SCHIZOPHRENIA: A NEW APPROACH
(CONTINUED)*

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The First Seven Years

Introduction

In the April, 1952 issue of this journal, Osmond and Smythies (47) suggested that schizophrenia might be caused by a defect in adrenaline metabolism. They called this hypothetical adrenaline derivative "M-substance" because they endowed it with mescaline-like psychotomimetic qualities but with an effective potency nearer that of adrenaline or even the hugely powerful LSD-25. They showed that mescaline and adrenaline were sufficiently alike chemically for such an intermediate to be at least imaginable. In addition, they emphasized that the mescaline experience and the more acute and dramatic forms of schizophrenia have many similarities. They hoped that researchers would hunt diligently for our M-substance.

A second paper by Hoffer, Osmond and Smythies (33) of January, 1954 reported that adrenochrome, an immediate derivative of adrenaline, might be a suitable candidate for M-substance. This paper presents further work with adrenochrome and its close relative, adrenolutin, Lund (1949), for consideration and scrutiny. We believe that our hypothesis can now be examined and tested by anyone wishing to do so. In 1954, though we did not know it then, this was hardly possible. In the last four years many of the difficulties which existed have been or are being resolved.

1953

In June, 1953, when we (with Smythies) completed our second paper, our task appeared to be straightforward. We planned to explore the adrenochrome model psychosis, to develop an assay for adrenochrome, and to measure it in schizophrenic, other mentally ill and normal people. If we found significant differences we intended, should it be necessary, to isolate the adrenochrome in schizophrenic people and try to fulfil Koch's postulates. We hoped to examine the great illness with our new tools and use our increased knowledge to develop a rational treatment and discover ways of preventing it. Because of our inexperience, our lack of resources and suitable equipment, the generally prevailing ignorance of the catechol indoles with which we were working (for less was

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known then than we realized) and to some extent sheer bad luck, this has taken longer than we hoped. However, we have had our share of very good luck and must not sulk if the cards have sometimes been against us.

Although our main interest in recent years has been the catechol indoles in our first paper (1952), Harley-Mason made the suggestion that the primary fault in at least some schizophrenic illnesses might be due to an excessive methylation of the phenolic groups of adrenaline to produce close analogues of mescaline. Recently, Armstrong and McMillan (1957) have identified homovanillic acid and 3-methoxy-4-hydroxy mandelic acid, both derivatives of noradrenaline and adrenaline containing methoxy groups on the phenolic hydroxyl. Axelrod (1957), Resnick *et al.* (1958) have shown that this occurs in normal subjects and schizophrenics. Schizophrenics excrete about one-third of injected methyl labelled adrenaline in the urine. After marsilid about two-thirds is excreted. This inhibition of monoamine oxidase increases the excretion of adrenaline. In schizophrenics, about 60 per cent. of the injected adrenaline is not accounted for. It has not yet been shown that these compounds play any particular role either in psychoses or anxiety.

The Synthesis of Adrenochrome

We lost our source of adrenochrome early in 1953. At first we thought this merely a temporary setback because we had many kind offers to supply us with it. We soon discovered that the generosity of our benefactors was not matched by an ability to make catechol indoles. Batch after batch of adrenochrome either started to deteriorate while in transit or arrived as a mess of sticky, black amorphous melanin compounds which were too insoluble to be tested for psychotomimetic properties. The deteriorating samples could be used a few times but were unsuitable for a series of cases. We longed for the brilliant red adrenochrome which Hutcheon, Lowenthal and Eade (1956) had so skilfully made for us. For while we had no way of telling for certain, then, whether it, a by-product, derivative, or even a contaminant, was the active substance, at least we knew what we were starting with. It was suggested that a "stabilized" adrenochrome would serve our purpose, Rinkel, Hyde and Solomon (1954). This proved to be the semicarbazone which is a wholly different compound whose chemical and physiological properties do not closely resemble those of adrenochrome.

In the intervening years, we have learned something about catechol indoles and we know that they are notorious among chemists for their fugitive nature. But at that time, we were less knowledgeable and our ignorance had disturbing results. We had reports from people who had used adrenochrome unsuccessfully. We gradually realized that apart from the many other variables, neither we nor they could be certain that they were in fact using adrenochrome, or that our previous positive results came from this or some derivative of it. Recently, we have had information about other closely related compounds which seem to be quite inert. Kluver (1957) has told us of similar experiences with porphyrins. We did not know about these matters four years ago and were puzzled and discouraged. How could other people be confident that we had ever had adrenochrome, especially when we could seldom produce any? Able men have declared that it probably does not exist except perhaps transiently and that it cannot be made in pure form, while others maintained that even if it could be synthesized as a stable product the presence of ascorbic acid and other reducing substances would quickly lead to its destruction in the body. Our

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unsuccessful attempts to get adrenochrome have been a source of embarrassment to us.

The Toxicity of Schizophrenic Body Fluids

While we tried to get a supply of adrenochrome with which to develop an assay method, we sought other ways of showing that a substance of this sort was present in the body. Remembering the fine work of the Machts (1956) with the shoot of the germinated lupin, we tried such varied agents as germinating wheat and oats, tomato seedlings, tadpoles, yeast and even wool. Some of these showed promise but none seemed to be worth developing. However, Fedoroff (1956) working with Professor Altschul, has perfected a cell culture test which shows a high degree of differential toxicity in schizophrenic serum, using the L-cell mouse fibroblast. This test, although too refined and difficult for routine diagnostic work, has, we think, a place in research. A number of these biological tests have been produced elsewhere during the last few years. Rieder (1957), followed by Burcell (1958), uses web-spinning spiders, Heath, Martens, Leach, Cohen and Angel (1957) and McGeer *et al.* (1957) respectively use extracts of schizophrenic serum and urine in monkeys, Winter (1957) uses injections of serum in trained white rats; Schwarzenbach (1957) has a very elegant method in which he measures changes in the germination of certain selected fungus spores. These spores respond to LSD-25, mescaline and adrenochrome in a specific manner at very low concentration. Streifler (1957) found that rat retinal tissues responded differently to schizophrenic and normal serum. However, the latest findings by Fedoroff and Hoffer (1956) that surgical patients also have toxic sera, complicates the picture, though it seems that the toxins are different in each condition. Any of these tests standing alone, as the Machts' did for so long, might be discounted by the sceptical or ignorant, but their concerted effect is to make a toxic substance seem much more probable.

