforced by the tranquilizers. They swept into Canada and then the U.S.A. from France, where they arose from the finding made by Dr. H. Laborit, a surgeon, that antihistamines, discovered in Italy, had marked relaxing and calming effects on people. The tranquilizers were astonishingly effective. When one has experienced what psychiatric wards were like in 1955, it is impossible to forget the excitement generated by these powerful drugs. The enthusiasm was boundless and soon led to a massive release of patients from mental hospitals. The drug companies holding the patents soon found themselves in the unique position of having a drug which needed hardly any advertising in mental hospitals. However, they were very generous in their advertising, which helped overcome the resistance from the academics who were still convinced of their psychosocial theories. The rapid establishment of the tranquilizers as the only treatment for schizophrenia was more persuasive than any other event in turning psychiatric attention to biological psychiatry.

However, tranquilizer theorists could point to no hypothesis which could account for their activity until much later when the dopamine hypothesis came along. Nor did the fact that tranquilizers were so helpful deter the psychosocial theorists, for it was merely another, even if more effective, sedative. The drug companies, ever aware of the sensitivities of psychiatrists, declaimed in their beautiful ads that tranquilizers merely facilitated psychotherapy. Thus, tranquilizers promoted the idea schizophrenia was biological but did not exclude psychosocial ideas of the cause.

The adrenochrome hypothesis violated the psychosocial hypothesis, for vitamin B_3 was not a sedative, nor was it a tranquilizer. How could anyone, ill because he had been exposed to a schizoprenogenic mother, recover by taking a vitamin? If they believed he had recovered, what did that do to their favourite hypothesis? It was easier to believe he had not recovered. This was made easier by avoiding the use of vitamins. To this day very few academics have tried the orthomolecular approach. There is the enormous risk one might have to change one's mind. They believed that orthomolecular treatment was inextricably bound to the adrenochrome hypothesis; that if they accepted one, they would have to accept the other. This of course was nonsense. We used the adrenochrome hypothesis to lead us to vitamins, but we might have come upon it serendipitously. The adrenochrome hypothesis may he completely wrong, but this has no hearing on whether vitamin B_3 is therapeutic for schizophrenics.

2. The use of vitamins in very large doses attacked all the classical nutritionists who were disciples of the vitamin hypothesis, i.e. that vitamins were needed in very small doses. Yet we were using doses of vitamin B_3 1000 times the RDA, and doses of ascorbic acid 60 times the RDA. It is believed by these fossilized vitamin theorists that larger doses are not needed, are not effective for anything and may be toxic. So convinced are they, that they think it is honourable to invent toxicities when none are present. These theorists have received massive support from the FDA, from major food industries and from physicians who know almost nothing about nutrition

or nutritional supplements. The classical theorists are not easily persuaded. Even though vitamin B_3, the niacin form, lowers cholesterol, elevates high density lipoprotein cholesterol, reduces mortality from cancer and cardiovascular disease, and increases longevity, it does not violate their idea, even with 3–6 grams per day (1000 to 2000 times RDA), for they either do not know niacin is a vitamin, or consider it is no longer acting as a vitamin. Most physicians think of niacin as a drug, and they have no objections to using drugs in megadoses, only to vitamins. Niacin's role in lowering cholesterol also arose from our Saskatchewan research into schizophrenia, as a side discovery following the adrenochrome hypothesis. Today niacin is exciting many academics because it has been shown to be so effective in the cardiovascular area, will "cure" a large proportion of juvenile diabetics if given within six months of onset, and has many other valuable therapeutic properties.

