

SCHIZOPHRENIA : A NEW APPROACH. II. RESULT OF
A YEAR'S RESEARCH.*

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ABOUT one year ago, with the encouragement of the Editor-in-Chief, a short paper appeared in this Journal entitled "Schizophrenia; A New Approach" (18). In this paper it was noted that mescaline and adrenaline have a similar biochemical structure. It was suggested that one of the aetiological agents in schizophrenia might be a substance or substances lying between these two; with the psychological properties of mescaline but effective in concentrations nearer those of adrenaline. Dr. Harley Mason elaborated this suggestion from the biochemical standpoint. For convenience these hypothetical substances were called, collectively, M substance. If M substance occurred in the body, it would account for the group of illnesses usually referred to as schizophrenia better than any hypothesis so far advanced. It has been the good fortune of the co-authors of that first paper (J. R. S. and H. O.) to be able to join forces with the third author of this paper (A. H.) to test the hypothesis. It is with the efforts of the last year that this paper is concerned.

A proposition such as this sounds simple enough to test when sketched on paper, but once it is tackled in the laboratory and the ward, many difficulties soon appear. Money must be obtained, technical help sought, workers from other disciplines must be persuaded to give their support. When all this has been achieved, and it is no small achievement, one has not even started. First of all one must decide where to start. In the range of substances which lie between mescaline and adrenaline there are many hundreds perhaps thousands of compounds. Some of these have been made and are well known to pharmacologists, but many have found no place in medicine and are hidden away in obscure corners of the literature, or having no effect on a particular experimental animal have never been recorded in print. To make or obtain such a large number of compounds would be costly and laborious, but this work and expense

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would be but a tithe of the effort required to test them. For, since animals are unable to talk and so inform us of their experiences, testing must always be done on human volunteers.

So, a year ago, although we had received the keenest support from the Director of Psychiatric Services of the Provincial Department of Public Health, Regina, and although the Federal Department of Health and Welfare in Ottawa had secured a most generous grant for us from Dominion funds, putting us in a position to start work, there remained an unanswered question, "Where do we start?"

In order to answer this question an extensive survey of the literature was made in greater detail than had been possible for the first paper. We paid special attention to the chemistry and pharmacology of substances known to produce disturbances in perception, feeling, thought and behaviour without marked changes of consciousness. This survey showed that both Lindeman (13) and de Jong (11) had been aware that a chemical relationship existed between mescaline and adrenalin, but neither of them had linked this with Cannon's conception of stress, nor did they suggest that it might have special importance.

De Jong had, in order it appears to be "objective," made his jumping off place the occurrence of catatonia in small mammals and discovered that if large doses are given an almost unlimited number of substances can cause catatonia. He paid little attention to whether the catatonia was produced by large or small doses, or whether the substances themselves were likely to occur in the animal body. His findings were, therefore, unlikely to be of much assistance to those engaged upon a research into schizophrenia which is remarkable for being accompanied by few clearly demonstrable biochemical, anatomical or electrophysiological changes even when the psychological disturbances are most disastrous.

We, therefore, limited our enquiry to substances which could produce psychological disturbances similar to those found in schizophrenia without causing clouding of consciousness, confusion, or gross physiological disturbances.

Hallucinogens.

As a working hypothesis we supposed that M substance was chemically closely related to adrenalin. This enabled us to narrow the search from hundreds of potential M substances to those lying on a continuum between mescaline and adrenalin. However, it was possible that the similarity in chemical structure between mescaline and adrenaline was purely due to chance. In order to test this inference we searched the literature to determine whether other compounds were able to produce psychological disturbances similar to mescaline and had a similar chemical structure.

When the literature is examined to catalogue these hallucinatory substances, which for convenience we have called the hallucinogens,* one is struck by their

* One must always offer some excuse for coining a long new word, but there is really no other satisfactory one. It is not a good word but seems to us less obscure than eideticum or phantasticum and begs the question less than "schizogen" or "schizophrenogen." As Klüver has observed when we take these remarkable compounds we enter a world beyond language, so it is hardly surprising that they may be difficult to name.

small number. Those that will produce their effects without being accompanied by other disturbing symptoms can easily be counted on the fingers of two hands and those whose chemical structure is known on the fingers of one hand.

We have so far obtained some information on five compounds which may be called the hallucinogens: mescaline, lysergic acid diethylamide, harmine, ibogaine and hashish. The active hallucinogenic principal in hashish has not yet been definitely established. The structure of the other compounds are shown below, with exception of ibogaine which is known to have an indole nucleus and is placed among the indole alkaloids, Mankse and Holmes (14).

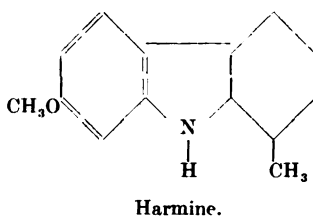
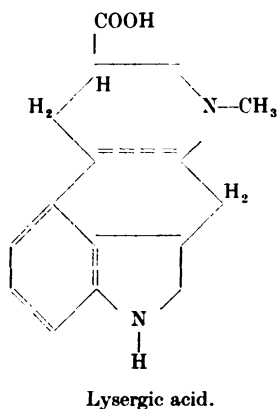
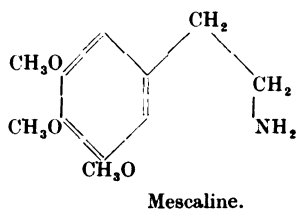


FIG. 1.

