THE EFFECT OF ADRENOCHROME AND ADRENOLUTIN ON THE BEHAVIOR OF ANIMALS AND THE PSYCHOLOGY OF MAN

By A. Hoffer

Psychiatric Services Branch, Department of Public Health, and Department of Psychiatry, University of Saskatchewan, Saskatoon, Saskatchewan

I. Introduction

Experimental psychiatry has been handicapped because the diseases of man most characteristically psychiatric cannot be reproduced in animals. The inner experience of the mentally ill patient

as transmitted to another person distinguishes the practice of psychiatry from the other medical specialties.

Research psychiatrists, lacking experimental animals have been forced to use human models. Man has never lacked chemical substances growing all about him which have allowed him to enter strange states of mind. But for thousands of years, these were sought for purposes other than to reproduce models of the natural psychiatric diseases of man (Osmond, 1958). Despite repeated hints and direct suggestions, the use of psychotomimetic chemicals has developed slowly. Lewin (1931), de Jong (1945, 1955, 1956), Kluver (1928), Stockings (1940), Ellis (1898), and Mitchell (1896) had shown quite clearly how the ingestion of chemicals or plant extracts produced unnatural or unusual states. The similarities between these new states of mind and schizophrenia seemed quite remarkable to these workers.

There has been notable resistance by many psychiatrists to using these chemicals for producing models of certain diseases. Perhaps this was due to the current preoccupation with psychological theories of etiology—especially of the so-called functional psychoses. Probably it was due to the natural reluctance of psychiatrists to produce a model of a disease which was so mysterious and baffling as schizophrenia. Most likely it was due to the primitive type of thinking which characterized psychiatry several decades ago so that differences stuck out much more clearly than similarities (see Bartlett, 1958). It seemed quite unlikely that experimentally produced psychiatric states, model psychoses, psychotomimetic experiences, or psychedelic experiences could advance our knowledge of the great functional psychoses. By the end of the first half of our century, Bleuler (1956) was secure in his belief that the experimental psychoses produced by lysergic acid diethylamide (which he had been one of the first to study) had nothing to offer to the student of schizophrenia.

The discovery of Stoll and Hofmann (1943) of the hallucinatory action of *d*-lysergic acid diethylamide (LSD) quickened interest in the use of models. *d*-Lysergic acid amide, a compound very similar to LSD, is the active fraction of ololiuqui (Hofmann, 1960; Hofmann and Tscherter, 1960; Osmond, 1955b). More recently, Hofmann *et al.* (1958) added psilocybine, the active principle of the Mexican

hallucinogenic mushroom, to the growing list of psychotomimetic chemicals. Mescaline will produce schizophrenic-like states in man, but between 300 and 500 mg is needed. This quantity is easily detected in body fluids. For this reason, it was thought unlikely that natural animal substances with a similar order of activity could be present and escape detection. But when 100 μg of LSD was shown to be equally active, it became easier to believe that similar quantities of active natural substances could be present. After studying mescaline, Osmond and Smythies (1952) suggested that there might be present in the schizophrenic patient substances with the psychological properties of mescaline and with a structure similar to that of epinephrine, since the reactions of normal volunteers to mescaline resembled schizophrenia.

In the course of our work on schizophrenia, Dr. Humphry Osmond and I also became interested in epinephrine derivatives which were indoles, as is LSD, rather than sympathomimetic amines like epinephrine or mescaline. In 1952, we presented our epinephrine metabolite hypothesis (adrenochrome) to the Dementia Praecox Committee, Scottish Rite Masons, New York; and in 1954, our first formal report on adrenochrome appeared (Hoffer *et al.*, 1954).

The purest preparations of adrenochrome available between 1954 and 1957 were bright red or black powders which were very unstable even when stored under optimal conditions at low temperature and devoid of oxygen. Adrenochrome in aqueous solution deteriorated in minutes and formed insoluble brown-black melanins. Heacock *et al.* (1958) removed traces of silver ion from the preparations of adrenochrome and formed stable crystals which could be stored at room temperature. Later Heacock and Mahon (1958) synthesized stable adrenolutin and other reduction compounds of adrenochrome (Heacock and Scott, 1959; Heacock and Laidlaw, 1958). A comprehensive chemical review of adrenochrome was made by Heacock (1959a). These chemical studies have greatly facilitated the study of the psychological properties of adrenochrome and its derivatives.

The adrenochrome hypothesis of schizophrenia has been discussed in some detail by Hoffer *et al.* (1954). Hoffer (1957a, b, c, d, 1958a, b, c, 1959a, b), Hoffer and Callbeck (1960), Hoffer and

Osmond (1955, 1959, 1960), Osmond (1955a, 1957), and Osmond and Hoffer (1958, 1959), and therefore will not be discussed further in this review.

The behavioral changes produced in animals are interesting from two points of view. Little is known about the action in the body of animals of the adrenochrome degradation products of epinephrine. The fact that adrenochrome produces marked changes is interesting because it enlarges our understanding of the function of epinephrine and its derivatives. Furthermore, clear and definitive evidence that adrenochrome changes animal behavior would provide corroborative support for its psychological activity in man. This would then make an adrenochrome hypothesis of schizophrenia stronger. On the other hand, if these compounds were inert when given to animals, it would make the adrenochrome hypothesis weak. Thus, these studies, while not crucial in themselves to the adrenochrome hypothesis, can strengthen or weaken it. Crucial evidence, of course, would be the demonstration that adrenochrome or adrenolutin is present in the human body and in greater quantities in patients ill with schizophrenia. The evidence for the presence of adrenochrome has been adequately reviewed elsewhere in some detail. As I have previously stated (Hoffer, 1960), in an *in vivo* system containing substrate, i.e. epinephrine and its degradative enzymes, it is inherently probable that adrenochrome may occur. The following investigators have suggested or implied as a result of their own researches that adrenochrome was a metabolite of epinephrine: Bacq (1949), Blaschko and Schlossman (1940), Braines *et al.* (1959), Bullough (1952, 1955), Fellman (1958), Foley and Baxter (1958), Greig and Gibbons (1957), Grewal (1952), Iordanis and Kuchino (1959), Kisch (1947), Korzoff and Kuchino (1959), Kuchino (1959), Langemann and Koelle (1958), Meirowsky (1940), Roston (1960), Takahashi and Akabane (1960). These studies are substantial but more impressive than conclusive. The following investigators have concluded that adrenochrome is present, have provided evidence for the presence in living beings of oxidized derivatives of epinephrine, i.e., adrenochrome and/or adrenolutin, or have shown how adrenochrome can be transformed *in vivo* into adrenolution or 5,6-dihydroxy-*N*-methylindole: Altschule (1960), Bell *et al.* (1959), Fischer and Landtsheer (1950), Fischer and Lecomte (1951), Gershenovich *et al.* (1955), Golden-

berg *et al.* (1950), Green *et al.* (1956), Hoffer and Kenyon (1957), Hoffer and Payza (1958), Jantz (1956), Kaufman and Koch (1959a, b), Lecomte and Fischer (1951), Maslova (1959), Noval *et al.* (1959a), Osinskaya (1957), Payza and Mahon (1959), Pickworth (1952), Rigdon (1940), Senoh and Witkop (1959), Sohler *et al.* (1961), Sulkowitch and Altschule (1959), Sulkowitch *et al.* (1957), Utevsky and Osinskaya (1957), Veech *et al.* (1960).

The kind of scheme suggested by Gerard (1960) will be followed in describing the activity of adrenochrome and some of its derived compounds. The effect of adrenochrome upon simple systems will be considered first, then upon the more complex systems, upon simple animals, and finally, upon the most complex animal, man. The animals that have been given adrenochrome range from spiders, fish, and pigeons to the mammals—rats, cats, dogs, monkeys, and man. The sections on cats and on man will include much original data.

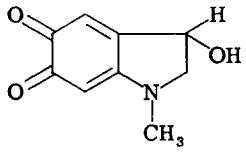
Activity in animals has been reported so frequently and consistently that it can no longer be doubted that adrenochrome is indeed active when given to animals. Activity in man has received less corroboration but all the published accounts (as against references to unpublished works) are corroborative. It would be remarkable for a compound so active in lower animals and mammals to be inactive in man.

II. Biochemistry of Adrenochrome

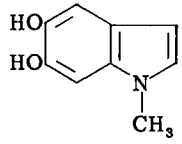
The structural formulas of adrenochrome and some of its derivatives are shown in Fig. 1.

The instability of adrenochrome, adrenolutin, and 5,6-dihydroxy-*N*-methylindole in aqueous solution leads to great difficulties in working with these substances. Biochemists, unaware of this difficulty, have consistently failed to demonstrate the presence of adrenochrome in body fluids. Since adrenochrome is decomposed by many solvents used in paper chromatography, e.g., propanol-ammonia-water and *n*-butanol-acetic acid-water, this is not surprising. Distilled water and 2% acetic acid are suitable solvents (Heacock, 1959b).

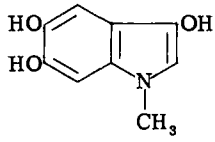
Reducing agents discharge the red color of adrenochrome solutions and cause an internal rearrangement of the molecule, forming quantities of 5,6-dihydroxy-*N*-methylindole and adrenolutin. The



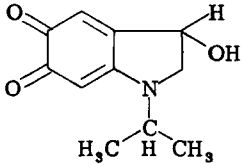
Adrenochrome



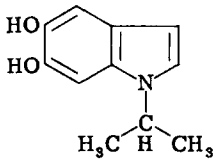
5,6-Dihydroxy-*N*-methylindole



Adrenolutin



N-Isopropylnor-adrenochrome



5,6-Dihydroxy-*N*-isopropylindole

FIG. 1. Formula of some adrenochrome derivatives.

relative amount of each depends upon the nature of the reducing agent and the conditions of the reaction.

Blood plasma, which is adjusted to optimal conditions of pH, ionic strength, catalysts, etc., quickly oxidizes epinephrine to adrenochrome. Some of the adrenochrome is rapidly transformed into adrenolutin (Leach and Heath, 1956; Hoffer and Kenyon, 1957). Ascorbic acid and glutathione, two natural constituents of blood, influence this reaction. Apparently adrenolutin and 5,6-dihydroxy-*N*-methylindole are relatively stable in plasma (Melander, 1957).