The medical establishment has a history of about 150 years of denying the important role of malnutrition in causing disease, and in the role of good nutrition in restoring health. This in spite of the fact that the major advances in our understanding of nutrition have been made by physicians who had to fight their colleagues for years before their ideas became acceptable: Francois Magendie (whole wheat bread supported life, white bread did not), James Lind (citrus fruits prevent scurvy), R. Chittenden (vegetarianism), J. Goldberger (pellagra, a disease caused by poor diets), A. McCann (disease arose from inadequate diets), Harvey Wiley (tried to keep our food clean), Elmer McCollum (vitamins A and B), Max Bircher-Benner (importance of whole foods, especially vegetables), R. McCarrison (importance of whole foods), H. Bieler (importance of good food), John Boyd (on good food and health), Max Gerson (treatment of cancer), Seale Harris (hypoglycemia), and T. L. Cleave (the saccharine disease). I have not listed an equally impressive group still working and trying to teach their colleagues. The amazing controversies in which they were engaged is detailed in Barbara Griggs' excellent book *The Food Factor*. By tradition, medical schools do not teach clinical nutrition, and their graduates seldom overcome this major defect in their education.

Another problem orthomolecular therapists faced was the over-valuation and extreme popularity of the tranquilizers. This was so intense psychiatrists refused to recognize tardive dyskinesia for many years after it had been described, for how could something so undesirable accompany the very helpful tranquilizers? Not only could vitamins not compete for attention with tranquilizer (xenobiotic) physicians, there was no need to be interested since tranquilizers had provided the answer. Another aspect was the rapidity of action of the drugs. Psychoanalysis had taught psychiatrists to be patient. Drugs taught them to be impatient, to demand rapid responses. Vitamin therapists need less patience than analysts, but more than drug therapists, for orthomolecular therapy works slowly, but it keeps on working whereas drugs alone eventually work against recovery. Psychiatrists accustomed to a rapid response to drugs in days or weeks would not wait months for orthomolecular treatment to achieve its maximum response.

B. Sloppy Science

By this we refer to sloppy scholarship, i.e. failure to read the literature and record accurately what was found. Again, the APA report contains a host of beautiful examples. These are pointed out in our Reply (Hoffer and Osmond, 1976).

We know of many examples of sloppy or bad science which were used to attack the adrenochrome hypothesis. One of the best examples was Dr. Max Rinkel's use of adrenochrome semicarbazide to test

adrenochrome's hallucinogenic properties. Not a chemist, he was footed by a drug company which had been marketing the semicarbazide for staunching blood flow. It was used by many surgeons and known as stable adrenochrome. It was not adrenochrome. Dr. Rinkel later published a correction but his first report, presented at an American Psychiatric Association meeting, received wide publicity and is still quoted by American textbooks of psychiatry written by eminent psychiatrists. Dr. Rinkel's correction was read at an obscure meeting at the Allan Memorial Hospital in Montreal and has been ignored by almost everyone since, even though we drew it to their attention. They were not pleased when we informed them and continued to refer only to the first Rinkel report.

Other examples include a brief study on chronic, deteriorated schizophrenics who were given one gram of niacin per day for twelve days, and based upon their lack of response it was concluded vitamin B_3 had no merit. The APA Task Force Report on Megavitamin Therapy abounds with such examples, which was treated with the utmost respect.

C. Other Difficulties

We will list merely two of these:

1. Definition of schizophrenia and the view it was a single disease, when in fact it is a syndrome, very heterogeneous.

2. Difficulty with the synthesis and study of pure aminochromes. The derivatives of the catecholamines are very reactive and there were few methods for capturing these fleeting molecules thirty years ago.

Political

The politics of science is not much different from politics in general; it is a conflict of ideas. The only difference is that most people unfamiliar with science are surprised when they discover science is quite like politics. They had thought scientists were above the thrust and parry of politics. Scientific politics have held back innovation in science for at least 300 years and perhaps longer. The politics of the adrenochrome hypothesis is a specific example of a much greater problem in science. The problem is how do new ideas become established, and how can one be sure these are good ideas (like the use of tranquilizers) and not bad ideas (like the psychoanalytic hypothesis)? We can not depend upon one person to make this judgement, for establishment leaders did not become leaders because they were bold and innovative and attacked the establishmerit. Dr. Linus Pauling asked Dr. Karl Landsteiner how he had developed his research ideas. He replied, "I think of thousands of ideas and throw away the bad ones." Unfortunately, the Paulings and Landsteiners are very rare and seldom influence the medical establishment.