These then are a group of compounds that have an indole nucleus in common, assuming that in mescaline the side chain can readily be fused by its amino group to form an indole compound. It might, therefore, be that the indole ring is associated with hallucinogenic properties, provided the compound is able to cross the blood brain barrier. This in itself did not bring us any closer to M substance since these compounds are all plant alkaloids and are unlikely to be present in the body.

Pink Adrenaline.

Shortly after we completed our first paper an observation was made by one of us (J. S.) in curious circumstances. In the hopes of interesting a young and brilliant historian in our work so that he could be persuaded to take mescaline, he was invited to listen to a recording of a recent mescaline experience of H. O.'s. As the recording continued it became evident that the interest and curiosity which it had at first evoked was soon replaced by anxiety and alarm. At last the historian remarked "I have also had such things happen to me." He then explained that for many years he had suffered from asthma, and that when he had a severe attack he would become "an adrenaline addict." He had experienced eidetic and hypnagogic imagery since childhood and had found that these large doses of adrenaline increased this imagery to an alarming extent and when his eyes were open "things looked different."

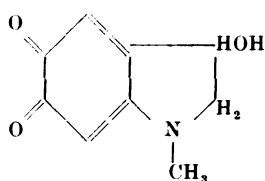
This valuable piece of information combined with a careful scrutiny of adrenaline and its near neighbours suggested that if adrenaline could be deprived of its pressor qualities it might itself be a hallucinogen. A search was then started among people taking adrenaline medicinally to see if they had similar experiences. We have discovered several. A young woman, asthmatic since she was seven, was controlled only by large doses of adrenaline. At the height of her adrenaline consumption she would have visual hallucinations of faces floating across the ceiling. These she related to the adrenaline injections and so did not endow them with any affect. Another woman with urticaria became frankly schizophrenic shortly after receiving an injection of adrenaline to control her allergic condition. The experience was of short duration. Another volunteer, who had the previous day taken lysergic acid diethylamide, was discussing his subjective impressions. He then volunteered that as a boy he had controlled his asthma by means of adrenaline sprays. Often after these sprays he had been aware of subjective changes very similar to this lysergic acid experience. Finally a young medical student reported that after receiving adrenaline to control his asthma he lost much of his ability to empathize; for instance, when driving, he is normally sensitive to the presence of children on the road who might be harmed. After adrenaline injection there was a tendency to allow the children to shift for themselves. Lindemann (13) showed that adrenaline injections markedly aggravated the symptoms of half the schizophrenic patients he studied.

At this point we were lucky enough to obtain another clue from Dr. Asquith, anaesthetist at the Regina Central Hospital, who told one of us that when he was in England during the late war he had been forced, owing to shortage of supplies, to use adrenaline solution which was somewhat deteriorated. Anaesthetists discovered that, if much larger doses were injected than usual, pressor effects similar to those of the fresh solution could usually be obtained. This was thought to be satisfactory until it was noticed that there were more unfavourable "reactions" than with the fresh solution. It appears that some of these reactions were psychological disturbances, sometimes of an alarming sort. No special study of these psychological upsets were made because they were transient and it was considered necessary to avoid them rather than to

investigate them. However, Asquith's observation drew our attention to "pink adrenaline."

At our first meeting in Saskatoon with our colleagues in the research, Professors Hutcheon, MacArthur and Woodford, we raised the question of "pink adrenaline" and put forward a suggestion about its composition. Hutcheon pointed out that "pink adrenaline" certainly contained among other things adrenochrome. In the exciting ten minute discussion which followed after Hutcheon drew the spatial formula of adrenochrome, it was shown that this substance was related chemically to every hallucinogen whose chemical composition has been determined.

The structure of adrenochrome is :



It is evident that we had stumbled upon a compound which has an indole nucleus in common with the hallucinogens, which is readily derived from adrenaline in the body, and which can be fitted into a logical scheme relating to stress. Under stress the quantity of adrenalin in the body will increase and this might be turned into adrenochrome in the schizophrenic individual.

Hutcheon agreed to synthesize and determine the toxicity of adrenochrome without delay. All our studies have been made with this synthetic adrenochrome.

It should be noted that adrenochrome, which is very unstable, is not the only substance which would be present in a decomposing solution of adrenaline. Such a solution could contain numerous degradation products of noradrenaline and adrenaline. This is the uncertain mixture that was given to patients who had been anaesthetized and possibly injected with morphine and atropine derivatives. Unfortunately, no study was made of these reactions so we can only speculate about the numerous possibilities.

Adrenochrome.

This substance was discovered in 1937 by Green and Richter (10) who found that it played a role as an hydrogen carrier in concentrations that fall within the physiological range. It was found in skeletal muscle in a concentration of about 1×10^{-7} moles. There is still some doubt whether adrenochrome is present in the body. Beyer (4) completely ignores adrenochrome. However, Bacq (2) states "adrenochrome and its derivatives are certainly the most interesting oxidized derivatives of adrenaline. It is an error to consider adrenochrome as an inactive substance because it has completely lost its classical sympathomimetic action." Martin (15) states that adrenochrome is pharmacologically inactive but it is biochemically active.