Differences Between Schizophrenics and Others

It follows from our hypothesis that there should be other differences between schizophrenics and those who do not have this illness. One would expect these to be associated with adrenaline metabolism and one would also expect that there would be perceptual anomalies. Hoffer (1954) has shown that 80 per cent. of schizophrenics respond differently to injections of atropine. This is of theoretical interest and compares favourably with many other diagnostic tests. It is, however, only a stopgap. Working on similar lines, Lucy (1954) showed that schizophrenics had an extraordinary tolerance for histamine and that this tolerance becomes progressively larger the longer the illness continues. Two of our patients have been able to take 75 milligrams of histamine base in one hour with little more than some discomfort. From Lucy's work, Weckowicz and Hall (1957) have developed a skin test using the speed at which a weal develops as an index of sensitivity. This clearly differentiates schizophrenics from normals and other psychiatric patients and can be done blind. He has also shown that schizophrenics are not generally unreactive as has been sometimes suggested. They respond to intradermal morphine, for instance, just as other people do. Furthermore, when nicotinic acid is given to acute schizophrenic patients for a period of two weeks, it raises the BMR more than in normal controls given the same amount, Hoffer and Callbeck (1957). These explorations suggest that both acute and chronic schizophrenics

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are a continuum and that long-stay patients are still pharmacologically active and not "burnt out" as has sometimes been thought. Adrenochrome itself is an antihistamine, Hutcheon *et al.* (1956). Lea (1955), following Lucy's work, gave a very elegant demonstration that allergies are far less frequent in schizophrenic soldiers than in a comparable group suffering from head injuries and suggested that a raised level of blood adrenochrome was responsible. Ehrentheil (1957) reports the same findings and gives a long list of other such reports.

Weckowicz (1957) and Crookes (1957) have shown that chronic schizophrenic patients have marked disturbance in the constancy of their visual perception which is in keeping with their time perception as shown by Lhamon and Goldstone (1956). It is curious that even now we know very little about the world in which schizophrenic persons live. There has been much talk about sensitive and empathic insights, etc., but very little maintained and co-ordinated effort to measure the perceptual difficulties of schizophrenic people. Yet one would suppose that such disabilities could have marked effect on their behaviour.

ADRENOLUTIN

In their initial work, Eade (1954) with Hutcheon drew our attention to 3,5,6-trihydroxy-N-methyl indole which has been called adrenolutin. In 1954, while visiting J. Harley-Mason in Cambridge, one of us (A.H.) was again reminded of its existence. Harley-Mason gave us a small bottle containing about 200 milligrams of it which he had had on his shelves for nearly two years. This was all that he had at that time. The adrenolutin consisted of smooth running, shining golden crystals which had a greenish sheen when looked at askew. They dissolved easily in water and were very stable in solution. Indeed this could be boiled without decomposing. We felt this would be much easier to work with than fugitive adrenochrome.

Accordingly, as we reported elsewhere, Hoffer (1957), we started to work with adrenolutin, using it orally on human volunteers because at that time we had no experimental animals available. The new compound seemed to be a powerful psychotomimetic and had the unexpected ability to spread its effect over several days, lasting sometimes a week or more. At first, we thought this was improbable but after it was repeated several times we had to reconsider our views. Our small store of adrenolutin soon ran out but since we knew that Harley-Mason was ready to make us more when we needed it, we did not preserve our original supply. Indeed as soon as we asked for a new lot, he was as good as his word and sent it. For the next two and a half years we saw no adrenolutin resembling that 200 milligrams. The second sample was an amorphous, khaki coloured powder and more than two years was spent in a series of frustrating and usually futile attempts to get either pure adrenolutin or adrenochrome. At times we almost began to wonder whether these substances were hallucinations rather than hallucinogens. The experts were polite but on the whole, sceptical. Yet we knew that we had seen them and experienced their effects but it was not easy to convince other people who had not had our experiences.

In 1955 and 1956, we did a series of double-blind experiments using the best samples of adrenolutin then available to us. There seemed no doubt that susceptible people gave a characteristic response. But our sample was not active enough to affect every subject. Yet we were loath to increase the dose

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because some subjects had prolonged responses lasting a week or more. Consequently, many of our findings, although interesting and highly suggestive, were not really suitable for statistical evaluation. Meanwhile our chemist colleagues continued to struggle with the synthesis of adrenolutin which now proved to be at least as difficult as that of adrenochrome. Indeed we made large quantities of the latter substance some months before the former. It is not easy to convey our disappointment during these hard months when we had tantalizing glimpses of a promised land. We were lucky that work by others, less direct than our own but no less valuable, gave us encouragement, and our therapeutic trial with niacin heartened us a little.

Niacin Treatment in Schizophrenia

We had always hoped that our new approach would help in developing a rational treatment for schizophrenia. In 1952, following observations on some preliminary cases, we started then as we have reported elsewhere, Hoffer, Osmond, Callbeck and Kahan (1957), a sustained trial of our new treatment. This consisted of massive doses of niacin or its amide ranging from 3 to 25 grams daily. We will not discuss this work in detail here. Table I from our recent paper outlines our results. These are that while niacin seems beneficial in early schizophrenia and apparently reduces the rate of relapse (one out of thirty-seven, viz. six out of thirty-six) when medication is continued, it is usually ineffective in long-continuing illnesses. An exciting and unexpected by-product of this nicotinic acid work has been the discovery, Altschul, Hoffer and Stephen (1955), now confirmed by Parsons and others (1956) at the Mayo Clinic, that nicotinic acid in large doses reduces the level of cholesterol in the blood. Further it will, as Altschul (1955) has shown, protect rabbits against artificially induced arteriosclerosis. Niacinamide, which is equally effective in schizophrenia, does not do this.

Table I

Effect of Nicotinic Acid on Treatment of Acute Schizophrenia

Treatment in Hospital	Follow-up Treatment	Number of Patients	Certified to Mental Hospital During Follow-up	Suicides
Nicotinic acid	Nicotinic acid ..	24	1	0
Other treatment	Nicotinic acid ..	13	0	0
Nicotinic acid	Other treatment ..	36	6	0
Other treatment	Other treatment ..	98	47	4

The Metabolism of Mescaline

Smythies, while holding a Nuffield Fellowship at Cambridge, collaborated with Harley-Mason and Laird (1957) on the problem of the mode of action of mescaline. The large effective dose of this compound, the slow mode of onset of its effects and the fact that it is quickly fixed to liver protein and during the phase of psychosis (or equivalent period in mice) little is to be found in the brain suggests that the active agent is either some metabolite of mescaline or a toxic bodily metabolite with whose detoxication mescaline interferes. Their findings were that 35 per cent. of the mescaline is excreted unchanged in the urine within 24 hours, only a trace in the second 24 hours and none after that. A specific metabolite, 3-methoxy 4,5-dihydroxyphenylacetic acid was also

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isolated in small amounts in a conjugated form. The rest of the mescaline was unaccounted for. Thus the problem of the cause of the "mescaline" psychosis remains unsolved.