In medicine about forty or more years are required in most cases before new ideas become part of the establishment. Sometimes it takes less time. It appears likely the use of niacin to lower cholesterol, and decrease deaths, may come in just under the wire - forty years. We first reported it in 1955. Only within the past two years has it become known to the academic establishment. It is well on the way, even though most physicians in the field still have not heard of it.

We hope a discussion of the politics of the adrenochrome hypothesis will alert the leaders of the medical establishment of the problem. At once we want to make it clear there was no paranoid conspiracy involved. There was no single person or single establishment orchestrating the opposition to the adrenochrome hypothesis. What might appear to be a conspiracy was rather a spirited defence by the establishment as if it had a leader. They were impelled by the need to maintain the establishment. They have attacked other investigators as well, as have establishments elsewhere. But two institutions, the National Institute of Men-

tal Health and the American Psychiatric Association, have taken a leading role, and a few of their members like S. Kety, L. Mosher and M. Lipton have been most active. The first two were very influential within the NIMH and the last chaired the APA committee for the APA report. Fortunately, Dr. Linus Pauling entered the field in 1966, especially after he published his paper "Orthomolecular Psychiatry" in Science, 1968.

The NIMH

The National Institute of Mental Health was created because the American government realized that too little was known about mental illness and how to deal with it most successfully. We can not remember when the huge building was dedicated, but one of us (A.H.) stood on the site on the edge of Washington, D.C., when it was still a tiny builders' shack. The psychiatrist in charge described some of his hopes about NIMH to A.H. Most of his hopes have not been achieved.

The first administrators of NIMH were psychoanalysts. This is not surprising since analysis had captured most of the academic centres, beginning with the Ivy League universities. Dr. John Weir, Medical Director, Rockefeller Foundation, in 1954 told us that the Foundation funds used to start up these psychiatric departments had been wasted. Apparently the Rockefeller Foundation did not pass on their conclusion to the new NIMH. The need to be psychoanalytically oriented was so powerful, Dr. S. Kety, trained in physiology, became an analysand for two years. NIMH was not very sympathetic to any biochemical or biological view of schizophrenia. Many years later their Schizophrenia Section, directed by Dr. L. Mosher, preferred psychosocial investigations to biological ones. He was a dedicated follower of the English poet-psychiatrist Dr. R. D. Laing. In his view he could not accept that vitamins could help schizophrenics even if every American psychiatrist did believe so. This was a statement he made at one of our hostile meetings between a few NIMH leaders and a few orthomolecular psychiatrists. In his view, a schizophrenic who improved after a year of milieu therapy was better off than if he or she had made the same degree of improvement after a few weeks on tranquilizers. He would, of course, never use orthomolecular techniques. NIMH tried to protect the analytic orientation by resisting funding tranquilizer research. It required a coalition of senators and congressmen who demanded they liberalize their policy before they did so. The top administrators were moved on to less demanding jobs, and major research grants were awarded to a large number of research groups. It appears that one or two studies, both positive, are not believed, and one required hundreds and thousands of studies all showing the same thing.

After that there was a slow drift of interest in biological psychiatry. An examination of recent reports from NIMH indicates they have gone a long way. This may be the atmosphere which allowed the recent reports to appear. Cadet, Lohr and Jeste (1986), Cadet and Lohr (1987), Jeste, Lohr and Mani (1985), and Cadet and Lohr (1987) discussed the hypothesis that oxidized derivatives of some catecholamines are involved in the etiology of schizophrenia. They had concluded that the dopamine hypothesis was inadequate for a number of reasons, but that free radicals or oxidized derivatives following increased dopamine turnover might be involved and could account for many of the clinical findings of the schizophrenics, especially its progression in chronic schizophrenia to produce the defect state. However, they did not refer to a single adrenochrome paper or even to the word adrenochrome, although they came close when they wrote about free radicals formed during enzymatic and nonenzymatic metabolism of catecholamines. It is possible they considered auto-

oxidized compounds from dopamine and noradrenalin not to be indoles or aminochromes (Hoffer, 1998).