There are three important bits of evidence for the presence of adrenochrome

in the body : (1) Adrenochrome and its oxime (adrenoxyl) form excellent haemostatic substances and have been used therapeutically as vitamin P factors. They increase capillary resistance as well. When adrenaline is injected into a rabbit haemostatic activity appears after four minutes, is maximal after seven minutes and lasts for hours. Adrenochrome injection produces maximum haemostatic activity after three minutes. This is then evidence that the oxidized product of adrenaline may be the hemostatic agent, not adrenaline itself. (2) Adrenochrome being a quinone possesses many properties of the quinones. It oxidises sulfhydryl groups of glutathione, proteins and enzymes and thus is able to inhibit the activity of many enzymes of the glycolytic cycle, Meyerhoff and Randall (17) and the enzymes of the tricarboxylic acid cycle, Woodford (20). It has thus been found that adrenochrome inhibits the mitotic rate of growing cells probably because it interferes with the glycolytic cycle, Lettre (12). Bullough (6) found that, when mice were stressed by overcrowding, the adrenal medulla increased in size by 80 per cent. while the cortex increased 30 per cent. The epidermal mitotic rate fell 60 per cent. They also reported that *in vitro* adrenaline was not an antimitotic agent but that *in vivo* it was, whereas adrenochrome was antimitotic both *in vitro* and *in vivo*. They concluded that the antimitotic factor in the stressed mice was adrenochrome. (3) Martin, Ichniowski, Wisnasky and Ansbacher (16) found that para-amino-benzoic acid inhibited the action of tyrosinase on adrenaline and this vitamin should, therefore, increase the sympathetic effect of adrenaline by blocking its conversion to adrenochrome. When administered to dogs it did increase their blood pressure and caused mild hyperglycaemia. This provides evidence that phenolases are active in the *in vivo* destruction of adrenaline.

There are at least five important ways, Bacq (2), in which the body detoxifies the rather large quantities of adrenaline that are produced by the adrenal medulla and the other sympathetic ganglia. These are :

- (1) by excretion unchanged in the urine ;
- (2) by storage of active adrenaline within the cells ;
- (3) by deamination of the side chain to form oxidizable aldehydes ;
- (4) by esterification of the phenolic hydroxyls ;
- (5) by quinone formation to adrenochrome and its derivatives.

The deamination is catalysed by the enzyme amine oxidase ; the esterification is catalysed by the enzyme sulfoesterase ; and the quinone formation is catalyzed by the enzyme phenolase. Of the three main detoxification mechanisms amine oxidase forms compounds with no autonomic properties and which are easily metabolized. Sulfoesterase forms inactive adrenaline esters and these are so excreted in the urine. Phenolase forms adrenochrome which has no pressor properties but does have other important effects. If therefore one blocks either amine oxidase or sulfoesterase the adrenaline may be diverted into adrenochrome.

Substances that block amine oxidase should, therefore, divert adrenaline into adrenochrome formation. Amine oxidase is present chiefly in the liver, intestine and central nervous system and converts adrenaline into 3, 4-di-hydroxyphenylhydroxyacetaldehyde. Burn (7) believes that amine oxidase plays a role in the sympathetic nervous system comparable to acetylcholine esterase

in the parasympathetic system. The enzyme has been found around the sympathetic nerve endings in blood-vessels, the nictitating membrane and the iris of the cat. It destroys noradrenalin more quickly than adrenaline. Blaschko (5) made the interesting observation that compounds having the structure $R-C-CH_2-NH-CH_3$ were inhibitors of amine oxidase. These findings have been supported by Beyer (3) who reported that phenylpropylamines having the amino groups on the terminal carbon were oxidized by amine oxidase, but that, if the hydroxyl groups were present on the ring, the compounds was oxidized by phenolase. If the benzene ring contained no hydroxyl and, if the amino group were on the carbon adjacent to the terminal carbon, neither enzyme could oxidise it. The following compounds contain the grouping found to inhibit amino oxidase; cocaine, ephedrine, indole, indoleacetic acid, phenylisopropylamine, desoxyephedrine, pervitin, benzedrine, oxidized derivatives of adrenaline (adrenochrome), caffeine, nicotine, methedrine, and lysergic acid.

Electroencephalographic and other Studies of Adrenochrome.

Woodford's (20) studies have shown that when adrenochrome gets into the cerebral cells it inhibits markedly intermediary metabolism of carbohydrates. Eade and Hutcheon's (8) studies on the lowering of body temperature by adrenochrome at the same time as body metabolism is increased, indicates that adrenochrome lowers body temperature by some central effect. This is suggestive evidence that adrenochrome can cross the blood brain barrier in contrast to adrenaline which is not able to do so. To test this possibility further intravenous adrenochrome was given to a series of volunteers (normals and patients) and E.E.G. records were taken on some. In epileptics with definite cerebral dysrhythmias the adrenochrome markedly increased the generalized arrhythmia within half an hour. The focal activity became more prominent. In people with a normal E.E.G. and a clinical history of epilepsy the adrenochrome clearly brought out the epileptic activity within half an hour better than metrazol does. In one schizophrenic subject the E.E.G. showed much dysrhythmia after adrenochrome whereas it was essentially normal before. A typical record before and after adrenochrome is shown below, Szatmari (19). This is further evidence that adrenochrome can rapidly cross the blood brain barrier and interfere with the oxidative processes of the cerebral cells. Further experiments are being made in animals with radioactive adrenochrome in order more definitely to localize the site of action of the adrenochrome.

