The Adrenochrome Hypothesis of Schizophrenia Revisited

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Introduction

For about one hundred years theories of schizophrenia have oscillated between physical or biochemical hypotheses on the one side and psychosocial hypotheses on the other side of the spectrum. The change in points of view over the years depended upon the sophistication of the various scientists and also upon the fashion of the era. This dichotomy is probably false since every factor which shapes the development of personality must also play a role in both the development of and in the recovery from schizophrenia.

Early biochemical hypotheses were simple and were more properly medical guesses. Physicians favoring this view accepted it as a disease and looked for the same factors which played a role in shaping other diseases. These included stress, infection, nutrition, trauma and so on. Physicians using pathology, physiology and bacteriology had been successful in developing treatments for a large number of diseases; naturally they would try similar techniques in searching for the cause of schizophrenia.

Psychosocial theories did not exist. I exclude the theory of demonic possession as this has never been considered a scientific hypothesis. Psychosocial theories arose from psychoanalysis especially after Freud described the Schreber case, the case of a paranoid judge, but few physicians were a-ware of this until psychoanalysis began to flower about thirty years ago.

Every factor ever found to cause disease has been examined as a cause of schizophrenia. Psychiatrists have never been persuaded of the truth of the hypothesis. It was, in fact, found that hormones which were clearly related to diseases such as Addison's and thyroid states also had a weak association with schizophrenia. Patients who suffer from too much or too little activity of the thyroid or adrenal gland may be psychotic. A few patients with hyperthyroidism had schizophrenic features. Perhaps even more with hypothyroidism (Graves' disease) were equally psychotic. We still see schizophrenics who become normal when their hyperactive, tumorous adrenal gland is removed.

A few patients with severe infections develop a schizophrenic syndrome but more often it is accompanied by memory disturbances, disorientation and confusion and is classed as a delirium. Chronic infections may cause similar reactions; GPI (general paresis of the insane), chronic syphilis of the brain at one time was very prevalent in mental hospitals and was difficult to distinguish from schizophrenia. Chronic rheumatic fever was once considered a cause.

Thus, out of a large number of mentally ill patients diagnosed schizophrenic, clear causes were discovered in a few. When this was established the disease was renamed; the patient was rediagnosed as GPI, or hypothyroidism, or pellagra and pulled out of the schizophrenic group. As a result the patients who were ill without any of these factors remained. They remained under psychiatric care while the other forms disappeared from psychiatry to be taken over by other specialists. By a strange irony, psychiatrists were always left with the hopeless untreated cases because no cause nor specific treatment was known. This has been hard on psychiatrists but has been valuable to schizophrenia for it has slowly purified the group. The schizophrenic syndrome has become more homogeneous and this process will continue. Orthomolecular psychiatry has

continued this process by discovering a number of new causes such as vitamin dependency, cerebral allergy and mineral problems, leaving even a smaller proportion of the total schizophrenic population unaccounted for.

Schizophrenia Hypotheses

Schizophrenia is a disease which has attracted hypotheses from nearly every school of thought. It is so variable in its course and symptomatology that there is something there no matter how it is approached. Biochemical hypotheses have also proliferated. They began with simple statements of difference. The indole hypothesis nearly one hundred years ago postulated that more indoles would be found in schizophrenic patients. Latterly most hypotheses center about the role of neurotransmitters such as the sympathomimetic amines, acetyl choline, serotonin and so on. This type of hypothesizing becomes much more difficult as the number of suggested transmitters increases so rapidly. All the sympathomimetic amine hypotheses derive from the work of Osmond and Smythies (1952) who pointed to the structural similarity of adrenaline and mescaline as well as to their potential hallucinogenic effects. All the amines derived from tyrosine may be involved. They have been investigated intensively for the past thirty years for their chemical properties, biochemical inter-reactions and end products derived from them. These investigators have been reluctant to look at the indole derivatives of these amines called aminochromes. The best known is adrenochrome from adrenaline. Other derivatives include dopachrome, noradrenochrome, their leuko derivatives or dihydroxy indoles and their yellow or trihydroxy derivatives such as adrenolutin and noradrenolutin. These substances are very difficult to make in a pure crystalline form and most research laboratories interested in psychiatric research did not have the skill nor resources for doing so. Nor were they motivated to acquire them because of the powerful criticism and biases of research groups such as the National Institute of Mental Health led by scientists such as Dr. S. Kety.

After H. Osmond had completed his studies with Dr. J. Smythies he came to Saskatchewan where he and I joined forces. Especially important was their observation that pink or deteriorated adrenaline caused psychological changes in a few asthmatics who used adrenaline sprays. This pointed to a reddish colored derivative of adrenaline. This turned out to be adrenochrome but deteriorated adrenaline also contained a large number of similar indoles in various states of oxidation. The indole structure of adrenochrome and of most of the hallucinogens then known, i.e. d lysergic acid diethylamide (LSD), harmine, ibogaine, drew our attention to the importance of indoles in searching for a schizophrenic toxin. This soon led to our adrenochrome hypothesis which Osmond and I presented first in 1952 to the Dementia Praecox Committee of the Scottish Rites Masons at the Canadian suite in the Waldorf Astoria Hotel, New York. Osmond and I can still remember the prophetic advice given us by a very eminent elderly scientist. He wished us good luck and then warned us to expect a tremendous amount of opposition. The adrenochrome hypothesis was published in 1954 by Hoffer, Osmond and Smythies.

Not much was known about adrenochrome and what little was known often turned out to be wrong. Thus it was generally believed adrenochrome was essentially an unstable, highly reactive molecule which could never be prepared as a crystalline, stable substance. The best preparations we could get or make were bright or dull red powders, sometimes almost black, which deteriorated even when stored under nitrogen and temperatures below -40 C and in minutes in solutions

at room temperature. Each new batch had a slightly different appearance but it was all we could get and I too accepted the false belief it would always be so. Later it occurred to me that this instability was due to its residual content of silver ions which were used to catalyze the oxidation of adrenaline to adrenochrome. In short our preparations were impure, dirty. Dirty organic compounds tend to be unstable. We had the same problem with its derivative, adrenolutin.

As soon as it occurred to me to remove the silver I directed our chief biochemist to dissolve a portion of the adrenochrome on hand, pass it through a resin column which would remove the silver and to recrystallize the pure adrenochrome; this solved our problem. The first time this was done we were able to prepare crystals of adrenochrome which were relatively stable even at room temperature in the dry state. The preparation of stable adrenolutin soon followed.

A few years later Prof. M. Altschule began to make and to use these stable preparations in his research. The group at the National Institute of Mental Health toyed briefly with the idea of studying adrenochrome but they did not know how to make any and were able to get a tiny supply by taking some from another scientist to whom I had sent some, without his permission. Later they gave us credit for it even though they had never requested I send them any and I had not done so. Unluckily a report by Dr. Max Rinkel killed interest in adrenochrome as an hallucinogen. He obtained a supply of adrenochrome semicarbazide, known commercially as stable adrenochrome. It was used by surgeons to decrease bleeding. Rinkel gave this inert material to a few subjects and found no hallucinogenic activity. He was unaware this substance is not hydrolyzed in the body, does not release adrenochrome and has different properties. Adrenochrome critics apparently never read Rinkel's subsequent report where he acknowledged his error.

Interest in the aminochromes 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. Graham (1978, 1979; Graham et al., 1978) for example explains the toxicity of levo dopa (l-dihydroxy phenylalanine) on the basis of its conversion to dopachrome which probably had adreno-chrome-like properties.