Thirty years ago, it was no secret to U.S.A research groups that NIMH was actively disinterested in pursuing adrenochrome research. In one case, a director of research was advised no grant would be made to his group if he persisted in studying adrenochrome. In another example a study of vitamin B_3 as treatment for schizophrenia was not given to a psychiatrist in the midwest because he had recommended one of us (A.H.) be a consultant to his study. It was instead allocated to a group in New Jersey which did not have the same precondition. Dr. L. Mosher was also on the APA committee which supported Dr. M. Lipton's previous conclusion that there was no merit in orthomolecular psychiatry. He had come to this conclusion even before the committee had been created by the APA.

The American Psychiatric Association

The APA reflects the views of the majority of its members. When the pressure on American psychiatry was great enough, APA responded by creating a committee, the APA Task Force on Megavitamins and Orthomolecular Therapy, chaired by Prof. M. Upton. The APA must have known Dr. Lipton had already publicly declared himself a vigorous opponent of megavitamin therapy. They allowed him to hand-pick his committee, which consisted of: (1) one of his junior professors in his department of psychiatry; (2) Dr. L. Mosher, (3) Dr. T. Ban, and two others. With these three committee persons and their well-publicized views against megavitamin therapy, it is not surprising the final report was very critical, hostile and negative. We have replied to this report (Hoffer and Osmond, 1976), and will not examine it any further.

Since then, the satellite organizations of the APA and psychiatric establishments at universities and at state government levels have used this APA report to deflect criticism from patients and their families. We doubt they have read the APA report carefully, or researched how it dealt with the references. Certainly they did not read our Reply. The Canadian Psychiatric Association based their negative report on the APA report, believing big brother must be right.

Orthomolecular Psychiatry

In 1968 and 1974, Dr. Linus Pauling examined the relation of vitamins to psychiatry. From his earliest studies of the chemical basis of sickle cell anemia, he had been interested in the molecular basis of medicine. By 1968 Dr. Pauling was convinced that using large doses of vitamins was biochemically sound and that their use in treating some mental diseases was justified. His paper in *Science* marked his entry as a new player on the scene. The power of his scientific accomplishments and the prestige of his name alerted the scientific world. There were two reactions. Biochemists were more interested, as were a few doctors. Slowly, more research reports dealing with vitamins were published in medical journals. But most doctors dismissed his ideas. They began to spread a rumour that Linus was becoming senile, or how could a Ph.D., non-M.D. scientist take a public stance on a subject they deemed entirely medical (psychiatric). Orthomolecular psychiatry is sophisticated, etiological and more effective than standard medicine which depends only on drugs (Hoffer, 1989).

Conclusion

The aminochromes undoubtedly are involved in almost every reaction in which catecholamines play a part. A vast new area has now opened for physiological and biochemical research. Thus, Ganguly (1989) and Ganguly, Beamish and Dhalla (1989) state "...oxidation products of catecholamines, such as adrenochrome, rather than catecholamines per se, may be involved in catecholamine-induced myocardial cell

damage. Previous studies have revealed that adrenochrome is capable of inducing coronary spasm, arrhythmias, ultrastructural changes and ventricular dysfunction." They suggest damage caused by pheochromocytomas is due to adrenochrome. Extra adrenaline is oxidized when other mechanisms for inactivating catecholamines are saturated.