Work in Other Centres Bearing on Our Hypothesis

The rise of tranquillizers, many of which have been developed from antihistamines or from Rauwolfia derivatives, was interesting to us, more so because recently it has been suggested that their main effect is on adrenaline metabolism. Their mode of action is still obscure and they have thrown very little light on the aetiology of schizophrenia. From our viewpoint the work of Heath and Leach has shown the greatest boldness and imagination. Its details are still disputed, but only the most bigoted or pedestrian could fail to recognize that the extraction from the blood of schizophrenic patients of a protein fraction which itself acts as a psychotomimetic is a notable happening. That these findings should have been greeted with a combination of open ill will, irritation, scepticism and intolerance, reflects the muddled state of many psychiatrists. This response was due in part to an inability by some workers to reproduce these results. This must have been due to technical failures as confirmation has now been reported by the KABI group in Sweden (1957). It seems that there may be in schizophrenic blood at least one aberrant protein fraction, which is closely related to ceruloplasmin and has been called taraxein by Heath and Leach. This substance seems to play a part in the metabolism of amines and increases the excretion of indoles in urine, Heath *et al.* (1958). We do not yet know exactly what takes place and more recent work, indicates that the suggestion that only ceruloplasmin is responsible for the conversion of adrenaline to adrenochrome is not correct, Payza and Hoffer (1958). However, differences in detail and the fact that it has not always been easy to separate taraxein does not reduce the importance of this work. Heath's and Leach's emphasis on the enzymic mechanisms complements our interest in the substrates and products with which they are concerned.

In 1954, a major objection to our hypothesis was that the body did not seem to produce enough adrenaline to form the quantities of adrenochrome, adrenolutin or derivatives required to produce model psychoses in our experiments. While there are other factors which we have discussed elsewhere, Hoffer and Osmond (1955), and will touch on later in this paper, Elmadjian and Hope (1957) and Gaddum, Krivoy and Laverty (1958) have shown that more adrenaline is made in the body than was previously supposed. Furthermore, local production of adrenaline analogues near neurones and the rate of turnover of adrenaline may be important factors independent of the blood level.

Since 1954, in addition to "adrenochrome" and "adrenolutin", other indolic or potentially indolic substances have been found to be psychotomimetic. Harmine, Pennes and Hoch (1957), and ibogaine, Schneider and Sigg (1957) have had these properties reaffirmed. TMA, Peretz, Smythies and Gibson (1955), has been added by one of us. Bufotenin, Fabing *et al.* (1956), has received some attention, while Sherwood's (1957) BGE and Szara's (1957) two compounds, dimethyl and diethyl tryptamine, give continuing support to our suggestion that of the known psychotomimetics most are indolic or potentially indolic substances. Table II shows those known in 1954 and those now known.

Although the psychological activity of adrenochrome and adrenolutin

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TABLE II

Psychotomimetic Substances

A.	1954:	Mescaline
		Lysergic acid diethylamide
		Harmine
		Ibogaine
		Hashish
		Adrenochrome
B.	1958:	Adrenolutin
		Dimethyl tryptamine
		Diethyl tryptamine
		T.M.A.
		Bufotenine
		Lysergic acid monoethylamide
		Lysergic acid morpholide
		The German's green compound
		B.G.E.
		3, 4 methylene hydroxy phenisopropylamine
		Methyl tryptamine
		Psilocybin
		Acetyl lysergic acid
		Methyl lysergic acid
C.	Delerients	WIN 2299
		Abood's compounds
		Nalline

in humans is not readily recognized by those who have had little experience with a variety of psychotomimetics, their effect on animals is easily demonstrable. Adrenochrome placed in the cerebral ventricles of cats in dosages of ½ to 2 mg. produces marked catatonic and trance-like states, Schwarz *et al.* (1956), Rice and McColl (1957). It is interesting that in all these experiments adrenochrome synthesized by C. Pfizer and Company or in Saskatchewan was used. Adrenochrome markedly inhibits the performance of trained climbing rats, Winter (1957), distorts the web pattern of the garden spider, Witt (1954) and produces clear catatonia in pigeons, Wojcicki and Hoffer (1957), and monkeys, Melander (1957). It does not, however, seem to be effective in mice, Smythies (1958). Such interspecies differences, however, are not in the least uncommon.

It is sometimes forgotten, especially by those mainly engaged in working with animals, that the great majority of people with schizophrenia do not suffer from catatonia. Most of our patients, particularly in the early stages of their illness, are noteworthy for the fleeting nature of their symptoms. Indeed, so difficult has it been to characterize exactly the early psychological changes of this illness that psychologists still disagree about the value of psychological tests in diagnosis, in spite of a vast literature which bears witness to the great efforts that are being made to find suitable ones. So those aspects of our work with adrenochrome and adrenolutin which seem least satisfactory to researchers keen for an imposing array of statistically significant tests are the ones which give particular plausibility to the possible role of psychotomimetic agents in schizophrenia. In well run hospitals florid symptoms have always been far rarer than in badly run ones, and when they occur they are often transient.

FURTHER WORK IN SASKATCHEWAN

Curiously, some authors who could not have read our papers carefully have foisted on us the notion that all indoles are psychotomimetic or con-

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versely, that we consider only indoles or potential indoles can be psychotomimetic. Having ascribed to us a viewpoint we do not support, they have then demolished this with irrelevancies. What we have done is to present evidence that most of the proven psychotomimetics whose active principles are known have, so far, been indoles or potential indoles, with the exception of the still disputed active principles of hashish and Abood's new atropine analogues, WIN 2299 and nalline.* Furthermore, we have, of course, never maintained that adrenochrome, adrenolutin or such other active derivatives as may be found, were the sole cause of schizophrenia. We have recognized at least two main groups of factors (1) those leading to increases in parasympathetic function and increased acetylcholine levels, and (2) those leading to increased quantities of adrenaline indoles or similar indoles. These are minimum conditions. One set of factors alone will undoubtedly yield some mental disorder but both are required for a clear demonstration. So far with the exception of hashish about which we do not have the necessary data, WIN 2299 and nalline, the psychotomimetic substances listed in Table II resemble either adrenaline or adrenochrome in structure. Abood's (1958) atropine-like compounds and atropine itself increases the production of adrenaline as do the acetylcholine esterase inhibitors.