The same reactions occur *in vivo* when adrenochrome is injected. Fischer and Lecomte (1951) found that most of the injected adrenochrome was converted to adrenolutin in rabbits, dogs, and cats. Fischer and de Landtsheer (1950) found adrenochrome disappeared rapidly from blood and was converted by liver and kidney into

adrenolutin. Jantz (1956) reported that blood serum obtained from alcoholic patients changed adrenochrome into adrenolutin more quickly than did normal blood serum. Hoffer and Osmond (1960) reported that adrenochrome injected into patients was rapidly removed from the plasma. In normal people the original control levels were reached after 30 minutes, but in schizophrenic patients, the plasma adrenochrome levels were still much above the preinjection value at 30 minutes. This also occurred in normal volunteers pretreated with LSD (but not when pretreated with bromo-LSD). Recently Sohler *et al.* (1961) found from radioactive tracer studies that adrenochrome injected in rats is partially converted to adrenolutin and 5,6-dihydroxy-*N*-methylindole. It is not surprising that these changes can occur, since blood does contain substances, such as hemoglobin, which catalyze these reactions.

The natural enzymes of blood which oxidize epinephrine to adrenochrome are not well characterized. Leach *et al.* (1956) believed that ceruloplasmin was the enzyme which oxidized epinephrine. Epinephrine is readily autoxidized in pure aqueous solution to adrenochrome, but it is not likely that autoxidation plays a major role in blood. Blood contains substantial quantities of proteins, and reducing substances which inhibit autoxidation. This fact and the fact that the oxidation of epinephrine in plasma is greatest under optimal conditions, support the suggestion the oxidation is enzymatic. Ceruloplasmin oxidizes epinephrine but not as quickly as epinephrine oxidase. The properties of ceruloplasmin, the enzyme which oxidizes *p*-phenylene diamine (PPD), are quite different from the enzyme which oxidizes epinephrine. Ceruloplasmin or PPD oxidase is strongly inhibited by amine oxidase inhibitors (iproniazid, semicarbazide, hydroquinone) and by epinephrine and adrenolutin, whereas epinephrine oxidase is activated by semicarbazide and iproniazid. Epinephrine, which inhibits PPD oxidase, is the substrate for epinephrine oxidase. A comparison of these two enzymes is given in Table I.

The effect of adrenochrome on many mammalian enzyme systems was summarized by Hoffer and Osmond (1960). Briefly, adrenochrome inhibits glycolysis in brain tissue under aerobic and anaerobic conditions, probably by inhibiting hexokinase and/or uncoupling oxidative phosphorylation (Cohen and Hochstein, 1960; Karzoff and Kuchino, 1959; Meyerhof and Randall, 1948; Park *et al.*,

TABLE I
COMPARISON OF PROPERTIES OF CERULOPLASMIN (*p*-PHENYLENE DIAMINE OXIDASE) AND EPINEPHRINE OXIDASE[a]

Variable	PPD oxidase	Epinephrine oxidase
Substrate	*p*-Phenylene diamine Epinephrine	Epinephrine
Activators	Copper Sulfanilamide Hemoglobin	Copper Semicarbazide Iproniazid
Inhibitors	EDTA Semicarbazide Epinephrine Adrenolutin Iproniazid	Cysteine Ascorbic acid Tris buffer
Optimum pH	5.0	6.8
Heat	Inactivates	Inactivates
Optimum salt concentration	0.04 *M*	0.05 *M*

[a] From Payza and Zaleschuk (1959) and Payza and Hoffer (1959).

1956a, b; Radsma and Golterman, 1954; Randall, 1946; Walaas and Walaas, 1956; Woodford, 1959). Adrenochrome markedly inhibits decarboxylation of glutamic acid in brain tissue (Holtz and Westermann, 1956), oxidizes simple amino acids, and is polymerized to brownish melanin pigments in brain, intestinal mucosa, and skin. It is an antagonist of serotonin (Stern *et al.*, 1956). However, its action is not always inhibitory or toxic. Derouaux and Roskam (1949) found that sympathetic nerves in the rabbit's ear did not fatigue as rapidly in the presence of adrenochrome. On the other hand Marrazzi (1957) and Hart *et al.* (1956) reported adrenochrome inhibited synaptic transmission as did epinephrine.

III. Action of Adrenochrome on Cells

It is not surprising that adrenochrome interferes with the growth and function of intact cells. Substances which inhibit respiratory reactions and glycolysis should be toxic for cells. Thus, Lettré and Albrecht (1941), Lettré (1954), and Frederic (1954) found that

adrenochrome and adrenolutin inhibited mitosis of cells. Bullough (1952, 1955) showed that adrenochrome, both *in vivo* and *in vitro*, inhibited mitosis in mouse epidermis. The effect on chromosomes *in vitro* was confirmed by Gelfant (1960). Schwarzenbach (1957) reported that adrenochrome was a very strong inhibitor of spore germination of some fungi. Hoffer (1954) found that crude adrenochrome acted as a plant hormone for *Avena sativa* (oat) seedlings, i.e., it inhibited the rate of growth of rootlets relative to shoot growth. Plant hormones may be indolic, such as indolylacetic acid.

Geiger (1960) demonstrated that adrenochrome is a very powerful toxin for cerebral neurons in pure culture. A concentration of 0.001 μg/ml (6×10^{-9} moles/liter) induced much more rapid and drastic changes in neurons than did either epinephrine or norepinephrine in the same concentrations. Recently, Dr. Ruth Geiger was good enough to show me a film she had made in which this action of adrenochrome on living neurons was demonstrated. The normal neurons pulsated slowly and rhythmically. When a small quantity of adrenochrome was added to the culture the cells began to pulsate more quickly and vigorously. Each cell appeared to develop contortions or convulsions in slow motion. After some time, the neurons rounded up in a spherical structure. Then the membrane must have ruptured for the cell disappeared leaving a spherical ring of dark fragments and pigmented material. LSD and serotonin also influenced pulsatile behavior but did not kill the cells (Geiger, 1960). Schizophrenic serum was also toxic.

IV. Effect of Adrenochrome on Fish

The effect of adrenochrome on fish behavior has received little study. Abramson (1955) added epinephrine to an aquarium containing Siamese fighting fish. In time, the water turned pink indicating that there had been some oxidation of epinephrine to adrenochrome, but no changes in behavior were observed. In contrast, Abood (1957) added small quantities of pure adrenochrome made from epinephrine by phenolases and did find changes in the behavior of the guppy. These divergent results probably are owing to either a species difference or to the different compositions of the adrenochrome. A deteriorated solution of epinephrine would contain adrenochrome and other degradation products of epinephrine, such as H_2O_2, which might antagonize the action of adrenochrome.

V. Effect of Adrenochrome on Spiders

In 1954, Witt reported that the spider *Zilla x-notata* was very sensitive to adrenochrome. (The adrenochrome had been made by a colleague in Bern.) As little as 200 μg of adrenochrome in fresh or old solution could be biologically identified and differentiated by the effect of web building if it was given less than 10 hours earlier. [Photographs of the adrenochrome effect on webs are shown by Witt (1954, 1958).] The web was substantially disorganized, which is in contrast to the effects of LSD, which made the pattern more precise, and of mescaline, which disorganized it slightly. Adrenoxyl supplied by Labaz, Brussels, was not active. This is not surprising, since adrenoxyl is not hydrolyzed to adrenochrome in the body (Fischer and Lecomte, 1949).

In December 1958, Witt tested adrenochrome and adrenolutin made by Heacock in our laboratory (Witt, 1961). The adrenochrome was given at the same time and in the same quantity as before but to *Araneus diadematus*, which responded like *Zilla x-notata.* Adrenochrome semicarbazone was inactive.

Dr. Witt reported the following action of adrenolutin: "We tested the adrenolutin from you in 10^{-2} and 10^{-3} solution. From 7 spiders which had had the high dose only one built a web the following day. This might indicate that this dose has an effect on building drive. Twelve spiders received the lower dose of adrenolutin equal to the effective adrenochrome dose; 6 of these spiders built the following day but their webs showed no significant changes." On the basis of this small number of experiments, Witt concluded that high doses of adrenolutin inhibited web building but that lower doses were not as active as adrenochrome.

As a matter of interest, the spider web disorganization produced by adrenochrome seems quite specific. LSD and mescaline produce different patterns. However, serum from catatonic patients disorganized the web of *Zilla x-notata* in a way very similar to adrenochrome. This can be seen by examining the pictures of webs after treatment with adrenochrome and schizophrenic serum (Bercel, 1960; Buehler, 1960).

VI. Effect of Adrenochrome on Pigeons

About three years ago, I made a series of observations, assisted by Dr. H. Wojcicki, on the effect of adrenochrome and adrenolutin

on the behavior of some pigeons. These were racing pigeons bred by Dr. Wojcicki, a psychiatrist and a pigeon fancier. Two pairs of birds were used, each weighing about 650 gm. These experiments were conducted over a 4-day period in October 1957 in my office. Each pair was kept in one cage, and the cages were placed side by side on a table.

A. Male Pigeon A

Male pigeon A was a very fine proud bird. He was very solicitous for his mate, female A. He firmly attacked any of the two pigeons B if they were placed in his cage, and he clearly dominated male B. If male A was removed from the cage and kept a few minutes out of sight of his mate, he went through a vigorous and consistent courting behavior when he was returned. When placed on the edge of the cage door, he would quickly hop in and then would vigorously coo and strut around his female for a short time.