We are now using adrenochrome as a routine in establishing the diagnosis of epilepsy since it so clearly brings out the epileptic activity. We believe that this is the first time a substance thought to be present in the body has been shown to effect the E.E.G. so markedly. The implications regarding epilepsy are being explored by our research unit.

Effect of Adrenochrome on Cerebral Respiration.

It has been shown that adrenochrome inhibits hexokinase (17) under anaerobic conditions. Naturally this would inhibit the entire oxidative system starting with glucose. Woodford (20) in confirmation reported that adreno-

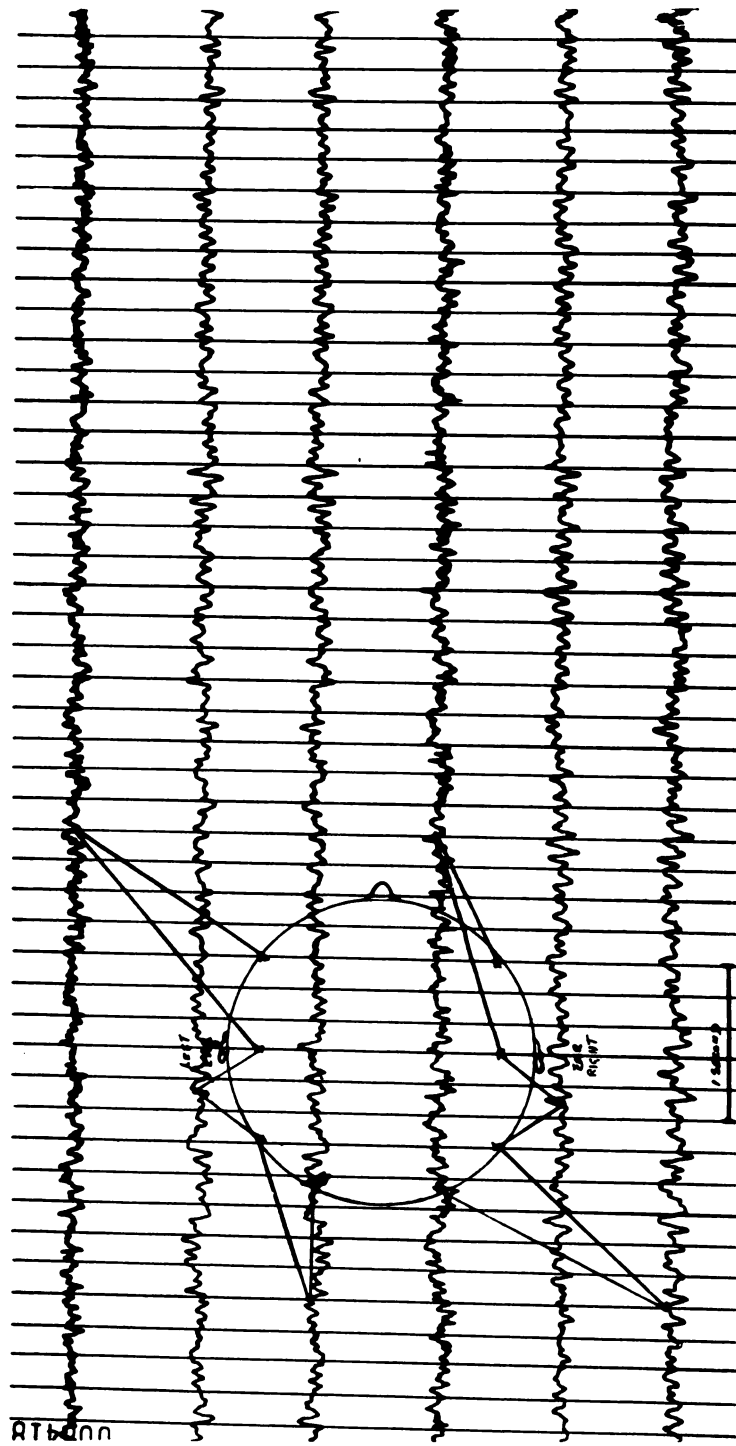


FIG. 2.—(a) Epileptic subject interseizure pattern.