To reproduce an acute severe schizophrenic psychosis (omitting for the moment the extremely important matter of social setting), both aspects of the model are required. This might be done by injecting large quantities of acetylcholine, which is difficult, or by inhibiting the choline esterase, which is simple. A combination of choline esterase inhibitor with adrenochrome and/or adrenolutin should accomplish this. Melander (1957) using this type of potentiation experiment, found that cats which did not respond clearly to 100 micrograms of LSD-25 alone, or to 5–10 mg. adrenolutin alone (100 mg. of adrenolutin will induce catatonia) became catatonic when given a small quantity of adrenolutin ninety minutes after 100 gamma of LSD-25 (5 to 10 mg. per cat).

Melander's contribution provides us with a method of inducing psychotic-like experiences of short duration, which has not always been possible. We have repeated Melander's work with cats, in humans using LSD-25 as the sensitizing agent and adrenochrome or adrenolutin as the psychotomimetic agent. Our normal subjects (more than twelve) showed little response to 35 micrograms of LSD-25 by mouth. After one and a half hours they were given 10 milligrams of adrenochrome by vein. Adrenochrome levels are assayed before LSD-25, before the adrenochrome, thirty and sixty minutes after adrenochrome has been given.

The clinical response after the 35 gamma of LSD-25 was slight and consisted mainly of an increase in tension. There was no alteration in adrenochrome levels. While the adrenochrome was being injected, a remarkable feeling of muscular weakness set in, there was some constriction of the chest and a need for deep breathing. This continued for some minutes. A few minutes later, a typical adrenochrome or adrenolutin experience begins. But this is sometimes as intense as that seen with 100–200 micrograms of LSD-25 and continues from five to nine hours. The experience is not an intensification of the usual LSD-25 experience but is an intensification of the adrenochrome

* The published accounts of WIN 2299, Nalline and Abood's atropine derivatives suggest that their effects are not wholly similar to mescaline, LSD-25, adrenochrome, etc. Clouding, confusion and some drowsiness occurred. However, testing procedures for some psychotomimetics in humans are hardly refined enough for one to be dogmatic.

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experience. With normals and alcoholics, we have found (1) changes in perception which include visual disturbances such as slight movement of objects, distortions, colour changes, difficulties in judging the distance and size of objects, changes in the perceived body and changes in time perception; (2) changes in thought with blocking, concreteness, paranoid thinking, feelings of passivity, social disinhibition; (3) fluctuations in emotions ranging from severe depression with suicidal ideas to transient euphoria; (4) inappropriate activities; and (5) catatonic features such as gross muscular weakness, shuffling gait, motor inco-ordination and negativism.

After the injection of adrenochrome, blood levels are elevated three- or four-fold but return to normal within two hours although the experience continued.

LSD-25 in psychotomimetic doses increases adrenochrome levels up to four-fold within two to four hours of administration, Hoffer (1958). It also blocks acetylcholine esterase, especially pseudocholine esterase. Thus LSD-25 on its own produces both conditions. At present, pseudocholine esterase is generally supposed to play only a small part in the transmission of nerve impulses. The finding that LSD-25 blocks pseudocholine esterase, Thompson *et al.* (1955), more effectively than choline esterase suggests that this should be reconsidered. Pseudocholine esterase may have an important role in normal brain function.

2-Bromo LSD which does not produce an LSD psychotomimetic experience also blocks pseudocholine esterase and thus reproduces the first set of conditions. However, it does not elevate adrenochrome levels and the second set of conditions is not fulfilled. We have pre-treated two subjects with ½ mg. BOL followed one and a half hours later by 10 mg. of adrenochrome. When the adrenochrome is injected the immediate reaction is similar to subjects pre-treated with LSD-25 but instead of the experience increasing in intensity, it decreases and within the hour there was no residual change. Adrenochrome levels were normal half an hour and one hour after injection. When BOL is given alone, the level of adrenochrome does not rise as it does after LSD-25.

We have found that LSD-25 stabilizes adrenochrome in blood *in vitro* and also increases the conversion of adrenochrome into adrenolutin, Hoffer (1958). Apparently the pathway leading to leuko-adrenochrome is blocked. In plasma, the conversion of adrenochrome to leuko-adrenochrome is probably enzymatic and is accelerated by adding ascorbic acid *in vitro*. LSD-25 may specifically inhibit this enzyme. The adrenochrome levels remain high for 48 hours after LSD-25 has been given. If ascorbic acid is given during the experience the adrenochrome levels stay within the normal range but there are marked fluctuations with some rebound in 24 hours. These two observations strongly suggest that LSD-25 also blocks conversion of adrenochrome into leuko-adrenochrome *in vivo*. It seems likely that the high adrenochrome levels are produced by this inhibition of adrenochrome destruction rather than by an increased secretion of adrenaline.

Taraxein also potentiates adrenolutin, Heath (1958), and may do so by stabilizing adrenochrome.

Hoff (1957) reports that serum from 500 ml. of blood taken from a normal subject one and a half hours after receiving 100 mg. of LSD-25 produced an LSD-experience when injected into another normal person. This serum could only contain much less than 10 μg. LSD-25, but there would be larger quantities of adrenochrome, adrenolutin and other substances.

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The Route of Admission of Psychotomimetics

There are many clues which emphasize not only the importance of the route but the manner of giving psychotomimetics—it is odd that this has had so little attention in recent years. The special preparations for smoking hashish or opium, the elaborate arrangements for snuffing cohaba, the complicated method of chewing the betel nut, even the careful steeping of tea or coffee, all emphasize the importance of proper preparation. While in the Kava-Kava ceremony we have evidence of an animal enzyme, ptyalin, being used to liberate an active principle. This is even clearer in the unusual methods of the Chuckchees in Siberia in preparing *Amanita muscaria*. It is doubtful whether many of us would relish the honour of drinking great draughts of our host's urine, however stimulating the results might be.

In our first experiments with "adrenochrome" we used subcutaneous injections* because we thought it would disintegrate in the stomach and we were not sure enough of its effects to use the intravenous route. When we later used "adrenochrome" intravenously for the first time, our subject, Mr. Charles Jillings, experienced great pain along the course of the brachial vein which seemed to be of an anginal type. He bore this courageously and was not nearly as distressed as his colleagues. We later found that if "adrenochrome" solution was mixed with blood before injection this did not happen. We started using "adrenolutin" orally because our first sample had not been tested on animals. Later we used "adrenolutin" by mouth and by vein. We have also tried it as a snuff by nasal inhalation without effect.