At 4:04 PM, male A was injected intraperitoneally with 5 mg of *d*-adrenochrome synthesized by Heacock *et al.* (1958). When returned to the cage, he responded normally to his mate. Five minutes later, there was no change. Eight minutes later, female A was removed and a few minutes later returned to the cage. Male A did not court nor coo. At 10 minutes, male B was placed in the cage. Male A did not attack him as he would have done normally. But 2 minutes later, he did fight and peck at male B. There was thus a delayed reaction to male B but there was no further evidence for any abnormality. Twenty minutes after the injection (4:24), another 10 mg of adrenochrome was injected. One minute later, the bird was listless and his feathers were droopy and bedraggled. Four minutes later, he was passive and disinterested. He allowed H.W. to pull his beak with no protest. Six minutes later, he remained passive and did not court the female when she was returned to the cage after an absence. When male B was placed in the cage, he did not attack him and appeared quite indifferent. Ten minutes later, male A was placed in cage B containing pair B. Normally, he would attack male B and court female B. This time, he did not attack male B and ignored female B for the several minutes he was left in the cage. When at 12 minutes, he was returned to female A, it was noted he was aphonic. His coo was a very weak and tremulous gurgle. Twenty minutes later, he was still able to fly normally but he sat on H.W.'s hand one minute before he flew away.

In general, male A became indifferent to his environment. He was disinterested in females and did not follow his routine courting behavior with his mate which he had always done before the injection.

The next morning male A was found dead. At autopsy, no pathological changes were found in the abdomen. It was apparently death due to adrenochrome [15 mg] and not to mechanical trauma caused by the injection.

B. Female Pigeon A

October 23, 1957, this bird was given 5 mg adrenochrome intraperitoneally at 4:13 PM. There was no observable change in behavior. The next morning,

she was normal. At 10:00 AM she was injected with 10 mg of adrenochrome. Eight minutes later, she was normally combative when a hand was placed in the cage, but there was much less startle reaction to a loud noise. This was the only change observed. Four hours later, she was normal.

October 30 at 9:35 AM, she was given 10 mg of adrenolutin. Fifty minutes later, she was less aggressive and did not fight the hand when she was teased in her cage. Fifteen minutes later, she required a great deal of provocation before she would respond although she appeared alert. At 11:00 AM, she refused completely to fight back. At 11:05, she suddenly flew sharply against the side of her cage toward the adjacent cage B where male B was standing. But when male B was placed in her cage, they ignored each other. Four hours after the injection, female A was normal and aggressively drove out the attacking hand from her cage.

November 1, 1957, she was given 25 mg adrenochrome at 2:05 PM. We wished to find out how much adrenochrome would kill this bird. Three minutes later, her feathers were fluffed and droopy and she vomited. For the next 12 minutes, she continued to retch and vomit and would not fight. Her eyes became glazed. One hour and 15 minutes after injection, she preened herself and began to recover. We estimated that her total reaction to 25 mg adrenochrome was less than her reaction to the 10 mg of adrenolutin.

November 4, she was injected with 30 mg adrenochrome at 1:19 PM. She quickly became very ill as before. She could not fly and when released did not fly but fell down. At 4:00 PM, she was dead. Thus she required twice as much adrenochrome for death as her mate.

C. Male Pigeon B

Pair B were nesting two eggs. The nest was in one corner of the cage and built of grass. This male was dominated by male A but was normally aggressive and fond of female B. He was devoted to her and dutifully did his share of brooding on the eggs. On October 24, male B was given 10 mg adrenochrome at 2:07 PM. Twenty-three minutes later, he vomited and had a tremor during which he stood and rocked back and forth. He blinked his eyes slowly and appeared sleepy. Three minutes later, his fighting behavior was normal but he had a slight tremor of his wing. Forty minutes after injection, his vocal ability was diminished and his voice became feminine, sad, and dull. Male pigeons lose their voices only when moulting. He did not court with enthusiasm and could hardly coo. One hour later, female A was placed in his cage. Normally male B would have driven her out but this time he ignored her. The next morning, he was normal.

Male B was then given 20 mg adrenochrome together with 100 mg ascorbic acid. One hour later, there was a slight and fleeting change; a few minutes later, he was normal. One day later, he was still normal, but 2 days later he was found dead.

D. Female Pigeon B

Female B was brooding two eggs and was very motherly and protective. She fiercely drove off a hand reaching toward the nest. This bird was injected

with 10 mg of adrenolutin. Five minutes later, she stood over her eggs but did not set on them. She then walked away from her eggs. Ten minutes after the injection she retched, then sat beside her eggs and blinked her eyes. Five minutes later, she was sick and her feathers drooped. She no longer retreated from the hand. Twenty minutes after the injection, H.W. placed her on his hand and walked from the office down a long corridor and back. She made no attempt to fly away but clung to his hand. This test we termed the Baruk test because he often demonstrated the effect of schizophrenic bile on pigeons in this way (Baruk, 1957). This pigeon was able to fly when she was released but was apparently not interested in flying. One hour later she had not returned to her nest.

The next day, the bird was studied again. At 9:00 AM she appeared disinterested and did not set on her eggs. By 2:00 PM she was much more alert and responsive. She fought against the hand vigorously and was better groomed. Four days later, she appeared normal. She had again started to set on the dead eggs in the normal way. At 1:57 PM, she was given 20 mg adrenochrome. Three minutes later she was ill, rocked, and once more refused to set her eggs. Four minutes after injection she vomited. One and a half hours later she had apparently recovered. She was now very alert and vicious when the hand was placed near her. She came toward the hand to attack. Late that night she was dead.

E. Discussion

It is not possible to draw firm conclusions from this study on only four birds, but each bird had several injections and the results were definite. A larger series would be required in order to complete this kind of study. The following tentative conclusions may be made: (1) Male pigeons are apparently more susceptible to death from adrenochrome than female pigeons. (2) Adrenochrome in nonlethal doses (10 mg) alters behavior, including courting, protecting the nest, and brooding. (3) Adrenolutin is more effective in altering pigeon behavior than adrenochrome. In one case, catatonia was produced.

Lehrman (1956a, b, 1958, 1959) and Lehrman and Wortis (1960) have examined the factors which influence cyclical breeding behavior in ring doves (*Streptopelia risoria*). This does not normally occur in birds kept in isolation from each other. According to these workers the presence of one bird stimulates the pituitary gland of the other; the pituitary hormones change courting behavior to nest-building, then to incubation. When birds were placed in cages with eggs they would normally begin to nest in 4 to 10 days. When progesterone was injected the birds nested almost immediately. Birds treated with estrogens sat after 1–3 days or after a

period of 11 days. Birds injected with prolactin appeared to be under considerable tension. In birds with no breeding experience (such as feeding squabs) the restlessness was not directed toward any specific response, whereas in birds with previous breeding experience the restlessness (tension) aroused approaches to the young. According to Lehrman, the hormones induce vascularity and tension in the birds' brood patch which thus becomes a source of irritation. This is reduced by setting on the smooth, cool, hard surface of the eggs.

It is possible that adrenochrome and adrenolutin interfered with the cyclical changes in the pigeons by markedly reducing tension. Hoffer and Osmond (1960) reviewed the evidence which suggested that adrenochrome and adrenolutin reduced tension in humans, which they ascribed to an anti-epinephrine action. Therefore, giving adrenochrome and adrenolutin to the pigeon which was brooding eggs might immediately reduce the tension and hence the urge to set. The fact that several days later, when the adrenolutin effect had worn off, the female again began to sit on her eggs supports this conclusion. Presumably the tension induced by the estrogens had by now returned.

VII. Effect of Adrenochrome on Mammals

A. Mice

Not much has been written about the effect of adrenochrome on mice. Laborit *et al.* (1957a, b) found that both adrenochrome and adrenochrome semicarbazide increased the tendency of mice for convulsions. LSD had no effect. Serotonin protected the mice against convulsions. Glutamic acid gave some protection. Eade (1954) found that adrenochrome produced sedation in mice, and before death the sedation quickly passed off and was replaced by progressive spasmodic clonic convulsions beginning in the hind limbs. Walking was uncoordinated. When disturbed, the mice hopped about, often leaping in the air and falling over backward.

B. Rats

1. *Review of Literature*

Eade (1954) gave adrenochrome to some rats in order to measure the lethal dose. Cause of death was respiratory paralysis

preceded by dyspnea, micturition, clonic convulsions, and exophthalmos. Later, Noval *et al.* (1959a) showed that impure adrenochrome could produce a "de Jong type" catatonia in rats. A dose of 10 mg/kg of crystalline adrenochrome in saline injected intravenously caused convulsions and death in half the treated rats in less than 15 minutes. After 8 mg/kg their physical activity was greatly reduced for many hours. On observing some of these rats given adrenochrome, it was noted that for the first few minutes the animals appeared sick but this soon passed. After that, they were disinclined to move about; when placed alongside a cold Bunsen burner, the animals grasped the burner with their forelegs and clung until they sank slowly to the table, doubled up, apparently exhausted, but still clinging. Purer adrenochrome was one fourth as toxic and appeared to be incapable of inducing the clinging behavior (Noval *et al.*, 1959b); this suggested to these investigators that decomposition products of adrenochrome may have been responsible for the behavioral effect.

Vallbo (1957) gave 20 mg/kg of adrenochrome to rats and saw no effect. However, 100 mg/kg of adrenolutin produced marked catatonia. The rear legs were quite relaxed. Neither chlorpromazine, promazine, perphenazine, nor acepromazine protected the rats against adrenolutin, but KABI-HdA8 did protect them completely.

2. *The Effect of Adrenochrome on Conditioned Responses of Albino Rats*

Grof *et al.* (1961), studied the response of Wistar rats to adrenochrome. They weighed about 200 gm, and received 6 and 8 mg/kg. The control group received physiological saline. Two kinds of observations were made: (*a*) a test of general irritability and activity, and (*b*) the effect on conditioned reflexes.

Rats given adrenochrome were significantly different from rats given saline in the orientation-searching experiments. There was a marked decrease in the duration of erect reactions (to 20% of the controls) and a marked increase in periods of immobility (which were doubled). Rats which were of a markedly inhibitive type showed enhanced excitation whereas those with medium or low inhibition became less irritable as the depth of inhibition was greater. The maximum inhibition of activity occurred 7 to 9 minutes after the injection.

For the conditioning experiments, rats were trained in two

groups of 6 animals each. The unconditional impulse was an electric shock applied to the floor. The animal avoided shock by running up a net. The conditioning signal was an optical signal of low intensity.