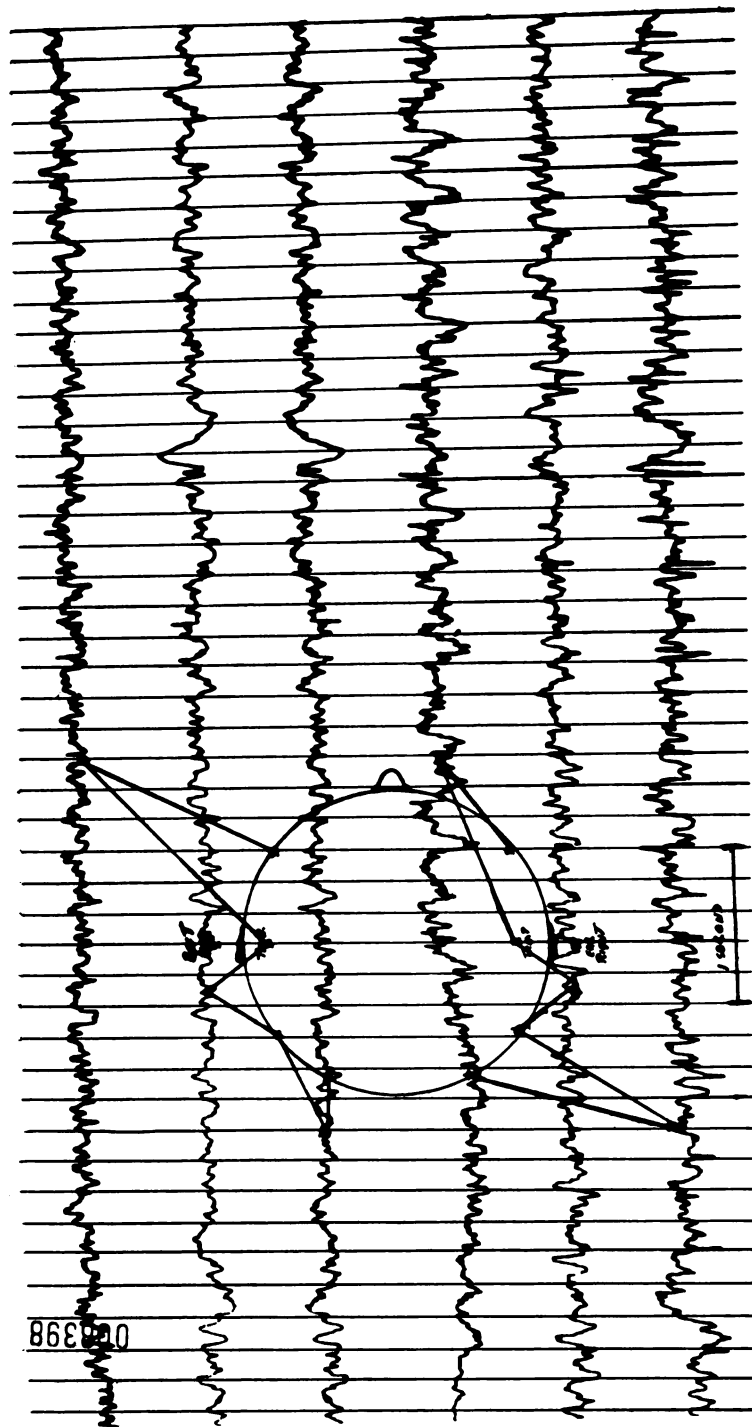


FIG. 2.—(b) Same E. E. G. run 45 minutes after 10 mg. of adrenochrome (intravenous).

chrome inhibited oxidation by brain tissue immediately upon addition to the system under aerobic conditions. Woodford (20) found that adrenochrome, in contrast to mescaline which requires a two to three hour preliminary incubation period with the brain tissue before consistent inhibitory results are obtained, shows inhibition immediately. Since the aerobic oxidation of both glucose and pyruvate is inhibited by adrenochrome, he interprets this as meaning that, in addition to hexokinase inhibition, an enzyme occurring below the pyruvate level is also blocked.

Some Pharmacological Experiments with Adrenochrome.

Eade and Hutcheon (8) found that the LD₅₀ of adrenochrome to be 137 mgm. per kg. Signs of intoxication included progressive paralysis of the hind limbs, dyspnoea, apathy and exophthalmia. They further found that adrenochrome has a hypothermic action in normal and adrenalectomized rats.

Some Psychological Effects of Adrenochrome.

Once the toxicity of adrenochrome had been established in animals it was possible to begin trials in humans. It was uncertain how such an unstable substance should be given or what sort of dose would prove to have any psychological properties. On 9.x.52 two of us (A. H. and H. O.) therefore decided to start on ourselves using very small doses to begin with. Unfortunately, we later discovered that there was some doubt about the quantity of adrenochrome used in these first experiments because it was weighed out in a new and unfamiliar balance.

The first subject (A. H.) received what we supposed was 1 mgm. in 1 c.c. of water subcutaneously. This makes a fine port-wine coloured liquid. The injection was accompanied by a sharp and persistent pain at the site of injection. There were no recognizable psychological changes. Blood pressure and pulse readings taken every five minutes for half an hour showed no change.

The second subject (H. O.) was given what we believed was 0.5 mgm. Again there were no pressor effects but there were marked psychological changes (see below).

Further experiments on our two wives and one of us (A. H.) using 1 mgm. subcutaneously produced some minor results, but by this time it seemed that our adrenochrome, which is very unstable, was beginning to deteriorate. On 16.x.52 5 mgm. of this deteriorating solution was given to H. O. and produced a response which was unpleasantly prolonged.