Many investigators have found evidence for the formation of adrenochrome in the body. Kaliman (1961) and Kaliman and Koshlyak (1962) reported rabbit heart tissue, kidney and brain but not liver and skeletal muscle, oxidized adrenaline to adrenochrome. Langemann and Koelle (1958) found cells of the intestinal mucosa formed identical-looking pigments from adrenaline and adrenochrome. Axelrod (1964) found an enzyme in salivary gland tissue which oxidized adrenaline to adrenochrome. The DOPA oxidase system in ocular tissue also produces adrenochrome (Angenent et al., 1952). Earlier Roston (1960) found coenzyme A inhibited formulation of noradrenochrome and adrenochrome. He suggested that the cytochrome system plays a role in controlling catecholamine oxidation reactions. A more complete discussion of adrenochrome as an *in vivo* oxidation product of adrenaline is given in Hoffer and Osmond (1967).

Hoffer, Osmond and Smythies (1954) suggested that in schizophrenics too much adrenochrome was formed, that it reacted in the body by producing perceptual and thought disorder changes, that it was the schizophrenic endogenous hallucinogen or more accurately the endogenous schizogen. The presence of this aberrant biochemical system would account for many of the physiological and biochemical findings present in many schizophrenic patients if not in all.

Too much adrenochrome could arise from excessive oxidation of adrenaline and in turn this would increase the production of toxic metabolites of adrenochrome such as adrenolutin. Osmond and I have described the adrenochrome hypothesis several times, in The Hallucinogens, (1967) and in Ortho-molecular Psychiatry edited by D. Hawkins and L. Pauling (1973) (Grof et al., 1961; Rice et al., 1957; Schwarz et al., 1956; Vojtechovskyetal., 1962).

The adrenochrome hypothesis can be described biochemically by a series of reactions as follows: a) Noradrenaline + methyl --> adrenaline b) Adrenaline+oxygen --> adrenochrome c) Adrenochrome --> leukoadrenochrome\> adrenolutin. We suggested that any reaction which diverted adrenochrome into adrenolutin rather than into leukoadrenochrome would cause or aggravate schizophrenia.

To test the hypothesis we pursued a series of studies beginning in 1952. These were supported by the Saskatchewan Department of Public Health for whom we worked, by federal health grants and by the Rockefeller Foundation. One does not test a hypothesis directly; the hypothesis predicts a series of sub hypotheses or ideas which can be tested. If the data supports these testable hypotheses it increases the probability the original hypothesis is on the mark.

1. Noradrenaline and adrenaline in the pure state do not cause hallucinations or schizophrenia, but decreasing the amount of adrenaline will ease the biochemical pressure toward schizophrenia; less will be available for conversion into adrenochrome. Theoretically, decreasing the production of adrenaline from noradrenaline by any means would be helpful. Since stress increases the formation of noradrenaline and adrenaline, reducing stress should be therapeutic, and it is. Diverting methyl groups away from noradrenaline will decrease adrenaline formation but this may not be possible since any general shortage of methyl groups may cause a methyl deficiency syndrome. Excessive quantities of methyl groups could be harmful but only where it led to an increase in the production of methylated hallucinogenic indoles.

2. Adrenaline is oxidized to adrenochrome in a two step process. One electron is lost, forming a highly reactive free radical, an oxidized adrenaline. It is readily changed back to adrenaline. The reversible NAD <-> NADH system is involved. If another electron is lost adrenochrome is formed but this is a one-way process. Adrenochrome is not reduced back to adrenaline. This may be a mechanism at synapses in the brain by which the body regulates the reactions of the neurotransmitter amines. Trihydroxy dopamine (6 hydroxydopamine or TOPA) is highly toxic to dopamine receptors, perhaps because of the formation of aminochrome at the receptor site thereby destroying it. Vitamin B_3 which controls formation of NAD is thus involved. With a relative deficiency of Vitamin B_3 too much trihydroxy dopamine may be converted into its aminochrome. Whatever increases oxidation of these central amines to their indole derivative will be hazardous to brain function while any reaction which reverses or inhibits them will be therapeutic. Adrenochrome inhibits synaptic transfer of electrical signals as do LSD and other hallucinogens. The oxidation is accelerated by increased oxygen pressure such as deep sea diving. It causes convulsions in mice. At autopsy these animals' brains have no adrenaline and are pigmented red. Radiation will accelerate oxidation and some enzymes, especially copper-containing oxidase, will do the same. Reducing conditions include ascorbic acid, glutathione which combine with oxidized free radicals and neutralize them. Vitamin E ought to play the same role. Heparin might be helpful if one could

obtain a heparinoid molecule which had no anticlotting properties. Heparinoids are complex polysaccharides which have a remarkable avidity for other molecules. They are efficient scavenger molecules (Jacques, 1979).

3. Deteriorated adrenaline, adrenochrome and adrenolutin are hallucinogens. This is an essential element of the adrenochrome hypothesis because it provides an explanation for the clinical symptomatology. The dopamine hypothesis does not provide for such an explanation unless it invokes some aminochrome mechanism. The methylation hypotheses do provide for methylated derivatives such as bufotenine.

The evidence for the hallucinogenic properties of adrenochrome and adrenolutin is provided in our book The Hallucinogens, Hoffer and Osmond (1967) and will not be repeated here. See also Hoffer (1962,1966), Grof et al., (1963) and Weckowicz, (1962).

Twenty-five years ago it was impossible to test the properties of noradrenochrome or of the other aminochromes as we did not know how to prepare pure material. This may still be a problem as these compounds are difficult to crystallize. None of the other neurotransmitters were hallucinogens. Serotonin is an indole with no striking psychological properties. It may be closely involved in catecholamine metabolism. Vander-Wende and Johnson (1970) reported serotonin was an effective inhibitor of both enzymatic and autoxidation of dopamine and noradrenaline. They suggested serotonin could modulate the activity of catecholamines. Most of the dopamine in the substantia nigra and caudate nucleus is in the soluble fraction of the cells while serotonin was bound. Thus, serotonin would not have any effect on dopamine until it is released, when a complex of the two would be formed. This is how serotonin could modulate dopamine's central activity. The presence of too much serotonin would decrease the formation of neuromelanin from dopamine. Perhaps this is why in Parkinsonism there is a depletion of melanin in the substantia nigra. Increasing serotonin might also decrease formation of adrenochrome.

Any reduction of these aminochromes should be therapeutic for schizophrenics (VanderWende and Johnson, 1979). They point out it has been difficult to relate either catecholamines or serotonin to abnormal behavior, because the role of serotonin in modulating the metabolism of catecholamines was unknown. The ratio of adrenaline to serotonin is critical. When a lot of serotonin is present relative to adrenaline, adrenochrome formation is suppressed. When the serotonin level is too low, formation of adrenochrome is accelerated.

They finally conclude, "Greiner recently reopened the question of the abnormal pigment formation in schizophrenic patients and concluded that there is an increase of melanin formation either from enzymatic or auto-oxidative mechanisms (Greiner, A.C., Dis. Nerv. System 29 (Supp.), p. 14,1968). Our postulation would provide a common basis for Cramer's observation and the suggestion by Wooley that the disease results from a deficiency of serotonin. Not only would adrenochrome formation be accelerated at low levels of serotonin and consequently melanin formation from epinephrine, but also melanin formation from dopamine; and norepinephrine would be freed from the inhibitory effect of the indole amine." Perhaps the efficacy of Vitamin B_3 is partially due to the increase in serotonin which follows administration of this vitamin (Scherer and Kramer, 1972).