Each group of rats was trained for seven sessions with 61 trials. In the eighth session, one group received adrenochrome, the other saline. With the adrenochrome group, there was a significant ($P < 0.01$) increase in the latency periods, which were doubled. There was also a decrease of intersignal reactions to one fifth of the control value ($P < 0.01$). These authors concluded that adrenochrome acted as an inhibitor of higher nervous activity in most animals but produced excitation in extremely inhibited animals.

3. *A Study of the Effect of Adrenochrome on Conditioning in Albino Rats*[1]

a. *Effect on Acquisition.* Wistar-strain albino rats (age 3 to 5 months) were used. A Mowrer-type shuttle box was used with a buzzer as the conditioning signal and an electric shock applied to the floor as the unconditioned stimulus. Adrenochrome was synthesized by Heacock. Freshly prepared solutions were injected at a dose of 25 mg/kg. The criterion of learning was 10 consecutive avoidance responses. The median number of trials with saline was 38.5 and with adrenochrome 98.5 ($P < 0.02$) using 12 rats in each group. This experiment was replicated later with new animals. All saline-treated rats performed to criterion in less than 140 trials, whereas 8 out of the 12 rats given adrenochrome had not learned by 140 trials. Using 90 trials as a median with saline, 10 were below, whereas with adrenochrome only 2 were below ($P < 0.01$).

A dose response study was later made with 10 rats in each group, using a randomized block design. The rats learned to criterion with saline and 6.25 mg, 12.5 mg, and 25 mg/kg of adrenochrome in 40, 52, 64, and 80 trials. For this range of dosage, the number of trials required to reach criterion of acquisition of the conditioned avoidance response (CAR) was a linear function of the logarithm of the dose given.

When adrenochrome was given in a very large dose of 80 mg/kg, about one-third of the rats died. The survivors when tested 14 to 34 days later disclosed no residual effect in that they learned as well as

[1] Data of T. Weckowicz (1961).

did rats not receiving adrenochrome. At autopsy, no changes were seen in the central nervous system.

b. *Effect on Performance.* Two groups of 10 animals were used. One group received adrenochrome first and saline 1 week later. The other group received these substances in the reverse order. Before the experiment, the rats were trained to a criterion of 18 out of 20 trials. One hour after the injection, they were tested again and were given 20 trials in 15 minutes. Overall, the rats given adrenochrome made significantly fewer responses ($P < 0.01$), owing to the poor performance of the group receiving adrenochrome first. Adrenochrome had much less effect on the group receiving saline first. The only difference was that animals which received saline first had received more training before being tested under adrenochrome. The difference in performance of the two adrenochrome groups was significant ($0.05 < P < 0.01$). Thus the more training the rats received, the less susceptible were they to adrenochrome. This is a very important observation, for it proves that the effect of adrenochrome was not due to marked physical weakness of the rats. In this experiment, it was also observed that rats given adrenochrome had many fewer anticipatory responses ($P < 0.01$). With 12.5 mg/kg, there was no effect on performance, but acquisition of the CAR was decreased with this low dose.

The ability of rats to jump away was tested by another method. An electric timer was connected to the stimulator which delivered 1.25 ma to the grid of the box. Both were then started and both stopped automatically when the rat escaped. Well-trained rats were used. Ten received adrenochrome, 25 mg/kg, and ten saline; all were tested 1 hour later. The mean speeds of escape were respectively 1.26 and 1.40 seconds. Thus, it is clear that gross motor impairment and/or complete lack of motivation may be excluded as the cause of lack of acquisition of the CAR.

c. *Effect on Extinction.* Twenty rats trained to criterion (18 out of 20 trials) were used. Ten received adrenochrome and 10 saline. Extinction trials were started in blocks of 20 followed by 15 minutes rest in the cage. The criterion was 10 consecutive non-responses to the conditioning stimulus—the buzzer. The score was the number of trials necessary to reach the criterion. For the 10 rats given saline, the following number of trials were required: 10, 172, 12, 210, 10, 39, 70, 130, 50, and 50. For adrenochrome, they were 10,

10, 10, 10, 10, 11, 10, 13, and 20. Chi-square for a median of 115 was 5.00 ($0.05 < P < 0.01$). Adrenochrome significantly accelerated extinction of CAR. In most of the adrenochrome rats, it was extinguished at once, but of the animals given saline 3 rats required more than 100 responses.

d. *Effect on Drive.* When trained rats were used and the intensity of the electric shock was varied, there was a slight trend for saline rats to escape at a lower intensity of current, i.e., at 0.22 vs. 0.25 ma, but the difference was statistically insignificant. However, when untrained rats were used and observed for startle responses (including jumps) the saline threshold was 0.14 and adrenochrome 0.19 ($0.05 < P < 0.01$). The threshold for naive animals was lower than for sophisticated animals. The intensity of current was set at 1.25 ma for one group and 2.50 for the other. Animals with adrenochrome at a higher drive level performed slightly less well. It was concluded that level of drive (or arousal) was not involved in the way adrenochrome affected CAR.

e. *Effect on Bar-Pressing.* The rats were tested in a Skinner box with food and water as the reward. They had to run to one end, press the bar, and return to the other end for their reward. After a constant rate of bar-pressing was obtained, they were injected and tested for 13 minutes. Adrenochrome significantly ($P < 0.01$) reduced the rate of bar-pressing. The difference was greater when the rats were less well-trained, i.e., received adrenochrome first.

f. *Conclusion.* Adrenochrome decreased the acquisition of the conditioned avoidance response and markedly accelerated extinction. The prolongation of acquisition was related in a linear way to the logarithm of the dose. In a Skinner box, the rate of bar-pressing for food or water was markedly reduced.

C. Rabbits

Krupp and Monnier (1960) studied the effect of adrenochrome on 12 rabbits. They observed these animals for changes in behavior, for changes in frequency of respiration and pulse, and for brain electrical activity. They injected 3.5 to 6 mg/kg of adrenochrome by vein. Behavior was influenced slightly. The animals reacted more strongly when stimulated by light or noise. There were slight changes in spontaneous motility of the free animals and a transient but slight decrease in pulse rate.

Vallbo (1957) found that adrenochrome 20 mg/kg produced no change when given intravenously (50 mg per animal); however, adrenolutin at 50 mg per animal (20 mg/kg) produced a stupor lasting 30 to 90 minutes. It may well be that the first *in vivo* demonstration of the conversion of epinephrine into adrenochrome was made by Rigdon (1940) using rabbits. They were shaved 24 hours before the experiment, and epinephrine was injected intradermally. This blanched the skin for several hours. If the surface of the skin was treated with xylol either before or after the injection, the skin became reddish brown in color. This appeared 15 to 30 minutes after the application of xylol. The only reddish brown pigment known to be related to epinephrine is adrenochrome. Several years ago, an injection of adrenochrome subcutaneously in my left arm formed a small brown pigmented area which remained over 3 months. Meirowsky (1940) showed that the production of pigment in human skin is highly increased by adrenochrome. Recently I injected 1 mg of adrenochrome intradermally into shaved rabbit skin. A faint brownish color remained in the skin for many hours. These observations suggest that under certain conditions epinephrine can be converted into adrenochrome by epidermis.

Walaszek (1960) reported that LSD, bufotenin, and *d*-adrenochrome potentiated in rabbits the pressor response which follows the topical application of epinephrine to the brain cortex.

D. Cats

1. *Literature Review*

Schwarz *et al.* (1956b) made the first study of the effect of adrenochrome and adrenolutin on cats. (Their paper should be consulted for more detailed description of the behavioral effects.) Pure adrenochrome (freshly prepared solution, pH 7.7), in doses ranging from 0.125 to 1 mg, was placed in the lateral ventricles, using permanent indwelling canulae. Adrenolutin (also freshly prepared solution, pH 7.6) was similarly injected, using doses of 300–650 μg. "Stupor and catatonia, as described by de Jong, were observed after the administration of adrenochrome and adrenolutin. After an initial gradual reduction in motor activity, the cats would finally sit in odd positions with their eyes wide open for long periods and howl. Although, for various reasons, the term 'waxy flexibility'

cannot be used as it would be in referring to human beings, the cats permitted their limbs to be placed passively in unnatural positions without immediately correcting them, or even resisting such positions. In the presence of a clear sensorium, other bizarre forms of behaviour were noted to follow the injection of adrenochrome and adrenolutin. Frequently, the cats were in a deep trance, with concomitant electroencephalographic changes; but they could always be alerted readily." (This description is from the study of Schwarz *et al.*, 1956b.)

Rice and McColl (1957, 1960), using a similar technique, gave a series of cats 0.6 mg/kg of adrenochrome. This resulted in a higher incidence of sympathetic rather than parasympathetic stimulation. Four minutes following the injection, animals began growling, meowing, and spitting. Eight minutes after injection a severe tonic seizure developed, which became tonic-clonic in nature. Following the convulsions the animals were immobile with flaccid muscles and they appeared semistuporous. It resembled the action of mescaline, rather than LSD. Schwarz *et al.* also observed this. All the cats given adrenochrome showed changes in habits, as did those given mescaline. None of the cats given LSD showed any change in habits. These authors observed that mescaline and adrenochrome appeared to affect predominantly various regions of the hypothalamus, diencephalon, medulla, higher brain stem, and motor cortex.

Vallbo (1957) reported that 100 mg adrenochrome per cat produced little change. However after 50 to 100 mg, intravenous adrenolutin (10–30 mg/kg) produced stupor and diminished interest in surroundings and in food; this lasted 15 to 30 minutes. According to Melander and Mårtens (1958, 1959), pretreatment with taraxein or LSD (15 to 20 μg per cat intravenously) markedly potentiated the effect and 2 to 3 mg/kg intravenously of adrenolutin produced drowsiness and muscle relaxation. Acetyl-LSD also potentiated adrenolutin but bromo-LSD did not.

Sherwood (1957) gave one cat 0.5 mg of crystalline adrenochrome. During the next 3 hours, the cat showed inappropriate behavior. It walked into its bowl of milk and did not lick its paws. It let itself be placed in unusual positions without protest. It preferred to lie down and was disinterested in grooming. But throughout, it remained affectionate toward Dr. Sherwood and it seemed fully aware of its surroundings. Čapek *et al.* (1960), as summarized

by Grof *et al.* (1961), also gave cats 1 to 2 mg of adrenochrome intraventricularly. The adrenochrome (Light's) produced changes similar to those described by Schwarz *et al.*, whereas their own adrenochrome produced changes similar to those described for mescaline.