Since the subcutaneous injections were so painful, the first intravenous injection was given to a volunteer, Mr. C. R. Jillings, M.A., clinical psychologist. It was believed that adrenochrome given by this route would be much less painful. 1.0 mgm. of adrenochrome was, therefore, diluted with two 3 c.c. of sterile physiological saline and injected into the left antecubital vein. Almost immediately after the injection Jillings experienced a very severe pain which travelled up his left arm to the praecordium. This lasted about 10 minutes and was accompanied by pallor and sweating. There were no obvious psychological effects apart from alarm and dismay in the experimenters. It was later dis-

covered that, if the adrenochrome solution is mixed with blood from the patient's vein, pain can usually be completely avoided.

Later A. H. and his wife both took 10 mgm. doses intravenously and had marked changes particularly in affect and behaviour. A. H. became overactive, showed poor judgment and lack of insight. R. H., his wife, became deeply depressed for four days and endured a condition which was indistinguishable from an endogenous depression. This unpleasant experience was aggravated by lack of insight, for she was unable to relate her depression to the injection of adrenochrome, although her change of mood came on immediately after it. An acute piece of observation by Dr. Roland Fischer, Ph.D. (9), suggests that this prolonged effect of adrenochrome was probably due to an attack of infectious hepatitis some years ago. It would therefore, be prudent to enquire about previous liver disease before injecting adrenochrome or other toxic substances into an experimental subject.

To those who are familiar with mescal and lysergic acid we would emphasize that judging from the little experience which we have, it does seem that adrenochrome is more insidious than these two hallucinogens, its effects last longer and possibly in consequence of this its administration is accompanied by a loss of insight. Since this may have serious results experimenters should guard their subjects very carefully.

Summary of an Account of an Adrenochrome Trial 9.x.52, 20-30 hours approx.
(Condensed from notes made at the time by the subject (H. O.).)

After the purple red liquid was injected into my right forearm I had a good deal of pain. I did not expect that we would get any results from a preliminary trial and so was not, as far as I can judge, in a state of heightened expectancy. The fact that my blood pressure did not rise suggests that I was not unduly tense. After about 10 minutes, while I was lying on a couch looking up at the ceiling, I found that it had changed colour. It seemed that the lighting had become brighter. I asked Abe and Neil if they had noticed anything, but they had not. I looked across the room and it seemed to have changed in some not easily definable way. I wondered if I could have suggested these things to myself. I closed my eyes and a brightly coloured pattern of dots appeared. The colours were not as brilliant as those which I have seen under mescal, but were of the same type. The patterns of dots gradually resolved themselves into fish-like shapes. I felt that I was at the bottom of the sea or in an aquarium among a shoal of brilliant fishes. At one moment I concluded that I was a sea anemone in this pool. Abe and Neil kept pestering me to tell them what was happening, which annoyed me. They brought me a Van Gogh self portrait to look at. I have never seen a picture so plastic and alive. Van Gogh gazed at me from the paper, crop headed, with hurt, mad eyes and seemed to be three dimensional. I felt that I could stroke the cloth of his coat and that he might turn around in his frame. Neil showed me the Rorschach cards. Their texture, their bas relief appearance, and the strange and amusing shapes which I had never before seen in the cards were extraordinary.

My experiences in the laboratory were, on the whole, pleasant but when I

left I found the corridors outside sinister and unfriendly. I wondered what the cracks in the floor meant and why there were so many of them. Once we got out of doors the hospital buildings, which I know well, seemed sharp and unfamiliar. As we drove through the streets the houses appeared to have some special meaning, but I couldn't tell what it was. In one window I saw a lamp burning and I was astonished by its grace and brilliance. I drew my friends' attention to it but they were unimpressed.

We reached Abe's home where I felt cut off from people but not unhappy. I knew that I should be discussing the experience with Abe and his wife but could not be bothered to do so. I felt no special interest in our experiment and had no satisfaction at our success, although I told myself that it was very important. Before I got to sleep I noticed that the coloured visions returned when I shut my eyes. (Normally I have hypnagogic visions after several minutes in a darkened room when I am tired). I slept well.

Next morning, although I had only slept a few hours, life seemed good. Colours were bright and my appetite keen. I was completely aware of the possibilities arising from the experiment. Colour had extra meaning for me. Voices, typewriting, any sound was very clear. With those whom I felt did not appreciate the importance of the new discovery I could have easily become irritable, but I was able to control myself.

H. O.'s Second Adrenochrome Experience 16. x. 53 (p. m.).

I had 5 mgm. of adrenochrome this time because we thought that it was probably deteriorating.

I saw only a few visual patterns with my eyes closed. I had the feeling that there was something wonderful waiting to be seen but somehow I couldn't see it. However, in the outside world everything seemed sharper and the Van Gogh was three dimensional. I began to feel that I was losing touch with everything. My sister telephoned and, although I am usually glad to hear her voice, I couldn't feel any warmth or happiness. I watched a group of patients dancing and, although I enjoy watching dancing with the envious interest of one who is clumsy on his feet, I didn't have a flicker of feeling.

As we drove back to Abe's house a pedestrian walked across the road in front of us. I thought we might run him down, and watched with detached curiosity. I had no concern for the victim. We did not knock him down.