Today there are around thirty candidates for neurotransmitters, most of whom are being investigated, but so far there is no evidence they are hallucinogens. The aminochromes are the only

ones. They are derived from the parent amino acid tyrosine via a sequence of amines l-dopa, dopamine, noradrenaline and adrenaline. Boulton (1978) provides a comprehensive outline of the relationship of these amines to each other.

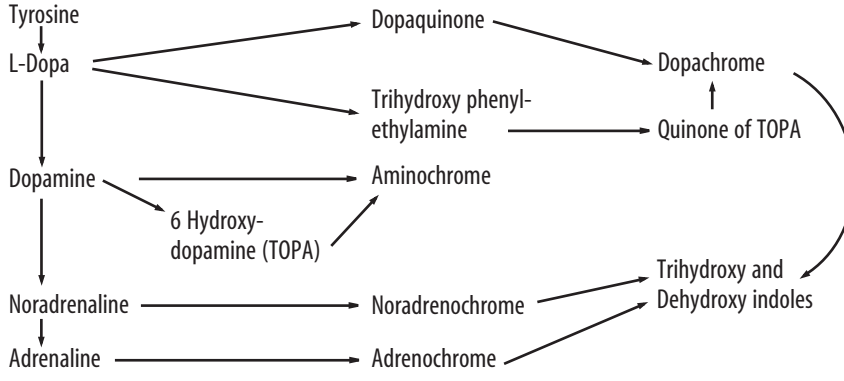
These amines all have the potential for becoming aminochromes. The proportion of each which does so is, of course, unknown since these reactions have been neglected by most investigators. L-dopa and dopamine are oxidized to aminochrome, noradrenaline to noradrenochrome and so on in a series of reactions illustrated in **Figure 1,** below).

Graham (1978, 1979) in a series of informative reports summarized the evidence these reactions are native to the brain. Our adrenochrome hypothesis was a model for one amine but equally well models all amines which are oxidizable into chrome indoles.

Very little of the chemistry of adrenochrome was known until Dr. R. Heacock began his studies in our research laboratories (Heacock 1959, 1965; Hutzinger, 1965). He found it readily changed into dihydroxy and trihydroxy N methyl indoles. We had found that adrenolutin (trihydroxy N methyl indole) was an hallucinogen. The dihydroxy derivative (leukoadrenochrome) created a pale yellow aqueous solution. We examined its psychological properties on a large number of subjects including normal people and patients with depression.

We soon discovered it was not an hallucinogen. On the contrary it tended to relax people; we used five milligram sublingual tablets. A large fraction of our patients noted marked relief from anxiety and tension within a few minutes and a few were "cured" of their anxiety. A large proportion did not respond but were not made worse. Its anti anxiety activity ranged from none to very remarkable. We could not continue our studies as our resources were limited and we could not discover that person who would respond except by a therapeutic trial. Two drug companies who were interested were looking for something which would act

Figure 1. The Adrenochrome Hypothesis



on nearly everyone as did the tranquilizers and antidepressive drugs which were then being introduced into psychiatry.

Thirty years ago the aminochrome pathway for destruction of the central amines was considered a very likely one. Doubt remained because adrenochrome had not been isolated from tissues. It could be seen when the adrenal medulla is sectioned it may turn red. This is adrenochrome, but this does not occur in the adrenal medulla in the body. There the medulla, containing noradrenaline and adrenaline, is surrounded by the adrenal cortex which is very rich in ascorbic acid. This stabilizes the amines as do other natural anti oxidants. We summarized the evidence for the formation of adrenochrome (Hoffer and Osmond, 1967; Hoffer, 1973). For about twenty years only the two other pathways of adrenaline degradation were studied, via monoamine oxidase and by orthomethylation. I believe the main reason is that there was no stable adrenochrome available commercially and neuro-psychopharmacologists did not want to make their own.

Also attempts were made to account for all the amines using tracer studies. The analysis, in my opinion, was so crude that claims that all the adrenaline decomposition could be accounted for via these two mechanisms only are completely unconvincing. In one study the adrenaline metabolites accounted for much more adrenaline than was injected. What we do know is that the proportion of the adrenaline diverted into all three pathways is not known. It likely varies a good deal. But even this is not as important as knowing what happens to the metabolites. Those that are retained in the body will (1) not show up in excretion studies, (2) have more significant effects in the body and may accumulate, increasing the damaging effect. The aminochromes easily polymerize to melanins which are excreted with great difficulty. Interest in the aminochromes is returning, perhaps because the other two pathways have been explored so thoroughly and no longer yield exciting new information. Graham concluded "an as yet undefined proportion of catecholamines may be oxidized by the routes given in Figure 1, (p.165) thereby providing the quinone species that polymerizes to form neuromelanin. Neuromelanin could then be viewed as a waste product of catecholamine metabolism accumulating progressively within the cytoplasm of the neuron with the passage of time." This accumulation is slow indicating that only a small fraction is oxidized. It also depends on maturation. Thus until a person reaches age six there is insufficient pigment in the brain to be detected without a microscope. Graham suggests that 6 hydroxy dopamine (TOPA) is toxic to the dopamine receptors because it is converted to its aminochrome. L-dopa appears to be beneficial in alleviating some of the symptoms of Parkinsonism but because it can be oxidized to aminochrome can accelerate the process of destruction of dopamine receptors. L-dopa does cause up to 20 percent of its recipients to become psychotic. Perhaps the proportion showing psychological changes will be greater when series of Parkinsonism cases so treated are examined by psychiatrists rather than by general practitioners and neurologists. L-dopa decreases the conversion of tryptophan into NAD forcing the body to depend more on food sources for vitamin B_3. Bender, Earl and Lees (1979) found that patients given L-dopa were as low in vitamin B_3 levels and in the amount of vitamin B_3 metabolite excreted in the urine as were pellagrins, yet they did not have pellagra. Probably they did not have pellagra because for this disease to develop there must also be a deficiency of tryptophan and exposure to sun. A deficiency of Vitamin B_3 would remove one mechanism available to the body to protect itself against the toxic effect of TOPA.

This will be discussed further on. Graham (1979) found that the volume of cells in the locus ceruleus and substantial nigra increased with age due to the accumulation of neuromelanin. He concluded "The administration of l-dopa would not only result in replenishment of dopamine as a neurotransmitter but would in concept present the catecholamine neurons with dopa and dopamine both of which could result in increased cell injury through auto oxidation and the production of cytotoxic quinones and free radical species. Thus treatment with l-dopa may accelerate neuronal degeneration while providing symptomatic relief." Strehler et al. (1959) measured the percent volume of human heart cells occupied by old age pigment. The average percent volume of this pigment increased one-half percent per decade. Old heart muscle cells may contain ten percent of this pigment. It does not occur under age 10. Since heart tissue can form aminochromes, it is likely this pigment resembles neuromelanin. Substances which inhibit oxidation should prevent heart muscle deterioration.

Patients with Parkinsonism take l-dopa for years during which there is time for toxicity to develop. L-dopa when used for short periods of time may be helpful in an unsuspected way. Friedhof and Alpert (1978) used l-dopa to reverse tardive dyskinesia. In one cast TD had been present for two years after tranquilizer medication had been stopped. He was given three grams of l-dopa per day for several weeks; at first the patient became worse but then he improved markedly. When l-dopa was discontinued all symptoms of TD disappeared and had not returned in three years. Friedhof et al. based their treatment on the idea that super sensitivity of dopamine receptors resulting from blockade (by neuroleptics) would respond to an increase in supply of dopamine with an adaptive decrease in receptor sensitivity. The same phenomenon does not operate in patients with Parkinsonism; they do not improve when l-dopa is discontinued as did Friedhof's patients with tardive dyskinesia. If dopamine is oxidized to aminochrome at the dopamine receptors some of them will be destroyed. Adrenochrome does block synaptic transmission. This would help the patients with tardive dyskinesia who receive l-dopa for a brief period but would not help Parkinsonism where the toxicity is chronic. If l-dopa is given to patients with tardive dyskinesia for long periods of time the results may not be so beneficial.