Catecholamines are involved in stress reactions and are neurotransmitters. Any compound (drug) which potentiates or inhibits the reactivity of catecholamines will be modulated by the presence of the corresponding aminochromes. The action of all the tranquilizers, antidepressants, and other psychoactive drugs will have to be reevaluated. It is likely subjects low in aminochromes will respond differently than subjects with high blood levels.

Aminochromes will surely have very important functions. They are not only by-products of catecholamine oxidation. It is necessary to reexamine Dr. F. E. Barr's very important work, "Melanin: The Organizing Molecule" (1983). In his abstract Barr wrote:

"The hypothesis is advanced that (neuro)-melanin (in conjunction with other pigment molecules such as the isopentenoids) functions as the major organizational molecule in living systems. Melanin is depicted as an organizational "trigger" capable of using established properties such as photon-(electron)-photon conversions, free radical-redox mechanisms, ion exchange mechanisms, and semiconductive switching capabilities to direct energy to strategic molecular systems and sensitive hierarchies of protein enzyme cascades. Melanin is held capable of regulating a wide range of molecular interactions and metabolic processes primarily through its effective control of diverse covalent modifications."

The main question remains. Is the schizophrenic syndrome caused by an oxidation-reduction state which: (1) favours excess formation of aminochromes; (2) inhibits the elimination of these aminochromes. The evidence which favours this hypothesis is stronger than ever. Only research, exemplified by cardiovascular research scientists, will provide the evidence we need. Will psychiatry once more lag several decades behind in examining these issues?

References

Barr FE, Saloma JS and Buchele MJ: Melanin; the organizing molecule. Medical Hypothesis, 11:1-140,1983

Beamish RE. Dhillon KS, Sinsal PK and Dhalla NS: Protective effect of sulfinpyrazone against catecholamine metabolite adrenochrome-induced arrhythmias. Am. Heart J., 102:149-152,1981.

Cadet JL and Lohr JB: Free radicals and the developmental pathobiology of schizophrenic burnout. Integrative Psychiatry, 5:40-48, 1987.

Cadet JL, Lohr JB and Jeste DV: Free radicals and tardive dyskinesia. Trends Neurosci. TINS, 9:107-108, 1986.

Clancy J, Hoffer A, Lucy J, Osmond H, Smythies J and Stefaniuk B: Design and planning in psychiatric research as illustrated by the Weyburn Clinic Nucleotide Project. Bull. Menn. Clinic, 18:147-153, 1954.

Dhalla KS, Ganguly PK, Rupp H, Beamish RE and Dhalla NS: Measurement of adrenolutin as an oxidation product of catecholamines in plasma. Molecular and Cellular Biochem., 87:85-92, 1989.

Ganguly PK: catecholamines and cardio vascular disorders: pathophysiologic considerations. Am. Heart J., 118: 868-872,1989.

Ganguly PK, Beamish RE and Dhalla NS: Catecholamine cardiotoxicity in pheochromocytoma. Am. Heart J., 6:1399-1400,1989.

Ganguly PK, Lee S, Beamish RE and Dhalla NS: Altered sympathetic system and adrenoreceptors during the development of cardiac hypertrophy. Am. Heart J., 118:520-525, 1989.

Graham DG: Oxidative pathways for catecholamines in the genesis of neuromelanin and cytotoxic Quinones. Molecular Pharmacology, 14:633-643, 1978.

Graham DG: On the origin and significance of neuromelanin. Arch. Path. and Lab. Med., 103:359-362,1979.

Graham DR: Catecholamine toxicity: a proposal for the molecular pathogenesis of manganese neurotoxicity and Parkinson's disease. Neurotoxicity, 5:83-95, 1984.

Graham DG, Tiffany SM, Bell WR and Gutknecht WF: Autooxidation versus covalent binding of Quinones as the mechanism of toxicity of

dopamine, 6-hydroxydopamine and related compounds toward C1300 neuroblastoma cells in vitro. Molecular Pharmacology, 14:644-653,1978.

Heacock RA: The chemistry of adrenochrome and related compounds. Chem. Reviews, 59:181-237,1959.