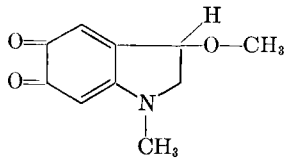
2. *A Comparison of the Effect of Some Indoles on Cat Behavior*

Dr. J. D. McColl, of Frank Horner and Company, Montreal, placed indwelling permanent canula into the lateral ventricles of some cats using the procedure pioneered by Feldberg and Sherwood (1954), described by Rice and McColl (1960). The cats were delivered by air express from Montreal to Saskatoon and all arrived in good condition.[2] Each cat was housed in its own cage, near each other in a special room where there were no other animals. The first time the cats were used, they were allowed to become familiar with each other since it was planned to work them in pairs in order to study their interaction. After that, the usual procedure was to inject one cat and then release the other so that both were free in the experimental room. Each experiment was a type of field experiment. No conditioning experiments were made at this time although in future work this will be done for a few of the chemical compounds. I was primarily interested in the qualitative effect of these compounds upon cat behavior and not on the quantitative relationship between dose and activity. After the injection, both cats were observed for 2 or more hours.

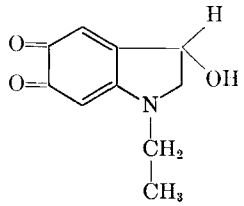
The chemicals were all synthesized by Dr. Heacock and his staff in our biochemical research section and were freshly prepared in saline just before the injection, which was temporarily painful. There was no residual effect of the injection and after 2 or 3 minutes the cats seemed normal. Each compound was given to each of the 2 cats once. Adrenochrome with heparin was given to an additional 2 cats.

In addition to adrenochrome, adrenolutin, 5,6-dihydroxy-*N*-methylindole, and *N*-isopropylnoradrenochrome (see Fig. 1), the following compounds were used:

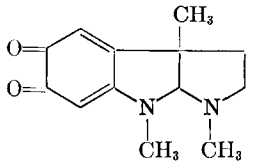
[2] I wish to express to Dr. McColl my gratitude for his helpfulness in this phase of our work. This kind of cooperation compensates for the many frustrations one encounters in the normal course of research.



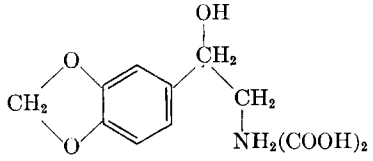
Adrenochrome methyl ether



N-Ethylnoradrenochrome



Rubeserine



3,4-Methylenedioxy-α-aminomethylbenzyl alcohol oxalate

The effects of adrenochrome and its congeners administered intraventricularly in cats are summarized in Tables II and III. These results were obtained from 2 cats; "BB," a medium-sized male cat of nervous excitable disposition, and "Big," a larger male cat, very friendly and affectionate toward observers. In addition, two other cats were the subjects of less extensive experimentation:

"Sandy" was a very affectionate quiet cat, and his reaction to 2 mg adrenochrome was studied alone and with heparin in order to test the limit of the protective action of heparin. August 23, 1960, he was given 2 mg in 0.5 ml saline. In 1 minute, he was quiet and indifferent. In 5 minutes, he walked in a clumsy way with jerky movements. He was restless, yowled several times, then became very unsteady and began to crawl backward. Then he began to circle around himself yowling all the time. His hind legs were not paralyzed but he seemed to have lost control of them. At 9 minutes, he no longer responded to stimuli. At 15 minutes, his respiration was very fast; he panted, yowled, and then urinated. At 60 minutes, he had been yowling and scratching his head for 40 minutes. Ten minutes later, his righting reflex was gone. At 4 hours, he could not walk at all. There was no recovery at 6 hours. Two days later, he was still unable to walk. At 3 days when he was examined, he had a series of convulsions. When he was removed from his cage and placed on the floor, a series of convulsions and convulsive flailings of his front legs were set off. He was friendly to observers but appeared very ill. He also had waxy flexibility. On the fourth day he was still very weak but he had begun to eat. However, on the fifth day he was dead. The brain was removed for examination. Gross

TABLE II

RESPONSE OF CAT "BB" TO ADRENOCHROME AND SOME SIMILAR COMPOUNDS

Compound	Personality reaction		Alertness	Motor activity	Gait	Autonomic changes
	To observer	To other cat				
Saline	Hostile	Hostile	Normal	Normal	Normal	No
Adrenochrome, ½ mg	Less hostile	Indifferent	Much decreased	Much decreased	Awkward, unsteady	No
Heparin, 1 mg	Hostile	Hostile	Normal	Normal	Normal	No
Adrenochrome, ½ mg, and heparin, 1 mg	Hostile	Hostile	Slight decrease	Slight decrease	Normal	No
Adrenochrome methyl ether, 1 mg	Very hostile	Very hostile	Normal	Decreased	Normal	No
5,6-Dihydroxy-*N*-methylindole, 1 mg	Hostile	Hostile	Much increased	Much increased	Normal	No
Rubeserine, 1 mg	Less hostile	Less hostile	Decreased	Much decreased	Normal	No
l-Epinephrine, 1 mg	Hostile	Hostile	Decreased	Much decreased	Weak, unsteady	Retched, vomited
Metanephrine, 1 mg	Hostile	Less hostile	Slight decrease	Slight decrease	Normal	No

TABLE III

RESPONSE OF CAT "BIG" TO ADRENOCHROME AND SOME SIMILAR COMPOUNDS

Compound	Personality reaction		Alertness	Motor activity	Gait	Autonomic changes
	To observer	To other cat				
Saline	Friendly	Indifferent	Normal	Normal	Normal	None
Adrenochrome, ½ mg	Hostile	Indifferent	Much decreased	Much decreased	Weak, incoordination	Licking, retching, vomiting
Heparin, 1 mg			No change from saline			
Adrenochrome, ½ mg, and heparin, 1 mg			No change from normal			
Adrenochrome methyl ether, 1 mg	Friendly	Indifferent	Much decreased	Much decreased	Weak, incoordination	Rapid respiration
5,6-Dihydroxy-*N*-methylindole, 1 mg	Very friendly	Very hostile	Increased	Normal	Normal	None
Rubeserine, 1 mg	Friendly	Indifferent	Normal	Normal	Normal	None
N-Ethylnoradrenochrome, 1 mg	Friendly	Indifferent	Normal	Normal	Slight weakness	None
Isopropylnoradrenochrome, 1 mg			No changes were observed			
Adrenolutin, ½ mg	Hostile	Hostile	Decreased	Decreased	Normal	None
l-Epinephrine, ½ mg	Hostile	Hostile	Normal	Much decreased	Weak, incoordination	Retching, vomiting
Metanephrine, 1 mg	Hostile	Hostile	Normal	Decreased	Incoordination	Normal

examination showed the canula placed inside the lateral ventricle and there were no visible areas of destruction or hemorrhage. The canula had not been displaced. Histological examination by Dr. R. Altschul, Professor of Anatomy, University of Saskatchewan, revealed no evidence of any injury. The cause of death remains unknown.

"Dracula" was a nervous, hostile, and suspicious cat. He never came to the cage door to be released and resisted being removed from the cage. When released into the room, he would immediately leap from the floor back into his cage if the door was left open and would crouch in it. August 25, 1960, he was given 1 mg adrenochrome in 0.5 ml saline. At 17 minutes, he became unsteady. He tried to jump back into his cage but was not able to leave the floor. He was placed on a stool in front of his cage and had only to walk across a small gap. But in doing so, he fell off the stool. At 31 minutes, he could hardly walk. He defecated. At 67 minutes, his hind limbs were still very weak. He was the same at 2 hours. During this experiment, he was able to defend himself well against attack from the other cat. One week later, he was given 1 mg adrenochrome with 1 mg heparin. For the next 2 hours, no change at all was seen. He remained normally active, had no difficulty jumping into his cage and eventually he became mildly affectionate to the observers.

3. *Discussion*

The changes observed in these cats were due to chemical action and not to the increase in cerebrospinal fluid pressure, since injection of saline, of heparin, and of several of the other compounds produced no change. This series of experiments was not extensive enough to determine which chemicals were most active. However, certain findings may stand. As a general rule adrenochrome and the compounds which could be formed from it were more active than the unnatural derivatives. Thus, *5,6-dihydroxy-N-methylindole,* which is formed *in vivo* from adrenochrome (Sohler *et al.,* 1961; Fischer and Lecomte, 1951), produced a condition characterized by increased alertness, increased activity, and increased aggressivity. But this increase in activity, which can be compared to a human hypomanic state, was appropriate and directed. Hostility was directed against the other cat and merely accentuated natural antagonism. The cats remained normally friendly or indifferent to the observers. *Adrenolutin* in one cat decreased alertness and activity, and produced marked weakness and incoordination of the hind limbs. The cat became abnormally hostile to the observer and to the other cat.

Two adrenochrome homologs very similar in structure (*N-isopropylnoradrenochrome* and *N-ethylnoradrenochrome*) produced hardly any change in behavior. The integrity of a single methyl

group on the pentavalent nitrogen seems important since an ethyl or isopropyl group attached here removed activity. It is clear the effect of adrenochrome placed in the brain ventricle is not due to an unspecific effect, whatever that may be. *Adrenochrome methyl ether* seems to resemble adrenochrome in activity more closely than any other compound. This compound, according to Heacock (1959b), will on reduction be changed into a dihydroxyindole, not a trihydroxyindole. It should therefore resemble both adrenochrome and 5,6-dihydroxy-*N*-methylindole. From the changes induced by adrenochrome and 5,6-dihydroxy-*N*-methylindole, it can be assumed adrenochrome will have certain properties (assuming an equivalence in dose response). It would be expected to produce in "Big" an attitude toward the observers which varies between moderate friendliness and neutrality; toward the other cat, neutrality and moderate hostility. Alertness would be normal, and motor activity decreased; weakness and incoordination would be present, and there would be some autonomic changes. These predicted changes are fairly close to what really did happen. If we use a similar extrapolation with "BB," the adrenochrome methyl ether would be expected to produce hostility toward observers and toward the other cat. Alertness and motor activity would be normal. Gait would be altered somewhat and there would be no autonomic changes. This prediction again is not far off from what did happen. In "Big," it produced a marked decrease in motor activity, incoordination, and hind limb weakness. "Big," a friendly cat, became hostile to the observers and to "BB." This corroborates the suggestion that some of the adrenochrome methyl ether is altered to a dihydroxyindole *in vivo*.