Vitamin B_3 appears to protect patients against tardive dyskinesia. Hawkins in a personal communication reported that over fifteen years he has not seen any cases among many thousands treated. In my own practice I have not seen any develop in twenty years. It may well be some of the protective effect is due to the lower doses of tranquilizer required but there is a direct protective effect as well, probably at the synapse. Kunin (1976) found that many cases of tardive dyskinesia disappeared quickly when manganese was given these patients. A few required both manganese and nicotinic acid. Manganese may have a protective effect by inhibiting aminochrome formation.

Friedhof et al. also treated ten schizophrenic patients with l-dopa over a four week period. The improvement was equivalent to that achieved by chlorpromazine. They suggested further studies should be done. This short term treatment may be comparable to the response of tardive dyskinesia but I would expect that chronic use of l-dopa will make schizophrenics worse unless they are protected against the formation of toxic aminochromes by large doses of Vitamin B_3, ascorbic acid and by other antioxidant procedures.

Friedhof (1979) is convinced that too many dopamine receptors are involved in genesis of schizophrenia. He suggested the tranquilizer Haldol might be given

to mothers to decrease the number of dopamine receptors in their children. I doubt many women would follow this therapeutic prescription. But since ascorbic acid is as active as Haldol it would be worthwhile to determine whether pregnant women given optimum doses of ascorbic acid would have children who would eventually be less apt to develop schizophrenia.

Melanin has some beneficial properties. McGinnes, Corry and Proctor (1974) found that melanin acts as an amorphous semiconductor threshold switch. Switching occurred at gradients present in some biological systems; only cytochrome had these properties but required higher potentials. No other biological substances had these properties. Melanins are found where electrical energy is transferred such as skin retina, midbrain and inner ear. Perhaps these areas contain semiconductor switches which are essential to their normal function. Melanins may also bleed off excess energy such as is received on the skin from the sun; skin tanning is a protective device.

Galzigna (1970) suggested a relationship between acetylcholine, a neurotransmitter, and catecholamines. Acetylcholine interacts with oxidized noradrenaline, yielding a complex which does not change to adrenolutin in ascorbic acid medium. It reacts similarly with dopamine. Both acetylcholine and nicotinamide increase the auto-oxidation of noradrenaline but the complex reacts differently with ascorbic acid. The acetylcholine/ noradrenaline complex is relatively stable but the nicotinamide/noradrenochrome complex is reduced much faster to dihydroxy indoles and adrenolutin. Galzigna postulates that if a central catecholamine leaks into the synapse an aminochrome could form; acetylcholine would stabilize it. Nicotinamide would increase its removal. "The leak of catecholamine and the stabilization of its oxidation products could produce an aberrant communication which, on the one hand, might be the chemical event leading to a short circuit between adrenergic and cholinergic systems and on the other hand, might be the origin of irritative foci of stabilized psychotogenic agents at cortical level. Both effects could possibly explain the onset of mental illness." Both Smythies (1976) and Teller (1979) reviewed the biochemical hypothesis relating to efficiently. Others may prefer a different schizophrenia. The sympathomimetic amines ranking. But then what are the phenomena we and their methylated derivatives have received should try to account for most of the attention. Before I outline these and a few others I should define what an hypothesis is supposed to do. Scientists wish to arrange their data in a meaningful way. This may mean that the data can be ordered along a mathematical model or can be accounted for by a formula or can be explained biochemically. Thus the rate of falling objects can be determined by a simple mathematical formula. The advantage of such an explanation or model is that it suggests new questions which are interesting to examine. In so doing it gives direction to future research. This will in turn lead to new discovery. An hypothesis is not necessarily true although one hopes to approach the truth. As supporting data are gathered the strength of the hypothesis improves but inevitably the new data will require that the hypothesis be modified. Hypotheses are evanescent and it is their fate to be altered; thus one asks of an hypothesis not that it be right but that it be fruitful. Of course it would be ideal if it could be both, but as there is no limit to the number of hypotheses there must be some constraint. The available data provide this constraint. The best hypothesis among competing ones is that which accounts most economically for more of the data than does any of its competitors. The continuing test will be its ability to program ongoing research.

Simple hypotheses merely proclaim that there is a difference; all the early hypotheses of schizophrenia were of this nature. Thus one worker would find that schizophrenics differed from controls by having too much or too little of a known body constituent or that they had a strange substance or group of substances not present in normal controls. Thus we had indole hypotheses, monoamine oxidase hypotheses and so on. These simplest of all hypotheses merely contain conclusions of research already completed. They seldom explain anything and seldom are creative in developing new insight about schizophrenia. Thus I will judge all hypotheses about schizophrenia in a hierarchy ranging from complex to simple. My inclination is to prefer complex hypotheses which account for the phenomena most

We should account for the phenomena inherent in the disease schizophrenia which we recognize to be a syndrome, not a disease. Schizophrenia is a syndrome of symptoms and signs centering about perceptual and thinking disorder. Following Conolly (1964) I believe these are the primary diagnostic changes. I have found these to be much more valuable than the Bleulerian criteria. If one avoids outcome criteria most psychiatrists will diagnose patients with perceptual changes (illusions, hallucinations) and with thought disorder. There has been an unfortunate tendency to wait for the outcome; thus a patient is not diagnosed until he has been ill with no improvement in twelve or fifteen years or some such arbitrary duration. This is equivalent to refusing diabetics insulin until they are nearly dead, or to refusing the diagnosis of arthritis until the patient is hopelessly bedridden with his joints fused out of position.

Once the schizophrenic syndrome has been diagnosed it is necessary to determine what has gone wrong. It is clear that a number of metabolic changes can precipitate schizophrenia. These include thyroid related disorders, adrenal gland related disorders, acute and chronic infections such as chronic syphilis of the brain, chronic rheumatic fever. They also include a number of orthomolecular syndromes involving vitamins, minerals and cerebral allergies.

The presence of the syndromes creates difficulty for the research psychiatrist especially when schizophrenics are compared against any control group. The normal control is fairly homogeneous in being not ill, not schizophrenic, but the sick group will contain varying proportions of patients who are schizophrenic because they are allergic to wheat, or to milk, or to candida or because they have too much copper or mercury or because they are Vitamin B_3 or Vitamin B_6 dependent. Homogeneous groups are essential in determining differences and must be used in controlled therapeutic experiments.

Modern statistical theory as used in double blind experiments has no theoretical basis unless the groups being compared are homogeneous so that a sample really represents the entire population. But the genetics of schizophrenia as it is accepted was based upon all schizophrenics of unknown origin, i.e. patients psychotic from known conditions such as hypothyroidism were excluded. Usually chronic patients were studied. This is the group which contains a substantial proportion of cerebral allergies as well as the vitamin dependencies. A general hypothesis of schizophrenia should try and account for this.

The minimum facts which should be accounted for are:

(1) That schizophrenia is primarily, but not solely, a genetic disorder, i.e. there must be a genetic potential for schizophrenia no matter what biochemical abnormalities are found.