Heacock RA: The aminochromes. Advances in Heterocyclic Chem., 5:205-290, 1965.

Hegedus ZL and Altschule MD: Aminochromes III. Transformation of epinephrine, adrenochrome and adrenolutin into plasmasoluble melanins during incubation in human blood plasma. Arch. Biochem. Biophys., 126:388-392, 1968.

Hegedus ZL and Altschule MD: Aminochromes IV. Hemolysis associated with the transformation of epinephrine, adrenochrome and adrenolutin into rheomelanins in human whole blood. Arch. Ing. Pharmacodyn. Ther., 186:39-47, 1970.

Hegedus ZL and Altschule MD: Aminochromes V. Excessive hemolysis associated with the formation of rheomelanins during incubation of adrenochrome and adrenolutin in the bloods of chronic schizophrenic patients. Arch. Ing. Pharmacodyn. Ther., 186:48-53, 1970

Hegedus ZL, Kuttab SH, Altschule MD and Nayak U: Isolation of melanin from human plasma lipofuscin. Arch. Internationales de Physiologie et de Biochemie, 89:393-398, 1981.

Hoffer A: The effect of adrenochrome and adrenolutin on the behavior of animals and the psychology of man. Ing. Rev. Neurobiol., 4:307-371, 1962

Hoffer A: The adrenochrome hypothesis of schizophrenia revisited. J. Ortho. Psych., 10:98-118, 1981.

Hoffer A: Oxidation reduction and the brain. J. Ortho. Psych., 12:292-301, 1983.

Hoffer A: Dopamine, noradrenalin and adrenalin metabolism to methylated or chrome indole derivatives: two pathways or one? J. Ortho. Psych., 14:262-272, 1985.

Hoffer A: Letter to the editor. Integr. Psych. 6:243 only, 1988.

Hoffer A: Orthomolecular Medicine for Physicians. Keats Publishing, Inc., New Canaan, CT, 1989.

Hoffer A and Kenyon M: Conversion of adrenaline to adrenolutin in human blood serum. AMA Archives Neur. and Psychiatry, 77:437-438, 1957.

Hoffer A and Osmond H: The Hallucinogens. Academic Press, New York, 1967.

Hoffer A and Osmond H: In Reply to the American Psychiatric Association Task Force Report on Megavitamins and Orthomolecular Therapy in Psychiatry. Canadian Schizophrenia Foundation, 1976.

Hoffer A, Osmond H and Smythies J: Schizophrenia: a new approach. II. Results of a year's research. J. Ment. Set., 100:29,1954.

Jeste DV, Lohr JB and Mani R: Quantitative neuropathology and aging. In, Biological Psychiatry 1985, IV World Congress, Sept. 8-13, Philadelphia. Ed. Shagass, C. et al.

Karmazym M, Beamish RE, Fliesel L and Dhalla NS: Adrenochrome induced coronary artery constriction in the rat heart. J. Pharmacol. Exp. Ther., 219:225-230, 1981.

Leach BE and Heath RG: The in vitro oxidation of epinephrine in plasma. AMA Arch. of Neural. and Psychiatry, 76:444450, 1956.

Osmond 14 and Smythies J: Schizophrenia: a new approach, J. Ment. Sci., 98:309-315, 1952.

Pauling L: Orthomolecular psychiatry. Science, 160:265-271, 1968.

Pauling L: On the orthomolecular environment of the mind; orthomolecular theory. Am. J. Psychiatry, 131:12511257,1974.

Sinsal PK, Yates JC, Beamish RE and Dhalla NS: Influence of reducing agents on adrenochrome induced changes in the heart. Arch. Pathol. Lab. Med., 105:664-669,1981.

Szatmari A, Hoffer A and Schneider R: The effect of adrenochrome and niacin an the electroencephalogram of epileptics. Am. J. Psychiatry, 3:603-616,1955.