In mid-1956 (as we have reported in this journal) Osmond and Hoffer (1958), we learned that oral inhalation might be more effective than by other routes. Since then, we have experimented with impure "adrenolutin", mixed adrenaline derivatives and pure adrenochrome solution, using a simple de Vilbiss No. 33 hand sprayer. These experiments have been suggestive. We have also used a Riker Medihaler (supplied by the courtesy of the Riker Corporation, Los Angeles), an ingenious device which delivers a measured quantity of aerosol adrenochrome suspended in Freon gas. Preliminary results suggest that adrenochrome by this route is many times more powerful than when given by vein. It is not easy to see why adrenochrome injected into the antecubital vein about 18 inches away from the lungs should be so much less effective than when squirted into them directly. It would appear that adrenochrome must be destroyed or bound by the venous blood in some way. It seems likely that a few dozen gamma at the most reach the brain direct from the lungs and they have a very disorganizing effect. The importance of this becomes clear when one realizes that in acute schizophrenia and LSD model psychoses the level of free adrenochrome in the blood seems to be of the same order that might occur in these inhalation experiments. These must clearly be repeated and greatly expanded, for they have unusual possibilities. It almost looks as if adrenochrome, when given this way, is as powerful as when instilled into the ventricles. Yet this is simpler, safer and involves no surgery. Recently Taubmann and Jantz (1957) have shown that adrenochrome by the sublingual route given in doses from 3–6 mg. produces a marked response. We have, ourselves, confirmed this now in five cases. This work is extremely important and interesting

* These quotation marks indicate that the substances we used at that time did not have the high chemical purity that is now possible but were a red mixture of adrenaline oxidation products certainly containing large quantities of adrenochrome; while adrenolutin was a yellow-green mixture often very high in adrenolutin, sometimes not high at all.

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and emphasizes once more the need for much greater attention to the route of administration.

Pure Adrenochrome and Its Consequences

It now seems that until early 1957 neither we nor anyone else could be sure that they had ever possessed pure adrenochrome. Indeed, some have openly and repeatedly averred that it does not and cannot exist. We did not possess such omniscience, but we have been very uneasy from time to time. A chance meeting which one of us (A.H.) had with Dr. Atcheson in Vancouver resulted in our being given a valuable clue. It is well known among indole chemists that indoles are very sensitive to even small quantities of metallic ion. Less than one part in a thousand may act as a catalyst so that the whole compound becomes unstable. Dr. Atcheson suggested that they might play a part in this instability. This has proved to be so and, working in our laboratory, Payza has already made micro quantities of pure crystalline adrenolutin. Shortly after this, he and Heacock (1958) succeeded in making much larger quantities of pure stable adrenochrome. This has brilliant dark red, lanceolate crystals which remain stable in air indefinitely and whose solution in distilled water is also very stable. About the same time, Abood (1957) discovered an enzymic way of making pure adrenochrome. Our information was passed on to Melander of the KABI group in Sweden and they are now making adrenochrome and adrenolutin in quantity. Adrenolutin purified of all adrenochrome and metallic ions appears once again as golden yellow stable crystals, like those originally synthesized by Harley-Mason.

Once we had obtained a pure supply of adrenochrome further advances became possible. Payza and Hoffer (1958) have already shown that it is synthesized in the body from adrenaline by an enzyme called adrenaline oxidase which they readily distinguished from ceruloplasmin. Adrenochrome is unstable in serum and turns either to leuko-adrenochrome Hoffer (1957), in the presence of ascorbic acid, or adrenolutin in the presence of ions of heavy metal. Adrenolutin does not combine with ascorbic acid but Melander (1957) has shown that it very readily combines with ceruloplasmin. Perhaps this combination of ceruloplasmin and adrenolutin can be disrupted by Heath's taraxein leaving adrenolutin free. Ostfeld, Abood and Marcus (1958) have shown that only analogues of his new hallucinogen that raises the blood level of ceruloplasmin are hallucinogens. Furthermore, subjects who fail to react to this new hallucinogen with hallucinations do not show this rise in blood ceruloplasmin. Payza and Mahon* (1958) have only recently perfected a method of measuring adrenochrome levels in blood and are currently attempting to do the same for adrenolutin and leuko-adrenochrome. This is in itself of great interest, but what is even more important is we may reasonably expect to discover new ways of measuring the by-products of adrenaline metabolism. Tests of pure adrenochrome and adrenolutin will help to show whether these are psychotomimetic substances in themselves or whether our previous results and the psychotomimetic effects of pink adrenaline were due to breakdown products of these substances. We do not yet know, however, how complicated these metabolic patterns may prove to be.

Adrenochrome Metabolism

A survey of adrenochrome plasma levels in all psychiatric patients shows there is no significant difference between them. However, schizophrenic patients

* Method available on request.

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have more adrenochrome in their cerebrospinal fluid than do other patients. Patients who are anxious and tense have lower than normal levels. The ratio of adrenochrome in cerebrospinal fluid to plasma, both drawn simultaneously, is 1·9 for schizophrenics (N=15), 0·9 for people with depression and anxiety (N=7) and about 1·1 for medical and surgical patients.

Adrenochrome is more stable in cerebrospinal fluid *in vitro* than it is in plasma. It is therefore not surprising that the levels are higher in schizophrenic cerebrospinal fluid and not in plasma.

Adrenochrome may be destroyed less rapidly in schizophrenics and form larger quantities of adrenolutin. To test this possibility an adrenochrome tolerance test was developed. This is similar in principle to the intravenous glucose tolerance test. This test has been given to schizophrenic patients, subjects not schizophrenic and normal volunteers after they were given LSD-25. These results are shown in Table III.

TABLE III

Tolerance for Ten Milligrams Intravenous Adrenochrome

Group	N	Initial Level μg./litre	Per cent. Change at 15 (mins.)	30 (mins.)	60 (mins.)
Schizophrenic	6	43	+280	+75	+107
Not schizophrenic ..	9	51	+170	−45	−23
Normal 35 μg./LSD-25* ..	6	48	+260	+100	+67
Normal 100 μg./LSD-25 ..	2	46	—	—	+170

* 2 hours before adrenochrome test.

The schizophrenic patients destroyed adrenochrome more slowly than other subjects and in this way resembled subjects pre-treated with LSD-25.

LSD-25 given to subjects causes an increase in adrenochrome levels, Hoffer (1958). When the adrenochrome levels are markedly elevated the experience is strongly visual with little tension. When there is little increase in adrenochrome the experience is characterized by extreme tension and anxiety with minimal visual changes. BOL-148, a substance that does not elevate adrenochrome, does not produce any unusual experience.