(2) That there is a genetic advantage

in having some genes for schizophrenia or else it would have disappeared long ago. This will appear mainly in first order relatives as I see no advantage in being sick. However, a patient well because of correct treatment will have the same advantages and no disadvantages (Huxley, 1955; Huxley et al., 1964).

(3) That severe stress, while not a cause, is certainly a negative factor and will usually make patients worse.

(4) In addition an adequate hypothesis should account for the clinical symptoms, the perceptual changes, the thought disorder and the inappropriate behavior which derives from these.

(5) The hypothesis should offer a mechanism for understanding why certain biochemical and physiological changes are often found. These include (a) autonomic disturbance, (b) a scarcity of physical symptoms of allergy when psychotic.

(6) Vitamin B_3 and B_6 dependency should be accounted for and the hypothesis should try to account for the therapeutic value of other orthomolecular treatments such as ascorbic acid and penicillamine.

(7) The hypothesis should allow for an account of the cerebral allergies.

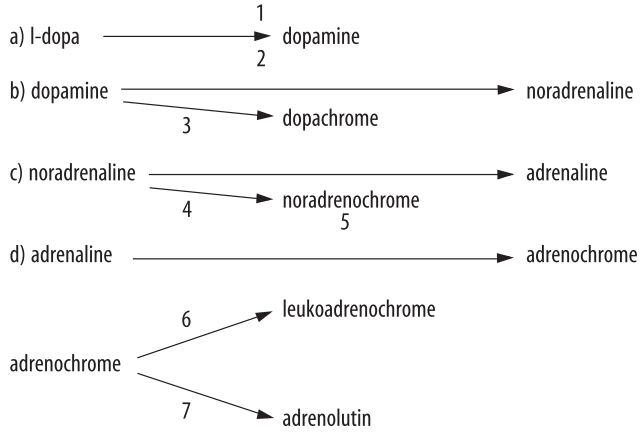
(8) Finally it should allow for the effect of some sympathomimetic amines and for at least some of the hallucinogens.

In conclusion anyone seeing the hypothesis and knowing nothing about schizophrenia should be able to describe it clinically, should be able to foretell what will make it worse and what treatments will be therapeutic. (**Figure 2,** below)

Reactions 1, 2 and 4 are essential as we can not live without noradrenaline and adrenaline. I suspect reaction 5 and reactions such as 3 are also essential when under proper control. Elsewhere I have suggested that the ratio of leukoadrenochrome to adrenaline (Hoffer and Osmond, 1960) helps to control anxiety. If this is true then adrenochrome is essential but only in very small amounts. Graham concluded that only a small proportion of the amines are oxidized to their aminochromes so that the red pigment areas in the brain only become visible to the naked eye after age six. Reaction 6 would then be therapeutic but reaction 7 is toxic.

The eight attributes of the good

Figure 2. The complete hypothesis.



hypothesis for schizophrenia can be accounted for by the adrenochrome hypothesis.

(1) Genetic basis: A genetic potential which favored reaction 7 over 6 could account for the phenomenon. For excess adrenochrome for any reason whatever would flow into adrenolutin which like adrenochrome is an hallucinogen. Leukoadrenochrome is not an hallucinogen. Any quantity of adrenochrome could be neutralized by diverting it into its leuko derivative. The same reasoning applies to every amine which is oxidized in the body into an amino-chrome.

(2) Physiological advantage: If there is an increased production of adrenochrome, properties of adrenochrome should be conferred upon the patient. Thus it is known that adrenochrome has antihistamine properties; schizophrenia should then impart antihistaminic properties, i.e. they should be less subject to physical expressions of allergy such as asthma, hay fever; adrenochrome has antimitotic properties. This suggests schizophrenics should be less subject to attack by cancer and should have lesser growth rates of rapidly growing tissues such as hair and nails. A few studies suggest that both these conclusions are true. I have had many patients who reported they did not have to have haircuts until they recovered when their hair began to grow at its normal rate. One patient had been bald for many years, her hair began to grow normally when she began to recover on Vitamin B_3 therapy. A decrease in growth rate should extend the life of these tissues i.e. these patients will not appear to age as quickly. However appearance is deceiving and it is likely that in chronic schizophrenia it is, as there is more rapid accumulation of old age pigment in brain and in heart i.e. that aging is accelerated.

Too much adrenochrome formation will increase the sensitivity of the schizophrenic to high oxygen tension. Fortunately there must be very few schizophrenics who are deep sea divers, at least at the beginning of their career as divers. Bean et al. (1955) found that animals with their adrenal gland removed withstood oxygen stress better; they withstood other stresses less well. When adrenaline is injected into normal animals or animals without adrenal glands oxygen toxicity is increased.

(3) The role of stress: Stress is harmful for two reasons. The increase in the production of noradrenaline and adrenaline will lead to an increase in adrenochrome and in those genetically disposed to reaction 7 instead of 6 this will increase the amount of adrenolutin which is toxic. Secondly any stress decreases the amount of ascorbic acid in the body. Most people are on very low ascorbic acid intake and can ill afford any losses. A decrease in ascorbic acid will increase reaction 5.

(4) The clinical picture: Adrenochrome and adrenolutin are hallucinogens for animals and man (Hoffer and Osmond, 1967). They cause perceptual changes, thought disorder, behavioral changes and depression as do other hallucinogens such as LSD and mescaline. Thus any reaction which increases the formation of these substances will cause the schizophrenic syndrome or will make it worse. Noradrenochrome has not been crystallized and therefore has not been tested but it would very likely have similar properties as would the aminochromes arising from l-dopa, from dopa-mine and from 6 OH dopamine (trihydroxy dopamine). Factors which increase reactions 3, 4, 4a, 5 and 7 will aggravate schizophrenia. This includes excessive methylation, excessive oxidation and a deficiency of antioxidants. Reactions which inhibit these will be therapeutic. Penicillamine tends to drive adrenochrome into reaction 6 thus increasing the ration of leukoadrenochrome to adrenolutin. This will help account for

its therapeutic properties. It is also a copper chelator and by reducing copper levels decreases the activity of copper oxidases, enzymes which drive these amines to their aminochromes.

(5) The physiology and biochemistry of schizophrenia: Schizophrenic patients are not normal. Physically they are ill; the signs include problems with skin and its appendages including acne, dry and coarse or too greasy hair, nail changes and some have a distinctive body odor which I have found only in schizophrenics. It disappears when they recover. Skin may be sallow and puffy. Signs of ill health include posture, lethargy; often they are too thin, less often too fat. It is this characteristic sick appearance which has led clinicians to keep on searching for those biochemical factors responsible, the toxin or the invading organism, and more recently the allergy or nutritional problem.

It would be unlikely that no differences would be found, for whatever sign is seen must have its internal equivalent. The main problem is that schizophrenia is a syndrome, not a homogeneous group. The commonality of the clinical symptoms and signs is probably internal and not as readily open to examination. There are therefore two main sets of biochemical factors, (a) those which are common to homogeneous groups and, (b) those common to the unique nature of schizophrenia. Thus the syndrome due to brain allergies will differ from that due to a Vitamin B_3 dependency or pellagra, in the syndrome factors. But all schizophrenics will have some things in common which cause perceptual and thought disorder

Table 1. A Comparison of some properties Of adrenochrome and changes found in some (1) schizophrenics.