I began to wonder whether I was a person any more and to think that I might be a plant or a stone. As my feeling for these inanimate objects increased my feeling for and my interest in humans diminished. I felt indifferent towards humans and had to curb myself from making unpleasant personal remarks about them. I had no inclination to say more or less than I observed. If I was asked if I liked a picture I said what I felt and disregarded the owner's feeling.

I did not wish to talk and found it most comfortable to gaze at the floor or a lamp. Time seemed to be of no importance. I slept well that night and awoke feeling lively, but although I had to attend a meeting that morning, I did not hurry myself. Eventually I had to be more or less dragged out of the

house by Abe. I had to get my car from a garage where it was being repaired. There was some trouble about finding it in the garage when at last I was seated in the driver's seat I realized that I couldn't drive it through traffic, although quite able to do so usually. I did not, however, feel anxious or distressed by this but persuaded the garage proprietor to drive me to my destination. I would, I believe, have normally found this a humiliating situation. I did not feel humiliated.

I attended the scientific meeting, and during it I wrote this note: "Dear Abe, this damn stuff is still working. The odd thing is that stress brings it on, after about 15 minutes. I have this 'glass wall other side of the barrier' feeling. It is fluctuant, almost intangible, but I know it is there. It wasn't there three quarters of an hour ago; the stress was the minor one of getting the car. I have a feeling that I don't know anyone here; absurd but unpleasant. Also some slight ideas of reference arising from my sensation of oddness. I have just begun to wonder if my hands are writing this, crazy of course."

I fluctuated for the rest of the day. While being driven home by my psychologist colleague, Mr. B. Stefaniuk, I discovered that I could not relate distance and time. I would see a vehicle far away on the long, straight prairie roads, but would be uncertain whether we might not be about to collide with it. We had coffee at a wayside halt and here I became disturbed by the covert glances of a sinister looking man. I could not be sure whether he was "really" doing this or not. I went out to look at two wrecked cars which had been brought in to a nearby garage. I became deeply preoccupied with them and the fate of their occupants. I could only tear myself away from them with an effort. I seemed in some way to be involved in them.

Later in the day when I reached home the telephone rang. I took no notice of it and allowed it to ring itself out. Normally, no matter how tired I am, I respond to it.

By the morning of 19.x.52 I felt that I was my usual self again.

Subject's Comment.

I shall make no attempt to elaborate or discuss these two experiences. I am satisfied that they represent a model psychosis, but each reader must decide for himself on the evidence of what I have written and what my colleagues report.

Observations by A. H. and N. A. on Subject H. O.'s Reaction to Adrenochrome.

Within 15 to 25 minutes of receiving the adrenochrome injection H. O. was preoccupied with the distasteful colour of the laboratory. He had never before made any comment concerning this. After he had described some of his experiences to us we showed him a reproduction of a Van Gogh painting which he observed very carefully for a long time. It was difficult to divert his attention toward some Rorschach cards we wished him to see. He stated they were not nearly as interesting. But when he did consent to examine these cards he refused to change cards until ordered to do so. Continual persuasion was needed to get a response. For this reason no complete evaluation

of the protocol was obtained. However, in response to upper centre D section of card No. 10 he gave the response "these are shrimps, no they are statesmen—they are shrimp statesmen." This tendency toward contamination or the process of loosely combining two associations is not typical of H. O. who normally tends toward high F plus per cent. On the other hand, in word association tests under normal conditions, H. O. does give above average distant responses but is able to report the path of the associative process with no difficulty.

The change in H. O., marked by strong preoccupation with inanimate objects, by a marked refusal to communicate with us, and by strong resistance to our requests, was in striking contrast with H. O.'s normal social behaviour.

On the occasion of H. O.'s second trial the most noticeable objective change was his withdrawal from people. After the laboratory session we drove to the home of A. H. H. O. entered, found a chair where he sat for approximately one hour intently examining the rug. He did not greet the group of people who were at the house nor enter into the discussion.

H. O. was anxious and fearful on retiring and once was found wandering about. In the morning he was easily distracted. He required two hours to dress.

Briefly, the changes noted were preoccupation with inanimate objects, negativism, loosening of the associative process, anxiety and distractibility.

DISCUSSION.

Adrenochrome is the first substance thought to occur in the body which has been shown to be a hallucinogen. Until it was discovered these peculiar properties had only been found in compounds derived from plants, whether from the peyotl (mescaline), or from an African bean (ibogaine), or from a jungle vine (harmine), or from rye rust (lysergic acid), or from the historic Indian hemp (hashish), or from that mysterious fungus *amanita pantherina**, which has tempted so few investigators, and whose active principle is completely unknown. The exotic nature of the hallucinogens catalogued here has made it possible for the sceptic to deny that anything like them could occur in the body, a rash assumption when we know that the body is capable of prodigious feats of chemical synthesis. It is now more difficult to assert that adrenochrome, or something like it, could not accumulate under certain circumstances, and produce devastating psychological disturbances long before any consistent physiological changes could be observed.

It is still a far cry from this to proving that over production of adrenochrome, or something like it, occurs in schizophrenia. However, we have shown that it could be adrenochrome, an immediate derivative of adrenaline.