Heparin had a clear and marked action in protecting the cats against adrenochrome. This was found in all 3 cats where the combination was used. The reasons for this protection are not clear, but it is possible heparin could bind the adrenochrome and keep it away from certain brain receptors. *Rubeserine* which is somewhat similar in structure to adrenochrome had practically no effect on "Big" but did alter "BB." It is not as strong a acetylcholine esterase poison as is eserine. *Epinephrine* produced marked weakness of the hind limbs, autonomic changes, and increased hostility in the cats. These changes are not unexpected as they reproduce some of the findings of Leimdorfer *et al.* (1947), Leimdorfer and Metzner (1949), and

Leimdorfer (1950). *Metanephrine* was not inert in these experiments. Evarts (1958) and Evarts *et al.* (1958) had concluded that normetanephrine had no central activity in cats and was not active either psychologically or physiologically. Metanephrine decreased alertness in BB and decreased motor activity. Evarts (1958) and more recently Bacq and Renson (1961) found some sympathomimetic activity for this substance. It is possible metanephrine is not inert centrally as is normetanephrine; this question should be examined further. In a parallel way, norepinephrine has little central activity as compared to epinephrine.

One mg of 3,4-methylenedioxy-α-aminomethylbenzyl alcohol oxalate placed on the ventricles of two cats did not produce any behavioral changes. Alles (1959), on the other hand, found that two similar substances, 3,4-methylenedioxy phenethylamine and 3,4-methylenedioxy phenisopropylamine, were psychotomimetic when studied in a few self experiments.

E. Docs

The only record of the effect of adrenochrome on dogs was reported in a series of studies from the Institute of Psychiatry, Academy of Medical Sciences, USSR (1959). They found that adrenochrome produced changes in behavior in dogs. When injected by vein, it alerted the fluorescence characteristics of plasma so that it resembled the fluorescence of natural schizophrenic blood plasma. Braines *et al.* (1959) reported that when normal human or dog serum was irradiated with an excitatory beam of light, it fluoresced. The fluorescent spectrum had two main peaks, one at about 2750 Å and a less intense one at 2440 Å. When schizophrenic serum was examined in an identical manner, there was no peak at 2440 Å. The second maximum is due to the emission of light energy absorbed by the peptide bonds and emitted by tryptophan molecules. When the dog was given adrenochrome by injection, the 2440 Å maximum vanished and the fluorescence curve resembled that found in schizophrenic serum. Schizophrenic serum given to dogs by vein produced a similar alteration in the fluorescence spectrum.

Kuchino (1959) observed that doses of adrenochrome less than 0.1 mg/100 gm body weight did not produce catatonic-like states in dogs but abolished conditioned reflexes. Braines *et al.* (1959) studied the combined effect of fear and adrenochrome on dogs. In

1941, he had shown that mild states of fear insufficient to produce catatonic symptoms intensified the effect of small doses of bulbocapnine (insufficient to produce catatonia) with the production of catatonic symptoms. More recently, he found that when a dose of adrenochrome which was not sufficient by itself to produce catatonic-like symptoms was introduced into an animal in a mild environmental stress it produced catatonic symptoms. Furthermore, adrenochrome even in small doses which do not produce catatonia in dogs affected the conditioned sterotypes, i.e., complexes of conditioned reflexes, although it did not affect individual simple conditioned reflexes. Complex habits were affected by adrenochrome before simple habits.

F. Monkeys

The most extensive investigation of adrenochromes effect on monkey behavior also comes from the Institute of Psychiatry, Academy of Sciences, Moscow. Kuchino (1959) reported, without giving details of his experimental method, that small quantities of adrenochrome (less than 0.1 mg/100 gm) abolished conditioned reflexes. Iordanis and Kuchino (1959) reported their studies of adrenochrome in greater detail. A monkey "Mashka" learned to obtain food by performing a complex sequence of steps; e.g., when a white light flashed, it had to pull a lever, press a button, pull a handle, and press a pedal, in that order. When a red light was flashed the monkey was not reinforced. Adrenochrome in doses of 0.7 to 1.2 mg affected learning habits for 2 to 5 hours. "Mashka" reacted to food and took it from the basket but did not react to the stimuli signifying food. In some experiments there were short sleep-like states after injection of adrenochrome. The adrenochrome does produce changes in conditioned reflexes very similar to 1 mg doses of chlorpromazine and to injections of schizophrenic serum. This did not occur after injection of normal human serum.

Melander and Mårtens (1958, 1959) reported that adrenolutin exerted only slight pharmacodynamic activity when given intravenously to monkeys in the dose range of 20 to 25 mg/kg. After premedication with taraxein or LSD, as little as 2 to 3 mg/kg produced drowsiness and muscular relaxation. Vallbo (1957) found that 25 to 50 mg per animal of adrenochrome produced activity. With adrenolutin, 25 to 100 mg given by vein (10 to 40 mg/kg)

diminished muscle tone, produced catatonia for a brief time, and diminished interest in their surroundings. With one monkey, 25 mg intravenously made him catatonic 15 minutes. He appeared stuporous with eyes closed.

Heath obtained some adrenochrome from Stockholm and injected it into monkeys. No change was observed either in the EEG or in their behavior. Neither was there any change after the injection of adrenolutin. However, Heath *et al.* (1959) found that in one monkey pretreatment with taraxein sensitized the animal to adrenolutin; it died after injection of 100 mg.

It is clear that very large quantities of adrenochrome are required to produce gross changes in behavior. Sensitization with LSD or taraxein decreases the amount required. But when very sensitive and refined behavioral tests are used, only 1 mg of adrenochrome (for a monkey weighing nearly 2 pounds) markedly altered complex learned habits. KABI-HdA8 given to the monkey protected it against 25 mg and later 50 mg of adrenolutin.

VIII. Effect of Adrenochrome on Electrograms

Slocombe (1956) and Slocombe *et al.* (1956) measured the changes produced in spontaneous and evoked electrical potentials in albino rats by serotonin, LSD, epinephrine, norepinephrine, and adrenochrome. All the compounds flattened spontaneous activity at the cortical and subcortical sites. The most effective was serotonin. The rest were effective in decreasing order of activity as listed. The changes were profound with thiopental anesthesia, but there was no change when ether was used. These authors believed the action was nonspecific on lower centers which have cortical and subcortical projections.

Krupp and Monnier (1960) injected adrenochrome into rabbits. There was a change in the EEG right after the injection. The amplitude of the spontaneous activity of the neocortex decreased, and slow wave activity disappeared. Simultaneously there was an increase in synchronicity in the hippocampus and thalamus. There was thus a typical arousal pattern. After intercollicular decerebration, adrenochrome produced neocortical desynchronization with a slight increase in hippocampal synchronicity. After adrenochrome, there was an increase in the arousal reaction to sensory stimulation. The excitability of the hippocampus and its connections to the

neocortex was increased. These authors concluded that LSD, mescaline, and psilocybine altered spontaneous electrical activity in a similar way to adrenochrome. All produced a sharp arousal pattern of activity. LSD caused desynchronization of the subcortex but the other three substances intensified subcortical synchronicity. LSD had no action on the "encéphale isolé" or the "cerveau isolé" but adrenochrome had a slight effect and the other two compounds a marked effect. Both adrenochrome and mescaline activated the hippocampus but did not release spontaneous discharges. LSD released spontaneous discharge and psilocybine decreased hippocampal activity.

Schwarz *et al.* (1956b), using the ventricular cannula technique of Feldberg and Sherwood (1954), found that after the injection of 1 mg adrenochrome the cats were drowsy for 24 hours. The deep EEG showed occipital 4 cycles/sec slow waves with low-voltage spike components spreading to the frontal region and then diffusely over the brain. Painful stimulation caused inconsistent arousal. An arousal pattern appeared when the animal was drinking milk. These authors described the EEG changes as a trance pattern.

Heath (1959) observed no change in the EEG pattern of monkeys. However, one monkey pretreated with taraxein was sensitized to adrenolutin and died after 100 mg. EEG changes then were present.

Hoffer *et al.* (1954) reported that adrenochrome produced pathological changes in the electrogram of some epileptic patients. A detailed report was presented by Szatmari *et al.* (1955). A few volunteers with normal electrograms were given 10 to 25 mg by vein. There was no change in the electrograms. Epileptic patients were given 10, 25, or 50 mg of adrenochrome. Five patients had a high-voltage, diffuses, paroxysmal abnormality with bilateral hypersynchrony and diffuse high-voltage 5/sec activity. Adrenochrome produced a marked increase of the dysrhythmia and an increased sensitivity to hyperventilation. In two cases, the threshold for convulsions was lowered.

Another group of 15 patients had focal activity showing spike, sharp-wave, and irregular delta activity in all cases, and diffuse bilateral slow activity in 10 of them. After adrenochrome, there was an increase of dysrhythmia, an increase in voltage and decrease in frequency, a marked increase in all cases of focal activity during

hyperventilation along with a spread of pathological activity in the opposite homologous cortical area, and in 4 cases a spontaneous increase in irritability of the focus.

Schwarz *et al.* (1956a) measured changes in depth electrogram induced by adrenochrome. Patient 1, a chronic paranoid schizophrenic, on three occasions was given 50 mg, 60 mg, and 75 mg of adrenochrome by vein. There was a moderate increase in bitemporal paroxysmal discharge of 2 to 7 cycles/sec, and increased persistence and amplitude of the focal temporal sharpwave discharge from the depths, in all three instances. Subject 2 was given 50 and 60 mg on two occasions. There was a moderate increase in paroxysmal activity. Patient 5, who had psychosis with epilepsy, was given 50 mg of adrenochrome. This produced high-voltage waves 2 to 3 cycles/sec, associated with drowsiness. The depth electrograms of patient number 1 resembled that reported for a schizophrenic by Sem-Jacobsen *et al.* (1955), but after adrenochrome, the focal sharp wave activity of maximum amplitude from the temporal region was persistent. The authors concluded "administration of mescaline, LSD, and adrenochrome can cause striking changes in the depth electrogram."