Property	Adrenochrome	Schizophrenia
Antihistamine	Weak	(a) increased tolerance for histamine (b) decrease in physical symptoms of allergies
Pigmentation	Melanin and neuromelanin formation	a) increased pigmentation of hair and skin (b) decreased incidence of graying of hair
Antithyroid	Increased oxidation	(a) thyroid disturbances (b) increased tolerance to thyroid hormone
Mitoses	Antimitotic	(a) decreased resistance to tuberculosis (b) decreased incidence of arthritis (c)decreased rejection mechanism (d)deviations in growth
Temperature control	Hypothermia	(a) low temperature (b) defective diurnal rhythm
Insulinase mellitus	Inhibitor	(a) decreased incidence of diabetes
Phosphorylation	Inhibits hexokinase	(a) disturbed carbohydrate metabolism
Ascorbic acid	Oxidation	(a) deficiency

(1) Documentation for these comparisons is given in detail in our book. From Table 27, page 338. THE HALLUCINOGENS, Hoffer and Osmond, 1967.

symptoms. The first set of biochemical physiological differences will be found in a small proportion of the population of schizophrenics. If in a hundred patients forty are cerebral allergies and forty are vitamin dependencies, if one measures a factor peculiar to the cerebral allergies then only a small proportion of the entire group will show this difference. The first or the syndrome set of factors will never be found in a large proportion of schizophrenics unless a pure homogeneous group is selected. Thus, if one were to fast one hundred patients and study only those forty who became well by the end of the fast then we would have a homogeneous group. But the schizophrenia factors should be common to a large proportion of the heterogeneous group. A factor present in a large proportion of patients is therefore closer to the real schizophrenic factor than a factor which is only slightly more prevalent in the group. This is a syndrome factor. These two sets of potential differences will account for a finding which has been noted over fifty years. This is that no matter what biochemical or physiological variable is examined the schizophrenic groups have a wider distribution of values. They have a larger standard deviation of the mean for these variables.

A number of differences have appeared over the years. These are present in a number of patients so that mean differences compared to controls are not large. In my opinion they are real and must be taken into account.

In 1967 in our book Osmond and I showed how the adrenochrome hypothesis could account for many of these changes. I have shown some of these changes (from Table 27, page 338 *The Hallucinogens,* Hoffer and Osmond 1967) in **Table 1,** (p. 172). It seems to me this is a good test of the adrenochrome hypothesis. Every hypothesis in existence and those still to come including one which will render ours out of date must also try to account for the clinical, biochemical and physiological findings in schizophrenia. (6) Is there a biochemical relation with the action of Vitamin B_3 and Vitamin B_6. Vitamin B_3 is a direct antagonist to adrenochrome. Early in our research we found that adrenochrome injected intravenously into known epileptics greatly worsened the EEG abnormality. One young patient with no previous psychotic episodes was given adrenochrome. Within a few minutes her EEG became more pathological, she became morose and quiet. A few days later she had to be admitted to a psychiatric ward for treatment of her first psychosis. Other patients were injected intravenously with nicotinic acid at the height of the adrenochrome-induced abnormality, within a few minutes their EEC returned to its pre adrenochrome level (Szatmari, Hoffer and Schneider, 1955; Schwarz et al., 1956). It is clear nicotinic acid can quickly reverse the adrenochrome-induced EEC pathology.

Vitamin B_3 also antagonizes the effects of LSD, especially the perceptual component (Agnew and Hoffer, 1955). When we were investigating psychedelic treatment of alcoholics with LSD we routinely terminated the reaction if it was too intense or too prolonged by giving our patients a gram of nicotinic acid.

There is no doubt that it is helpful for many schizophrenics. This certainty is based upon four double blind controlled experiments, upon over fifty clinically controlled trials, on my own experience over twenty-five years, on the experiences of a large number of orthomolecular psychiatrists and on the absence of experiments which are a repetition of the kind of therapeutic trials we have run Pyridoxine was established as an important treatment for autism by Rimland (1978); Rim land, Callaway and Dreyfus (1978) and by Lelord et al. (1978,1979) by double blind controlled experiments using homoge-

neous groups. These were conducted with infantile autism groups, the most difficult group to treat. Pyridoxine can work in one of two ways or by both. It is essential for the conversion of tryptophan into nicotinamide adenine dinucleotide (NAD). It is also required to replenish the pyridoxine removed from the body of patients who have too much kryptopyrrole (KP). This is a substance first discovered by Irvine et al. (1969) primarily in schizophrenic patients under our direction (Hoffer and Osmond, 1963). Later Pfeiffer (1975) and Pfeiffer et al. (1974) developed a quantitative assay and demonstrated KP bound irreversibly with zinc and pyridoxine causing a double deficiency. KP is an animal hallucinogen (Walker, 1975); it has not been tested in humans.

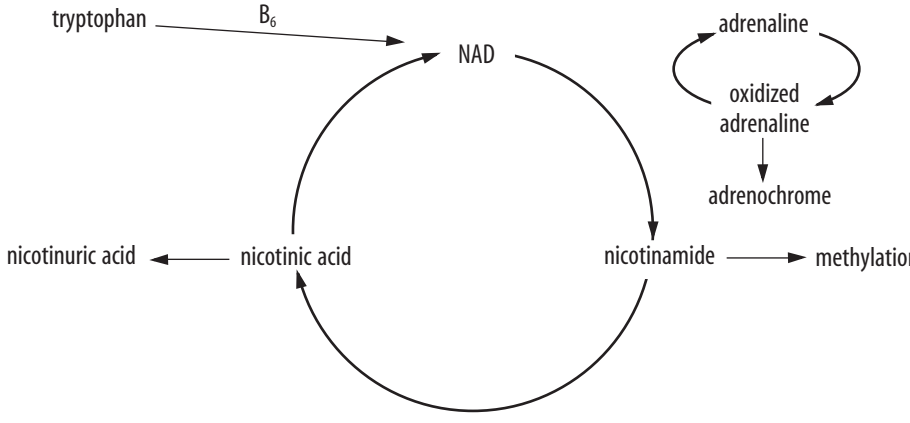
Vitamin B_3 and B_6 tie in with adrenochrome by the following mechanism. (**Figure 3,** below)

In the absence of enough NAD, oxidized adrenaline rapidly continues to be oxidized to adrenochrome. This reaction is not reversible. When there is enough NAD, oxidized adrenaline is reduced to adrenaline. This, I assume, is the normal process. The deficiency of NAD should therefore cause or, if it is already present, intensify schizophrenic symptoms.

A deficiency of NAD is present in the Vitamin B_3 deficiency disease pellagra. Pellagra is caused by a diet deficient in Vitamin B_3, by a diet which is too low in tryptophan, too low in absorbable Vitamin B3 and too rich in leucine. When too much leucine is present too much Vitamine B3 is lost in the urine. This is reversed by isoleucine, i.e. iso-leucine is an antidote against the pellagra producing property of leucine.

In patients with pellagra the blood levels of tryptophan are low because of the diet. Pellagra is the best natural model of schizophrenia. Many years ago pellagrins filled southern mental hospitals especially in the spring. Dementia praecox was the older name for schizophrenia. Pellagra was one of the differential diagnoses for this disease, the other being syphilis of the brain and scurvy. It may also be a model for Hunting-ton's chorea (Still, 1979). One of my patients with

Figure 3. Mechanism of vitamin B_3 and B_6 tie-in with adrenochrome.



H.C. lost nearly all his symptoms when treated with Vitamin B_3, ascorbic acid and large doses of Vitamin E. As with pellagrins schizophrenics also had low plasma levels of l-tryptophan in contrast to phenylalanine and tyrosine levels which were not different from non schizophrenic controls. After four weeks of treatment the plasma tryptophan levels increased and in women this increase was associated with clinical improvement (Manowitzetal., 1973; Gilmouretal., 1973).