TABLE IV

Effect of LSD-25 and BOL-148 on Adrenochrome Levels in Plasma With and Without Ascorbic Acid Treatment

Group	N	Treatment	Adrenochrome μg./litre 0	2	4	6	24	48
Normal and alcoholic	7	LSD-25 100–300 μg. ..	66	227	216	139	117	74
Normal	2	LSD-25 100 μg. 5 grams ascorbic acid before LSD	84	170	115	—	84	—
Normal	3	LSD-25 100 μg. ascorbic acid before and during LSD experience	68	74	59	—	82	54
Normal	4	BOL-148 500 micrograms ..	82	59	—	—	—	—

The evidence provides strong support to our contention that adrenochrome metabolism is disturbed in schizophrenia.

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Discussion

1. *A New Approach and Research Method*

More money is now available for research in psychiatry and scientists such as biochemists, organic chemists, pharmacologists, neurophysiologists, etc., are being drawn in. Much of this new work is aimed at the biological aspects of schizophrenia in the hope of relating specific biological disturbances to special psychological abnormalities. We must, if we are to use the scientific method, construct an hypothesis and test it vigorously by trying to refute it. When planning research of this sort there is a hierarchy of hypotheses which must be borne in mind.

One hypothesis is that schizophrenia derives from a specific biological fault of either metabolism or cybernetic function of the nervous system. A counter hypothesis to this is that of at least some psychoanalysts who hold that the disturbing factors are primarily psychological and that anyone subject to a particular spectrum of conditions in early childhood will develop this illness. The biological hypothesis suggests a specific genetic fault. As we have observed, an advantage of our hypothesis is that we can include psychological stress factors in the biological aetiology, since if the metabolic fault is in the biochemical mechanism subserving the organism's response to environmental stress, if this mechanism is overloaded, breakdown must result.

A research programme based on psychoanalytic procedures can hardly avoid being less efficient than one based on biological investigations for several reasons.

1. After nearly sixty years, there is little evidence of a scientific sort deriving from experimental and statistical procedures that the psychoanalytic hypotheses are true. There is even less that they are of use in the understanding and treatment of schizophrenia. Indeed, there is some doubt among psychoanalysts themselves as to how far their theories apply to the illness.

2. The theoretical structure of psychoanalysis as a science is primitive. It describes a series of "entities"—"Ego", "Super-ego", "Id", etc., which are supposed to have certain properties and inter-relations. There are, of course, no such entities, and the whole system is a convenient way of describing behaviour, dreams, fantasies, etc., and their inter-relations by means of metaphor disguised as analogy and passed off as fact. This is not uncommon in the early stages of any science and may be found in 18th century chemistry when it was bedevilled by the phlogiston theory, or in general medicine in the days of Brown, Broussais and Stahl.

3. Even if we admit that psychoanalysis has some scientific status, this must still be judged primitive for two further reasons. First, it lies at a lower level in the positivistic hierarchy than biochemistry, its rival from our point of view. For psychological explanations are to be reduced, by the laws of the hierarchy to which psychoanalysis, claiming to be a science, must subscribe, to more fundamental physiological and chemical explanations and not vice versa. Amongst other things "more fundamental" implies in medicine "more useful in devising new treatments" for it is in treatment that medical theories are tested. Secondly, as Popper (1958) points out, the theories of psychoanalysis can be plausibly applied to all human behaviour. They are susceptible to all manner of "confirmation". But because they are really descriptions masquerading as explanations and because of their generality and their many escape clauses, such as reaction formation, they cannot be refuted. So far, they have been of low predictive value, but even if this were not so it is by their

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irrefutibility that they cease to be scientific theories, for every scientific theory can, in principle, be refuted.

However, while one may favour a biological approach, the question is which one and at what level? There are two main hypotheses to choose from, the cybernetic and the pharmaco-biochemical. The former implies that schizophrenia is due to a failure in the brain mechanism brought about by inherent faults in design. One can imagine that so complex a mechanism could have its own mode of breakdown like those found in computors, due to the failure in cybernetic organization rather than metabolism. This fascinating hypothesis is not yet testable because we are still so very ignorant about the cybernetic function of the brain. We do not know yet how the millions of neurones co-operate in their computing and classificatory functions. The micro-electrode only tells us about a few neurones, while the EEG gives us the summated activity of several millions. Smythies (1958) has recently suggested a new way of tackling this problem. But even so, apart from crude methods like E.C.T. and lobotomy, no therapeutic intervention in the cortical circuits is yet possible. So this approach, although of great theoretical interest, seems difficult and unlikely to lead to therapeutic advances. We come then to the hypothesis that the disease may be due to an error in chemical metabolism. Such an error could result in faulty electrical behaviour and cybernetic function of the brain, leading in turn to psychological and social disturbances.

A chemical hypothesis can be subdivided into three main possibilities.

(*a*) The excessive or *de novo* production of a toxic metabolite causing illness by the disruption of intermediary metabolism (cf. phenylketonuria).

(*b*) The relative or complete absence of a necessary metabolite (cf. diabetes).

(*c*) The lack of balance between a pair of complementary systems.

These three possibilities must be subdivided into conditions in which a fault occurs in the brain and is limited to it and those in which the whole body is involved. These faults could be either genetic or acquired as a result of exhaustion of the mechanisms underlying stress, and negative emotions such as guilt or feelings of inferiority, or to a combination of both.

One is faced with looking for a metabolic fault. What should one look for? Literally millions are possible, which should be investigated? There are in fact only two choices. One can be guided by a strong hypothesis (which will be specific, based on known facts, able to explain these facts and will be testable) or a weak hypothesis which will not be able to explain known facts, hard to test; in short a shot in the dark.

The history of science indicates that one should only resort to a weak hypothesis in desperation when no strong one is available. Indeed, the only function of a weak hypothesis is to gather facts for developing a strong hypothesis. For instance, an example of this procedure would be to measure all manner of physiological variables in schizophrenia (i.e., blood cholesterol, iron, cobalt, vital capacity, steroid hormones, etc.) in the hope of finding deviations from normal which would suggest an hypothesis. A less extreme example would be to re-examine those numerous tests said to be positive in schizophrenia and to find correlations between them. Although this might be valuable as a preliminary, it is clearly inefficient to do so while strong hypotheses exist and until they have been refuted decisively by experiment.

Our New Approach adapts Koch's postulates to a metabolic illness. We have asked the following questions:

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1. "What chemicals can produce a clinical state resembling schizophrenia?" We then noted a number of substances which could do this.