Grof *et al.* (1961) gave 6 subjects 20 mg adrenochrome sublingually. In 5, there were marked changes between 30 and 90 minutes. Alpha activity was slightly disintegrated. Theta waves appeared with spikes and the EEG became hypersensitive to hyperventilation. There was no correlation between the EEG changes and the intensity of the psychological changes.

IX. Effect of Adrenochrome and Adrenolutin on Humans

Hoffer *et al.* (1954) observed that adrenochrome produced psychological changes in man. Since then, several additional studies have been recorded but not in great detail. Only the methods used and summaries of results have been given, due to the difficulty in having journals accept long clinical reports.

In this review, results of experiments with adrenochrome and adrenolutin will be outlined in greater detail.

A. Adrenolutin Double Blind Experiments

Although the influence of faith or lack of faith cannot be eliminated, it may be minimized by using the double blind design. This

research was briefly recorded in 1957 (Hoffer, 1957c, d); the reader is referred to those outlines for a description of the research design.

Normal intelligent subjects were used. They included graduate students, medical students, and graduate nurses. The volunteers were paid for their time. They were told that two new but psychologically active compounds were being used, neither one being LSD or mescaline and that any changes which did occur would be mild and of short duration. Volunteers with a known history of severe physical or mental disease were excluded. All subjects received the compound at 6.00 PM. The observers were one psychiatrist and one psychologist. They knew that the subject would get one of four possible combinations as follows: (*a*) adrenolutin followed by adrenolutin, (*b*) adrenolutin and placebo, (*c*) placebo and placebo, or (*d*) placebo and adrenolutin. Each experiment was run in the evening and repeated 1 week later.

We hoped that the observers would record their observations free of bias. Secondly, they attempted to predict after the two experiments were completed whether the subject had received placebo (riboflavin) or adrenolutin. In testing the predictions of the observers against what the subjects had really taken, a very harsh criterion was used. The assumption was made that all subjects given adrenolutin would react in a clear and noticeable manner and that no subjects given placebo would react. Even with well known hallucinogens like LSD, this would not be true. I have seen many subjects have no reaction to 100 μg of LSD and a few have failed to react with anything but increased tension to 500 μg. Anxiety will induce some volunteers to have some LSD-like reactions. But inasmuch as there was no way of knowing what proportion of subjects would react, there was no other way of testing this. The first thirteen subjects were tested between October 4 and December 19, 1955, using fresh adrenolutin which had been synthesized by Pfizer and Company, New York. The second series of twelve subjects was tested between January 9 and April 13, 1956. By this time, the adrenolutin, which when fresh had been yellow-green, was dark green in color. There was no doubt it had deteriorated. The observers were able to predict the drug given to the first series at the 5% level of confidence. But this was not possible with the second series. This provides some evidence that autoxidized derivatives of adrenolutin are less active psychotomimetics than is pure adrenolu-

tin. It might be argued that the series should have been discontinued as soon as it was noticed the chemical was changing. But this would have biased our data in favor of a positive result. Furthermore, it was then impossible to get any more. Each sample sent to us by various manufacturers was as dark and deteriorated on arrival as our own stock had become.

Another way of examining the data statistically is to examine the recorded data for certain changes. These as recorded by Hoffer (1957c, d) were summarized from records made by the observers and by the subjects before the compound given was known. The code was not broken for each subject until all the written material which forms the raw data was complete. I have reexamined the reports and from data published there (Hoffer, 1957c) scored each subject for the presence or absence of definite changes. This is shown in Table IV. In all categories but anxiety, the evidence of

TABLE IV
EFFECT OF ADRENOLUTIN AND RIBOFLAVIN ON MENTAL STATUS OF VOLUNTEERS IN A DOUBLE BLIND STUDY[a]

Type of change	Number of subjects showing this change	
	Receiving adrenolutin	Receiving placebo
Perception	12	1
Thought	14	1
Mood	3	1
Anxiety	1	7
Personality	3	1
Carry-over, next day	8	1
Total number subjects	20	14

[a] From Hoffer (1957c).

abnormality was much greater in the subjects given adrenolutin, but they were singularly free from anxiety.

This kind of report provides merely the dry bones of a study. For this reason, I will now give in clinical detail a few typical cases which were recorded many years ago. It might be argued that rather than report data obtained with adrenolutin now known to be less pure than it could have been, it would be desirable to repeat the study with stable crystalline adrenolutin. The reasons we have

not done so involve economics of research, priorities, and faith. It is doubtful whether several repetitions of similar experiments would be any more convincing than the original ones. Skeptics are not convinced by over-selling one's point of view. What would be more convincing would be reproduction of similar work by other investigators. One independent corroboration is worth several repetitions by the same worker. Fortunately several research groups have begun to provide some corroboration as will be shown later.

The following accounts include 2 subjects who had both riboflavin (placebo) and adrenolutin, 1 subject who had placebo twice, and 2 who had adrenolutin twice.

1. *Subjects Receiving Adrenolutin and Placebo*

a. *Miss B. X.* (Riboflavin). Miss B. X., a graduate nurse, was tense for the first half hour and felt her speech and thinking were slow. At the end of the first hour, no change was seen. Two hours after starting, no changes had occurred. She remained alert and interested, and felt stimulated by the questions hurled at her to test her thinking. At 10:00, she was sleepy and very tired. For a moment, the printed word appeared altered. She slept well. The next morning, she was normal.

One week later, she received adrenolutin. There was no change the first half hour. Then she noted she was much less anxious than she had been the previous week at this time. At 7:00, she was relaxed and cheerful and felt it was amusing she did not do as well on the tests. While doing the Bender Gestalt test, she could hardly keep from laughing. She was not able to do the 100-minus-7 test correctly nor make simple conversions of grains to milligrams. These are routine for nurses and she had done very well the previous week. The investigator seemed much funnier to her. Her conversation was flippant and for her inappropriate. At 8:00, she was indifferent to pain or the proceedings and found everything amusing.

When the stroboscope was flashing before her closed eyes at 12 per second, she saw a bright white light rimmed with red. This turned into a large moss rose. At 9:30, she was depressed but not tired. The experience of the testing, etc., appeared very silly to her and she could not understand why she had been so free in her conversation. Later, she had a frontal headache.

That evening, she arrived home elated and very talkative. She was amused by the research and remained hilarious to an unusual degree. The next day, she was normal. She reported that she had felt unusually disinhibited socially and had made remarks she would have made only to a close friend or sister and not to strangers. She had been much more relaxed with the second EEG run. There was less fatigue during the first experiment and the whole evening had passed more quickly.

b. *Dr. L. J.* (Adrenolutin). Dr. L. J., a very intelligent intern, wrote the following account after his first session:

"From the period of 5:30 to 6:00, I had a vague feeling of apprehension and some very very slight anxiety not knowing quite what to expect but knowing that the experiment, generally speaking, was considered boring by several of my friends who had taken the test. At 6:00, I took the drug and from 6:00 to 7:00, I noticed several interesting features. The first thing I noticed was that I was mildly to moderately anxious of what was happening in spite of the fact that I was in fairly familiar surroundings and knew the psychiatric personnel who were examining me. I was made particularly anxious by some of the questions that were asked by the psychiatrist. I found that I was completely unable to answer fairly simple questions. I felt a definite frustration and some humility and also a quite marked antagonism towards the psychiatrist because he insisted on asking questions I was unable to handle. I felt that I was definitely putting on a very poor performance to begin with and I assumed that if I had had a drug that in the first hour it would probably have little effect and that most of my slowness in performing these questions was either due to anxiety or to sheer stupidity. I was quite apologetic about not answering the questions smartly. I had definite symptoms of moderate anxiety—my hands were very cold and extremely sweaty. I felt upset, I had marked tachycardia and a feeling of discomfort in the epigastrium which is extremely uncommon for me. From the period 6:30 to 7:00, I noticed an increasing inability to perform the questions. I could remember the facts presented to me quite quickly in these mathematical questions, but I lacked the energy, the initiative to carry the solution through to a final answer. I was almost incapable of setting up the equations in any manner. Towards the latter part of the questioning, drawing close to 7:00 I believe, I could hardly even entertain the questions and this I attributed to my marked anxiety. I found this most frustrating and upsetting experience for I seemed to lack ability to localize my thoughts in a forward direction in handling these relatively simple arithmetic problems which I should imagine would be at grade eight level. I, towards 7:00, also began to feel a tremendous lethargy and apathy towards things in general and this I attributed to the fact that I was overtired when the experiment began which on looking back is probably not exactly true. Some time after 7:00, I found it extremely difficult to concentrate on the questions being asked me because during the application of the electrodes portions of my hair were being snipped off and also acetone and compressed air were used during this procedure, all of which I found fairly distracting. At about this time which I would imagine would be 7:30, although I could not be sure, my attitude seemed to be changing somewhat and I had lost much of my initial anxiety and this was being rapidly replaced by a type of apathy which seemed to be increasing to tremendous fatigue. Accompanying these feelings, I began to lose my feeling of initial humility and also much of my initial hostility. These feelings were being replaced by a feeling of disinterestedness. Also a feeling that I was rather above these frivolous questions that were being asked of me. My examiners no longer seemed quite as friendly as they had formerly and I felt rather like they were young schoolboys wasting the government's money asking rather stupid and superfluous questions. At one point, during this procedure, I was asked to interpret some proverbs. Because of the distractions going on around my head,

I adopted a policy of answering the questions as quickly as possible and with as much dispatch as possible and sloughed off the answers in an effort to get them behind me as quickly as possible. Although the questions did not irritate me, I felt them rather frivolous and somewhat senseless and my main object was to get that part of the questioning over with as quickly as possible and likewise get the evening over with as quickly as possible because the whole thing by this time had become rather boring. I thought my questions to the proverbs being asked were sometimes rather clever. Likewise when I was asked such questions as "why are people taxed" and "what is the function of government" etc., I thought my answers to these were quite concise and astute and at least would be sufficiently good to satisfy this young group of upstarts that were attempting to question me. Towards 8:00, I found the results of the stroboscopic examination were not too disagreeable although rather tiresome. The flicker fusion test following the stroboscopic examination required a good deal more concentration for at this time I felt very fatigued, very apathetic and very often during the flicker fusion test, I would just take a rough stab at what I estimated was the fusion point. I had lost my enthusiasm completely for the experiment but considered that I would play the game and continue with the experiment just to please my examiners who I felt were carrying on in a rather frivolous manner.