Removing either nicotinamide or nicotinic acid from the pyridine nucleotide cycle will decrease the formation of NAD. Nicotinamide is a good methyl acceptor becoming N methyl nicotinamide. This molecule can no longer participate in the pyridine cycle. Nicotinic acid combines with glycine to form nicotinuric acid. It is excreted. These types of reaction decrease the availability of NAD. Mysko (1977) found that methylation of nicotinamide to N methyl nicotinamide was increased in schizophrenics compared to normal controls. It correlated with the presence of hallucinations. With clinical improvement the excessive methylation of nicotinamide disappeared. A decrease in available NAD will allow adrenochrome production to increase and increase the pressure toward schizophrenia in those genetically predisposed to convert it mostly into adrenolutin.

Graham suggests the well-known toxicity of 6 hydroxy dopamine (also called tri-hydroxy indole or TOPA) is due to its conversion to an aminochrome. This aminochrome would be very similar in structure and in properties to adrenolutin, an hallucinogen. Graham's suggestion is a good one; the aminochrome is a very active free radical and unless destroyed very quickly will combine and destroy other molecules. Since TOPA would be attracted to the dopamine receptors its oxidized derivatives would be there ready to destroy the dopamine receptors. This is what TOPA is believed to do. Adequate amounts of NAD at the same receptor would decrease the formation of the aminochrome and thus protect the receptor. This idea has not been tested. This hypothesis suggests that ascorbic acid and Vitamin B3 in adequate quantities should protect dopamine receptors against TOPA in the same way that they do protect against the psychosis-producing quality of levodopa. Graham suggests that levodopa while giving patients temporary symptomatic relief will at the same time hasten the destructive effect on dopamine receptors by levodopa. Our work suggests that Parkinsonism disease should be treated with Vitamin B_3 and ascorbic acid to protect the patient against the destructive action of levodopa.

(7) Cerebral allergies: Only a proportion of all patients with cerebral allergy are schizophrenic. There must therefore be another mechanism involved. The allergy triggers a reaction but other mechanisms determine whether the end result will be an anxiety state, depression, fatigue or schizophrenia. In my opinion only patients with the genetic potential for schizophrenia will develop it. They must, if we follow the adrenochrome hypothesis, be able to produce too much aminochrome and adrenolutin-like derivatives. In fact the allergic reaction may invoke this reaction.

Adrenochrome is a weak antihistamine. When the body begins to release too much histamine it takes counter measures. Increased secretion of adrenaline is helpful. Physicians use adrenaline injections in an emergency to save patients threatened with severe allergic reactions, adrenaline provides an immediate relief. If some is converted into adrenochrome this would provide a sustained antihistamine effect. Leukoadrenochrome and adrenolutin may also have similar properties. A person genetically programmed for schizophrenia can invoke this reaction

much more readily; a person unable to make enough would have a less effective defense against these allergic reactions.

If we assume the adrenochrome/adrenolutin defense mechanism is triggered the result will be (1) a reduction in the intensity of the somatic allergic reaction, i.e. less rash, less asthma, etc.,

(2) the effect of the increased amount of adrenochrome and adrenolutin, i.e. the schizophrenic syndrome. It may be that only an allergic reaction will trigger the adrenochrome/adrenolutin defense. These patients will be normal when not exposed to the allergen and schizophrenic when exposed.

Thus, some patients will be psychotic because they require large amounts of Vitamin B_3, B_6 to keep the adrenochrome/adrenolutin reaction under control, others will require an allergy-free environment (including food) while many will require both. Optimum doses of these vitamins will protect many cerebral allergies with little environmental intervention while others will require an equally vigorous anti allergy approach.

Before I became familiar with cerebral allergies I often had to use nicotinic acid dosages of 12 grams a day. When these patients discontinued their milk, or wheat, or sugar, or whatever they could no longer tolerate these high dosages. Whenever I find patients who can tolerate these quantities I immediately investigate them for allergies. My experience suggests that patients free of cerebral allergies can seldom tolerate more than six grams per day.

Unless clinicians are aware of these syndromes they will continue to make the same errors made by Ban and Lehmann (1970, 1975) and Wittenborn (1973, 1974). They will continue to use populations containing a large proportion of cerebral allergies for vitamin-only trials and will achieve the same negative results. The chronic population used by these investigators contain the greatest proportion of cerebral allergies. Our original controlled experiments were carried out on entirely acute and subacute populations which contain the fewest cerebral allergies. They contain the greatest proportion of vitamin dependent patients.

(8) Most of the hallucinogens resemble the amines or their aminochromes in structure and in properties. This is the observation which pointed at the amines and at the indoles. It is likely hallucinogens would not be hallucinogens if there were no natural mechanism in the body with which they interfered. For example some of our early work with LSD suggested that it required endogenous adrenochrome for its complete hallucinogenic activity (Hoffer et al., 1959).

I will examine the other hypotheses and show how they do or do not fit these eight criteria. These hypotheses have been reviewed by Teller (1979) and Smythies (1976). I will divide the other major hypotheses in two: (a) the methylation hypothesis, (b) the dopamine hypothesis.

The methylation hypothesis derives from Osmond and Smythies (1952). Briefly it suggests that under certain conditions amines are methylated to form hallucinogenic derivatives such as mescaline or bufotenine. I do not mean that mescaline is in fact formed, but that similar molecules with similar properties could be TOPA and could conceivably form such a compound. Excessive methylation would be toxic, a reduction in methylation would be therapeutic.

The dopamine hypothesis simply states there is either too much or too little dopamine activity in the brain. The excess dopamine hypothesis is supported by a number of findings. Many neuroleptics block dopamine receptors and Haldol is one of the most powerful dopamine receptor blockers. However, ascorbic acid which in the brain is as active as Haldol is not a tranquilizer. It has been valuable in controlling anxiety in some schizophren-

ics and has "cured" a few schizophrenics when 20 grams per day was used. Other supportive findings are that hallucinogens can affect dopamine receptors, that l-dopa will make patients psychotic and many reward pathways are controlled by dopamine turnover. Not favoring the dopamine hypothesis are the known observations that tranquilizers do not cure patients, nor is dopamine turn-over related to symptom remission. The dopamine hypothesis rests entirely on pharmacological evidence (Carlsson, 1978). See also Teller (1979) and Van Kammen (1979).

Chouinard and Jones (1980) suggested that schizophrenia is a dopamine deficiency disease. Muller and Seeman (1977) found an increase in the number of dopamine-binding sites in rat brains treated with neuroleptics. Increases have also been found in some schizophrenic brains. Further, Chouinard and Jones (1980) describe a supersensitivity psychosis. This is a response to chronic tranquilizer treatment. They believe that the dopamine deficiency excites a compensating increase in the number of dopamine receptors. It is an attempt by the neurons to retain their sensitivity to the neurotransmitter dopamine.

I would expect that any dopamine deficiency would arise by one of two mechanisms. If there were a decreased synthesis of dopamine from l-dopa there should be a deficiency of the other catecholamines which follow. There does not appear to be a deficiency of noradrenaline and adrenaline in schizophrenic patients. A deficiency of dopamine could be due to an increased turnover, i.e. it would be used up too rapidly. An increase in the oxidation of dopa-mine to aminochrome would cause a relative deficiency of dopamine in the brain without necessarily decreasing the intensity of the other metabolic pathways. It would also lead to some destruction of dopamine receptors where presumably the oxidation occurs. This could explain the increase in dopamine receptors, adaptive enzymes increase in quantity when more substrate is present. Perhaps the dopamine receptor attached to the neuron has the same adaptive capability.