* Since this paper was written Mr. Aldous Huxley has given us an account of the preparation of *amanita pantherina* which may explain why it has not commended itself to western experimenters. The active principle is excreted in the urine of those who have ingested it. The hospitable Siberian chews the fungus himself and then offers his most favoured guest a brimming bumper of his urine. The hallucinogenic substance remains potent after four to five passages through the human body so that when one has enjoyed it one passes it on to someone else. Amongst the Siberians, less honoured guests receive the hallucinogen after it has been used by several others. It only remains now to carry out this experiment with schizophrenic urine.

At this point somebody usually says "how can you explain such a complicated illness manifesting itself in so many ways, by such a simple mechanism?"

Those who put this question are often surprised to find that we have also thought about this. If one agrees that M substance could exist then there is no reason why it should not produce a wide variety of clinical pictures.

We have listed ten of the variables involved and there are probably more :

- (1) The cultural setting.
- (2) The personality of the patient.
- (3) The age of onset.
- (4) The rate of production of M substance.
- (5) The quantity of M substance produced.
- (6) The exact compound or compounds produced (small changes in chemical structure causes great differences in their physiological and psychological effects ; *e.g.*, adrenaline, noradrenaline, adrenochrome, amphetamine, mescaline).
- (7) Specific localization of cerebral enzymes inhibited by M substance.
- (8) The capacity of the body for storing M substance. (It is believed that some adrenochrome is stored in the red cells of the blood and other tissue cells (2).)
- (9) The capacity of the body for detoxicating or destroying M substance.
- (10) The success which the sick person has in dealing with the psychological disturbances produced by M substance. (This very important variable is partly determined by culture. A person, who has a frame of reference which allows him to deal with astonishing experiences, is less likely to disintegrate under the stress of a psychotic disturbance than one who has not.)

It would be possible to elaborate this but at this time it is not relevant.

Only when M substance has been isolated and identified can we begin to understand the mechanisms which produce schizophrenia. Once we understand these mechanisms it may be possible to design a rational treatment based upon exact knowledge, and not, as at present, upon guesswork.

Although we have answered our original question, in doing so we have posed many new questions.

There is the immediate question whether adrenochrome itself plays any part in schizophrenia. This in itself will be hard to answer because we have to search for a fairly unstable compound in a concentration of about one part in five million.

Then where exactly does adrenochrome inhibit cerebral metabolism? What is the meaning of the E.E.G. change which we have observed? What can we learn from the strange psychological changes in mood, perception, thinking and behaviour? And each of these questions, in itself, is the forerunner of a whole series of other questions. At present we cannot answer any of them, but perhaps as Archibald MacLeish pointed out :

" We know all the answers, the answers,
It is the questions we do not know."

The importance of a hypothesis may lie more in the questions which it allows us to ask than in the answers which we receive.

SUMMARY.

Using a hypothesis first published in this journal last year the authors and their colleagues of the Saskatchewan Schizophrenia Research Group have shown that adrenochrome, a derivative of adrenaline, has psychological properties similar to those of mescaline and lysergic acid. This is the first time that a substance which probably occurs in the human body has been found to be active in this way. Adrenochrome has also been shown to produce E.E.G. changes in normal and epileptic people and to inhibit the aerobic and anaerobic respiration of brain tissue in the Warburg apparatus. Future work in this field is discussed. Those who wish to work with adrenochrome are warned of certain dangers.

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APPENDIX.

For those who Intend to Work with Adrenochrome.

If we are to learn more about schizophrenia, experiments with volunteers are essential, but these must be done with proper care. The toxicity of any sample of adrenochrome must, of course, be determined on animals, using the usual methods. Since it is a very unstable substance only freshly prepared solutions should be used. The solution should be mixed with the subject's own blood before intravenous injection; failure to do this results in great pain. We do not at present know why this should be.

It seems to us that adrenochrome's most dangerous properties are psychological ones. Subjects who have been given mescaline or lysergic acid cling to the essential experimental nature of their experiences, and derive considerable help by reassuring themselves that they will soon be over it. Those who have had adrenochrome appear to be liable to lose insight quickly and become unable to relate their experiences to the injection which they have received. It may be that the insidious nature of adrenochrome's action erodes insight, or perhaps it has some specific property which the others do not possess. Whatever the cause this loss of insight requires special care. Until we know more of this new model psychosis (to use Fischer's excellent term) produced by adrenochrome, it would be prudent to assume that it will be effective for at least 24 hours and to supervise the subject for that period of time. It is possible, though not certain, that large doses of niacin (1 gr. by mouth or 100 mgm. intravenously) may counteract the effect of adrenochrome.

In selecting volunteers we suggest that, until more is known about adrenochrome, those with a bad family background, who have history of liver disease or psychotic episodes, or whose Rorschach responses are suspicious should for

the moment be excluded. Close supervision for 24 hours should include an absolute refusal to allow the subject to drive a car. We have some evidence that the capacity to relate time and distance may be subtly disturbed by adrenochrome. This could be disastrous.

We do not wish to appear alarmist, but believe that we should make other workers in this field aware of some of the troubles that we have encountered. It seems to us that we have a special responsibility to those who are prepared to trust us with the temporary custody of their minds and bodies to further man's knowledge of himself.

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