2. "Which of these chemicals resemble more or less closely known human metabolites?" We then noted the relationship between mescalin and adrenaline. This led at once to an initially strong hypothesis that the metabolism of adrenaline or a relative such as serotonin is at fault in schizophrenia. The strong hypothesis must then be subjected to the usual tests to see whether it accounts for known facts and allows one to predict new ones accurately.

At the moment, only the serotonin, the adrenaline oxidation product hypotheses and the acetylcholine hypothesis can be considered strong, and they may be reducible to a common hypothesis.

Table V shows the known aberrant facts about schizophrenia in 1954 when two of these hypotheses were first made public and the facts which have since been gained; showing the predictive success of each.

TABLE V

	Known Facts	Does Model Account for this	How
1.	Genetic factors	Yes	Abnormal enzymes (e.g. adrenochrome reductase).
2.	Stress factors	Yes	Increase in adrenaline, therefore of adrenochrome.
3.	Stress amelioration therapeutic	Yes	Decreased production of adrenochrome.
4.	Self perpetuating	Yes	See equations. Adrenochrome inhibits choline esterase.
5.	Negative association allergic illness and increased resistance histamine	Yes	Adrenochrome antihistaminic.
6.	Negative association asthma and conversion one into other	Yes	Assume lack of adrenaline in asthma. Adrenochrome would be low.
7.	Negative association diabetes mellitus	Yes	Adrenochrome strong anti-insulinase.
8.	Increased pigmentation	Yes	Adrenochrome precursor of melanin pigments.
9.	Response to ET, Niacin, ascorbic acid	Yes	Decreased production and increased destruction of adrenochrome.
10.	Choline esterase inhibitors contra-indicated	Yes	See equations.
11.	Sympathomimetic amines contra-indicated	Yes	See equations.
12.	Different indoles in urine	Yes	See equations.
13.	Positive association growth disturbances	Yes	As above.
14.	Positive association with tuberculosis	Yes	Adrenochrome antimitotic for fibroblasts.
15.	Increased resistance thyroid	Yes	Adrenochrome is anti-thyroid.

We therefore urge with Bain that the resources available for the biological aspects of psychiatric research should be directed in the main to studying the metabolism, physiology, and pathogenesis of adrenaline, serotonin and of enzymes such as ceruloplasmin and adrenaline oxidase, as well as searching for new psychotomimetic agents chemically allied to known human metabolites. For there is no reason why the group of schizophrenias should not develop from sev-

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eral different metabolic failures all resulting in different psychotomimetic agents.

These are not academic considerations, for we know of research on both sides of the Atlantic in which the elementary mistake of following a weak hypthesis or none at all is being made. This is a sheer waste of time, talent and money which has been done far too often in the past to bear repetition.

2. *A Model of Schizophrenia*

We do not seek a perfect model because this would imply that we know all about the illness being modelled, so that we would not be considering a model but an experimentally induced illness—a very different matter. We only require a model which will account reasonably well for the known facts, better than previous ones. It must also be testable.

Our model combines three sorts of variables in a useful relationship. These are:

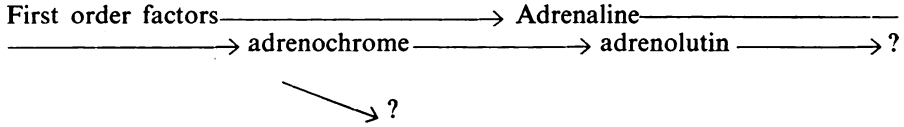
1. Aetiological variables, which working alone or in concert, start physiological and psychological changes.

2. Internal mechanisms which respond to these first order variables.

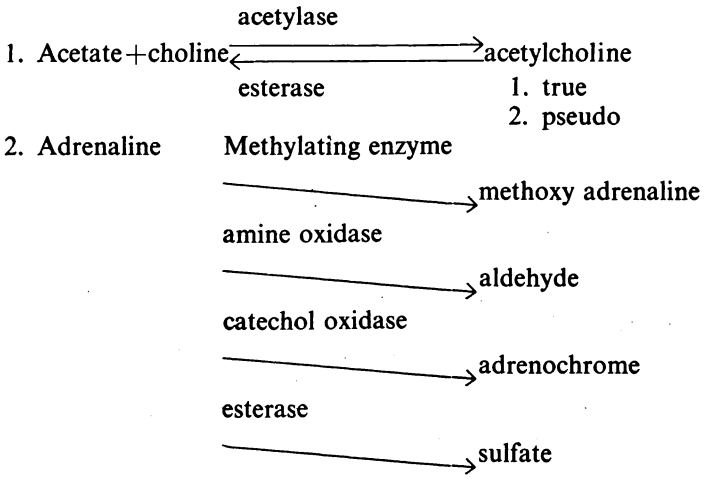
3. Clinical syndromes developing from first and second order variables.

Unless we differentiate between these three sets of variables chaos ensues. They are rarely differentiated in psychiatric writings.

Our model postulates the following: first order variables include genetic and social factors, physique and temperament, personality and life experiences, tensions and stresses. Some combination of these (and it may differ not only in each case of schizophrenia but in each attack of the illness in the same person) triggers physiological changes which increase the production of adrenochrome, adrenolutin and their derivatives.



Second order variables are concerned with the metabolism of acetylcholine and adrenaline leading to high concentrations of either adrenochrome or adrenolutin. This is a complicated system of which we have only an outline —but it may be sketched in provisionally like this:



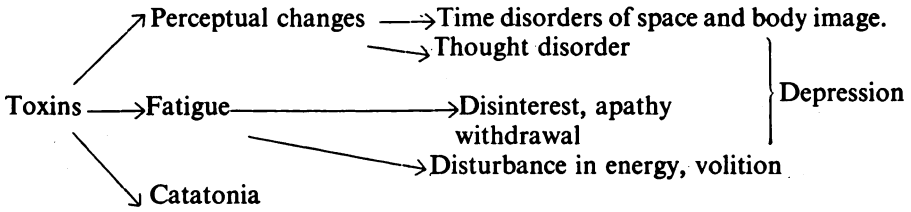
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3. Adrenochrome reductase → leuko-adrenochrome

hydrogenase → adrenolutin

There are at least two factors in our model, increased acetylcholine and increased amounts of indoles or allied catechol, quinone or methylated amines which otherwise resemble adrenaline. It is probably modified by other variables. Pseudo-choline esterase seems to play some special part in psychic activity for it is blocked preferentially by that most potent hallucinogen LSD-25. Substances which block choline esterase alone produce psychological changes only when administered in such large amounts that other changes may mask this, such as DFP, etc. With LSD-25 both conditions are met for adrenochrome levels are increased. BOL-148, which blocks choline-esterase but does not increase levels (see Table IV) is not psychotomimetic.