I have referred to the possible interrelationship between serotonin and dopamine. A deficiency of serotonin would increase the conversion of dopamine to aminochrome. Smythies (1976) elaborated the dopamine hypothesis by involving serotonin. He suggests there is an imbalance between dopamine, which is too active, and serotonin, which is not active enough. This fits in with the serotonin-dopamine aminochrome idea. It also involves tryptophan as a source of serotonin and the nucleotide cycle, i.e. Vitamin B_3. Increased doses of Vitamin B_3 would (1) increase NAD levels which decreases oxidation of dopamine to aminochrome (2) increase serotonin levels by blocking the conversion of tryptophan to NAD. In turn the increased serotonin could inhibit formation of aminochrome from dopamine. A deficiency of Vitamin B_3 would by the same reasoning increase formation of aminochrome and perhaps account for a deficiency of dopamine at the synapse and an increase in dopamine receptors.

Serotonin can inactivate monoamine oxidase, one of the enzymes which inactivates sympathomimetic amines. It apparently is changed to an aminochromelike auto oxidation product which attacks the enzyme. Glutathione protects the enzyme (Klemm and Baumgarten, 1978). Inhibiting monoamine oxidase will drive more of the catecholamines into other pathways including the aminochrome pathway. TOPA also inactivates catechol O-methyl transferase via an aminochrome intermediate. This enzyme is the second enzyme which inactivates catecholamines (Borchardt, 1975). Thus aminochromes can block both of the systems which do not lead to aminochromes. It is also possible serotonin is changed into similar

aminochromes under certain conditions. Thus Baumgarten et al. (1978) suggest the toxicity of 5, 6 dihydroxy tryptamine requires oxygen to form an aminochrome. This would polymerize to form a melanin-like compound.

There are a number of other ideas which I would not class as hypotheses since they are really crude findings between schizophrenics and others in a few studies. These include monoamine oxidase low in some patients, creatinine phosphokinase in muscle, autoimmune, endorphins. Perhaps with more research these ideas may achieve the rank of hypotheses. A review of the relation of brain amines and peptides to psychiatric illnesses is provided by Smith and Copolov (1979).

The adrenochrome hypothesis logically fits in with hypothesis. In brief the adrenochrome/adrenolutin all of the eight criteria. The methylation hypothesis is a more holistic one with methylation conforms to only two but if the adrenochrome and dopamine being a part. hypothesis is accepted methylation conforms with Recently Horrobin (1977, 1979) presented a four more, but then it becomes superfluous. prostaglandin deficiency hypothesis of Methylation is then merely a reaction involved in the schizophrenia. This is probably the only new adrenochrome/adrenolutin hypothesis. The same hypothesis which does not require an ad-comments apply to the dopamine adrenochrome/adrenolutin mechanism but which is not necessarily antagonistic to it. Horrobin points out (1) antischizophrenic drugs stimulate prolactin which stimulates prostaglandin synthesis, but Horrobin does not consider Vitamin B_3 and B_6 anti-schizophrenia and fails to discuss whether these are related to prostaglandin metabolism, (2) schizophrenics tend to be more resistant to pain and inflammation and more resistant against arthritis; prostaglandins may be involved, (3) drugs known to be prostaglandin antagonists cause schizophrenic-like syndromes. Horrobin states the prostaglandin hypothesis may be reconciled with excess dopamine activity, to the endorphins, to cerebral al-

Table 2. Eight prerequisites to which a good hypothesis of schizophrenia must conform.

Item	Adrenochrome	Methylation	Dopamine *
1.Genetic	yes	yes	yes
2.Genetic advantage	yes	no	no
3.Stress	as an antihistamine	no	no*
4.Clinical symptomatology	yes	no*	no*
5.Clinical physiology	yes	yes	yes
6.Vitamin B_3 and B_6 therapeutic	yes	no*	no*
7.Cerebral allergy	yes	no*	no*
8.Relation to hallucinogens	yes	no*	no*

No* means methylation and dopamine could be active here only via an aminochrome derivative.

lergy and to a role for zinc.

The adrenochrome hypothesis immediately called attention to Vitamin B_3 and ascorbic acid as potential treatments for schizophrenia. The fact that we have indeed found these substances so helpful is a plus for the usefulness of the hypothesis. Osmond and I did not foresee that these vitamins would have a specific reaction with brain receptors. Mohler, Pole, Cumin, Pieri and Kettler (1979) reported that nicotinamide is a brain constituent with benzodiazepine-like activity. It has the same order of activity as the highly potent benzodiazepine. Thomas and Zemp (1977), Tolbert et al. (1979, 1979a) found ascorbic acid to be as active at the dopamine receptors as Haldol, one of the most potent tranquilizers. I will be surprised if future research fails to disclose a direct effect of these vitamins in the synapse and at the receptor site with one of the many amines which appear to play a role.

The Possible Relationship of Endorphins to Schizophrenia

Endorphins are small polypeptides with amino acid sequences found in B lipotropin from the anterior pituitary gland. Some of them have opiate-like activity. They are found in all areas of the brain and in cerebrospinal fluid. It has been suggested they are related to schizophrenia. Too little or too much is suspected (Verebey et al., 1978). So far the evidence is not persuasive for either idea. For awhile it looked as if dialysis might be useful in treating schizophrenics; Osmond and I, (1967) considered on theoretical grounds it might help. Recent reports do not support the earlier positive claims (Diaz-Buxo, Caudle, Chandler, Farmer and Holbrook, 1980).

Perhaps more thorough studies will isolate those schizophrenics who are helped by dialysis. Dialysis removes many molecules from blood so its therapeutic effect is not necessarily tied to any endorphin idea. I find Dohan's idea (1978) more appealing. He suggests that the basic biological defect in schizophrenia is genetic impairment of the gut and other barrier systems which eases the passage of food-derived neuroactive (exorphins) polypeptides from gut lumen to brain cells.

The evidence is reviewed by Ross-Smith and Jenner (1980). (a) There is an inverse association between consumption of cereals and gluten and the incidence of schizophrenia. (b) Gluten and casein hydrolysates produce exorphins which act like endorphins. (c) Large molecules can enter the bloodstream from the gut and penetrate into the brain. (d) Schizophrenics do show an association with immune reactions.

The exorphin reaction may be a specific one, an example of what can happen with any food to which a schizophrenic is allergic. They may well belong to the cerebral allergies. There is little doubt gut and brain are somehow related (Bloom, 1980). Eight physiologically important gut hormones are known, another seven types of gut hormones are peptides also active in the brain. These are a vasoactive intestinal peptide, substance P, enkephalin, bombesin, somatostatin, cholecystokinin and neurotensin. It may take many decades before these relationships are explored fully.

Conclusion

The adrenochrome hypothesis accounts for the syndrome schizophrenia more accurately than do any of the competing hypotheses. The two main competing hypotheses are superfluous since they are accommodated by the adrenochrome or more accurately the aminochrome hypothesis. In the research developed by Dr. H. Osmond and me this hypothesis has been very successful in giving direction to our research which began about thirty years ago. It provides insight into the experiential world of our patients lead-

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ing to several useful perceptual tests, i.e. the HOD test (Hoffer and Osmond, 1961; Hoffer, Kelm and Osmond, 1975), and the EWI test (El Meligi and Osmond, 1970). It helped originate the use of large doses of Vitamin B_3 for treating schizophrenia patients and for alleviating the symptoms created by LSD. It also predicted the therapeutic use of ascorbic acid, again in large doses. Both these vitamins are important components in orthomolecular treatment as applied to schizophrenics. Finally it helped point to the catecholamines as significant factors in the etiology of schizophrenia.

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.

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