Third order variables result from these previous changes. It may be that some clinical and psychological changes are affected by two main sorts of disturbances, (*a*) Sensory—changes in perception and (*b*) Motor—usually marked fatigue and inertia but sometimes great energy and excitement due, of course, in each case to the toxins of the disease. This may be illustrated:



In our opinion the very disorganizing effect of changes in perception, especially those connected with changes in perception of the self and levels of reality has received far too little attention. The schizophrenic person with an impaired sense of self and reality must surely find social adjustment increasingly difficult. Once the web of mutual expectations and obligations which hold us in social contact with our fellows is disrupted, isolation results. As communication between the sick person and his group becomes more tenuous, a greater or lesser degree of alienation occurs, so that communication may never again be re-established. Alienation may lead to a solitary life outside a mental hospital or to expulsion and incarceration. The outcome depends not only on the sex, age, temperament, physique and intelligence of the sick person, but also on the customs, tolerance and sophistication of the community. Thought disorder requires much exploration—but it is not easy to imagine that "normal thinking" would persist when perception of time has been greatly changed—let alone the many other perceptual modes.

The three sets of variables inter-react. For instance, perceptual changes may make a parent look strange or hostile, which will increase stress variables aggravating in turn those of the second and third order. It is a balanced system

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where alteration in one set of variables results in a shift in the whole. We believe this model accounts for schizophrenia better than other ones. To illustrate this we have listed data about schizophrenics generally agreed to by psychiatrists who consider that these patients are suffering from an illness and not simply from a faulty reaction formation.

3. *The Way Ahead*

Perhaps this is the place to state unequivocally that we do not claim that our hypothetical M substance is identical with either adrenochrome or adrenolutin. They are only two out of many possible immediate derivatives of compounds lying between tyrosine and leuko-adrenochrome. What we do claim is that they are the first (and indeed at present the only) candidates for M substance which can be obtained as pure stable chemicals and for which there is evidence that they are both psychotomimetic and can occur in the human body. A full study of adrenochrome and adrenolutin both in and out of the body may lead us to even more promising candidates.

Taubmann (1937), Abood (1958), Sherwood (1957) and our own observations suggest that a variety of chrome indoles and amines exist which require the most careful study. Adrenochrome and adrenolutin are the only two so far which our tests suggest are present in the body, but this does not of course mean that they are necessarily the only ones to be found. We should not dogmatize as to whether substances can or cannot exist in the body simply because we cannot make them in the test tube, for this may reflect more on our chemical ineptitude than on any inherent difficulty of synthesis *in vivo*. The last fifty years have shown repeatedly that a substance may be important even though hard to synthesize and to assay. Our evidence suggests that many so-called "inactive" substances may have to be reconsidered. One can reasonably ask, "Inactive in what context?" A very powerful pressor substance may be a very sluggish psychotomimetic and vice versa. In the present state of knowledge no derivative of adrenaline should be acquitted of activity—a verdict of not proven will encourage frequent revision of status as tests for different sorts of activity are discovered. It is misleading to judge activity only in terms of a particular quality, such as its effect on leech muscle, without a proviso that there are other sorts of activity.

To make full use of the discoveries now being made another set of prejudices, which have in recent years acquired much unwarranted respectability, must be discarded. This is the notion that the effects of mescaline, LSD-25, adrenochrome, etc. more closely resemble toxic confusional rather than schizophrenic illnesses. Attempts to differentiate between a toxic confusional (delirious) and schizophrenic condition on a clear-cut "either/or" basis suggests a greater precision than is yet possible. Pretensions of this sort, for all their superficial attraction, are unscientific. What one finds is a continuum with clouding of consciousness and confusion at one end and disturbances in thinking and mood at the other, with changes in perception sometimes present and sometimes absent. In such a continuum over-lap is likely and this is what is found.

Schizophrenia and the effects of mescaline or LSD-25 can be compared in terms of similarity or difference, depending upon the requirements of the observer. We have found that similarity has been useful, but it is surely time to jettison the misleading, meaningless, though frequently repeated statements that the effects of LSD-25, mescaline, adrenochrome, etc., are "only toxic

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states". Louis Lewin (1931), the father of psychopharmacology, long ago emphasized that the mescaline experience did not resemble a delirium. Less exact observers than he, claiming an undeserved authority, have greatly added to the difficulties of those who work with these substances by confusing the issue. The work now being done makes it essential that we have a deep knowledge of these schizophrenic-like experiences. As we have noted elsewhere there is no prospect that the clinical illness, schizophrenia, will ever be reproduced experimentally, because, in our view at least, an ethical experimenter would not be able to duplicate the necessary psychosocial conditions.

While our main interest lies with this great illness whose nature we have been exploring, we are aware that the discovery of a new group of active metabolites of adrenaline may have repercussions reaching beyond schizophrenia and indeed outside psychiatry. Fascinating though these are, we shall not discuss them here.

Conclusion

Only modest effort is now required to test our hypothesis. Adrenochrome can be made and measured both *in vivo* and *in vitro*. Adrenolutin can be made but cannot yet be measured accurately. The enzymes which convert adrenaline to adrenochrome are known and we know something about the way by which adrenochrome becomes adrenolutin and leuko-adrenochrome. These substances have been or are being tested by a variety of routes in both animals and humans. Radioactive techniques should help in exploring the metabolism of these adrenaline derivatives. Once we understand their metabolism better it may be possible to prevent their formation, to neutralize their effects if they are formed or to hasten their destruction in the body. In this way we may combat a great disease and extend our knowledge of body and mind. We hope that our model of schizophrenia will be used, tested and finally, when it has been replaced by a better, discarded. Like any other scientific hypothesis, it is a step cut in the melting ice of history to let us climb a little higher. It is not a niche for an idol.

Summary

The authors discuss the last five years work of the Saskatchewan group and develop their hypothesis relating adrenaline metabolites to schizophrenia. They also discuss work done in other centres. They indicate some of the difficulties encountered not only in synthesizing adrenochrome and adrenolutin but also in working experimentally with them in human subjects. The successful synthesis of pure stable adrenochrome and adrenolutin has made chemical assay possible. Using their adrenochrome assay, they have found differences between adrenochrome metabolism in normals and schizophrenics. While these require exploration the authors believe that their hypothesis is strong enough to warrant attention or to see whether others can confirm their findings. While adrenochrome and adrenolutin are at present the only metabolites of adrenaline which can be obtained as pure stable compounds and have psychotomimetic properties, there is suggestive evidence that others will be found.

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