"The culmination of the tests came when I was given the critical thinking test which I found extremely difficult. It seemed to never end and I must have taken well over an hour to perform it. Not only did I find the questions difficult but I found the instructions difficult to understand and I believe most of my time was spent trying to figure out what was required of me in the test rather than getting on and doing the actual questions. I found that I had to read over the questions perhaps two or three times and even then was not entirely clear as to what was intended. I was fairly discouraged and rather depressed, and thoroughly fatigued, and yet I had a supreme apathy much as a lotus eater must have had. I was very thankful when the test was finally finished. Following the experiment I returned to my ward where I had several duties to carry out. Although I felt very very tired and certainly ready to go to bed, I felt that I was in my right mind actually. I had to start an intravenous injection and to my chagrin I had great difficulty, making four or five attempts. However, this did not particularly upset me although it must have upset the patient somewhat and I continued to attempt to start this intravenous with some abandon. Later that night at 4:00 in the morning, I was required to get up to give another intravenous injection on the ward on which I worked. For this duty which was to be carried out on a ward some considerable distance from where I sleep, I decided I would get out my bicycle which was kept in a cupboard close by my room and ride down to the ward, which I felt was a very practical thing to do at that hour. I had not done this before, although that evening I thought it would be a very sensible thing to do. On reaching the ward, I again experienced considerable difficulty giving an intravenous injection but again this did not worry me very much. This is perhaps unusual for me for when I miss intravenous injections, I normally become quite disturbed when I miss them for the second time. However, at that hour I didn't

think it mattered if it took three or four or even five trys which I again carried out with the same abandon as previously. The next morning I awoke and I was quite tired, still very very apathetic, and with a rather dull headache. I was unable to pick up any speed in my work throughout the morning and even into the early afternoon and although I had a fairly heavy schedule of work ahead of me, I was unable to muster the necessary energy and initiative to carry out these various duties. The fact that I couldn't seem to carry out these duties didn't really worry me too much at any time. By the following evening, however, I felt I had considerably more energy, I was more awake and more able and willing to carry out the necessary daily tasks. The following day I felt completely normal in all respects. On looking back over the whole evening, I might say that I had received a depressant drug which made me very apathetic, rather depressed and did not seem to completely abolish my anxiety. Although I felt anxious, I didn't seem to be really able to do much about it because of this tremendous sense of fatigue. Generally speaking, I felt I had done only moderately well or rather poorly on the tests, particularly on the first few and especially on the critical thinking test. I regarded the evening as rather unpleasant and one which placed a considerable strain on me. As a result, I was not particularly looking forward to the next week's experiment, which I was afraid might have a somewhat similar effect."

One week later, Dr. L. J. was given riboflavin. At 6:30, there was no change. At 6:45, he was able to do calculations better than the previous week. At 7:00, he did pretty well but failing to give a correct answer to a problem made him upset and anxious. At 7:45, he seemed more relaxed, somewhat elated, and full of good humor. This he described as his normal personality. The rest of the evening, there were no changes. The following day, he was sure he had placebo the second time because he had been wide awake, more attentive, and much more alert. The questions had been easier, there had been no headache, no fatigue, and the memory for the evening had remained clear. He concluded the second drug was either a placebo or an euphorient.

His own account follows:

"On this Monday, in spite of the fact that I had again stayed out rather late Sunday evening, the day before the test, I was in moderately good spirits when I embarked upon the test. I felt somewhat more confident about what was going to happen. I knew that the test would be somewhat similar and therefore I had no particular apprehension. At 5:30 to 6:00, I had the usual flicker test which I did with some enthusiasm as before, knowing that they would be rather boring but that it could be well tolerated. From 6:00 to 7:00 my reactions were considerably different from the previous week and I didn't feel nearly the anxiety that I'd had. My hands remained warm and dry, I was attentive and relaxed. The psychiatrist fired a similar type of question at me involving the rather simple arithmetic questions. Unlike the previous week, I did not have a certain sense of panic and confusion but was able to make at least an effort at working out an equation. I was making a sincere and somewhat enthusiastic effort to at least make a good stab at the question even though I might not be able to get the answer. The fact that I couldn't get the answer didn't particularly worry me as it had the week before. I seemed

generally able to give more answers this week in a quick and more accurate manner. I did not feel the humility nor was I as apologetic when I made mistakes on this occasion. My examiners did not arouse the antagonism and hostility in me as they had done previously. I felt in a quite good humour from the hours of 6:00 to 7:00. I seemed to be able to muster the necessary energy and initiative and enthusiasm to tackle the questions even though I probably would not get the right answer. I was not particularly discouraged or depressed at all and was in an exceptionally good mood when we moved on to the second part of the experiment which again consisted of the EEG and stroboscopic examination. . . . I think I did a better job on the proverbs although there were one or two which I seemed to have a mental block in explaining. On the questions of abstract thinking . . . my performance was better than the week before. On the EEG and stroboscopic examination, I think the results were markedly different from the previous week. At no time was I really aware of geometry and symmetry to the field that I saw; there were no definite centres of light particularly and no straight radiating lines coming off the centre of light. . . . The critical thinking test, I noticed a very marked subjective difference. I was able to understand the instructions immediately on reading them over. I found the questions quite difficult and still not clear today, but I was able to make what I thought was an astute try at the questions and on the whole, I felt much better about the test when I finished than the week before. I felt that I was clearer in my mind, my judgment was better, and I had definitely done the test in a more precise and much more rapid manner. I believe that I had bettered my time by perhaps twenty minutes to half an hour. I felt no particular sensations other than one of extremely well being. I was much more awake at that hour than I usually am.

". . . In retrospect, looking back over the evening, I felt the whole experience was much more pleasant the second evening and I think that I actually enjoyed it. I was able to maintain my interest throughout it and I seemed able to bring my powers of concentration to bear on all the questions so that I could give them all a good try. I didn't feel any anxiety and was in extremely good spirits throughout the evening. I felt quite kindly towards my psychiatrists who I felt were my colleagues and generally felt that the experiment on the second evening was well worthwhile and that the tests were astute ones. As a final conclusion therefore I think that on the first evening I was given a depressant drug, which made a very unpleasant evening for me. On the second evening, I was given an euphorient drug, a stimulant type of drug and the evening was quite passable. However, the drugs are of such a subtle nature that following the first evening, I would not be sure that I had had anything and even following the second evening, taken by itself, I could not be sure that I had had anything. However, in comparing the two evenings, there was a very very marked difference in the way I felt and therefore I must have had contradictory types of drugs on these occasions."

After the two sessions had been completed the subject was very concerned. For most of the week after having had adrenolutin he was very disturbed because of his unusual paranoid ideation during the first experimental night, which he had not disclosed to the investigators. On the second day after the

first experience he reported to me that he had not told the two investigators everything that had occurred as he had been instructed to do. What had happened was now worrying him since he was quite certain he had had placebo. I asked him to come for an interview after he had finished the second half of the experiment because I then did not know what he had had.

After the experiments were over, he reported what he had neglected to tell the two observers. During the first experiment, he was asked his opinion of socialized medicine. He immediately felt very strongly that the two observers were both communists and were trying to draw him out. He thought he would play along with their little game and tried to draw them out in order to obtain evidence that they really were communists. This he proceeded to do by agreeing with everything they said about socialized medicine. He watched them carefully for evidence. He felt B. was a very sinister person although he had known him before. Finally he saw B. pick up a pencil marked "Government of Saskatchewan." This immediately confirmed his suspicions, for who but a communist would get a pencil from the Government of Saskatchewan? He then became preoccupied with the EEG procedure. The next morning, he could not understand how he could have had these ridiculous ideas. He felt so guilty over this he did not wish to tell anyone. For the next few days, he was very quiet and subdued on the wards, quite unusual for him.

2. *Subject Receiving Adrenolutin Twice*

Miss H. G. This graduate nurse was given 50 mg adrenolutin. Before taking the chemical, she was exceedingly tense and her hands were wet with perspiration. At 6:30, she suddenly noted a marked sense of relaxation and some lightheadedness. At 6:40, her head felt funny and she felt her thinking was fuzzy. She had difficulty following conversation. The observers' faces seemed distant from her and she became suspicious of one. She was strongly aware of being watched. At 7:00, she seemed to be small and the two observers towered over her and looked down at her. She considered these visual changes foolish. Words hopped up and down on a page and she had difficulty concentrating. Her thinking was very sluggish and she could not solve elementary nursing arithmetical conversions. At 7:40, there was no more fuzziness and she was relaxed. Words still moved up and down on the page. At 8:00, her hands were dry and this surprised her as she felt she should have been anxious and was not. At 9:00, after the EEG test, she was uneasy and felt oppressed by the stroboscopic light and thought things were closing in on her. At 9:35, she was relaxed again and there were no more visual changes.

The next day, she wrote the following account:

"After the third test, it appeared to me that perhaps I was being looked down upon and the letters of a psychology book had a dancing movement up and down. It was difficult to convince myself that the words were moving when I knew they should not be.

"I was quite disturbed at not being able to do my calculations and thought Dr. Hoffer would think I was very incompetent as a nurse. During the EEG, I was very disturbed at the technician who was just talking too much and not paying attention to his work. My head hurt and I could have screamed out but

I told Dr. Hoffer I was all right. The flashing light gave me a suffocating feeling and I felt like running away or telling them to stop, but couldn't. Later, I went to the bathroom and felt like getting away from the experiment. There were some people in the hall. I thought they were looking at me and thinking I was foolish.

"The next three tests seemed very foolish but I still maintained I was interested. I did not care how I had done. Before going home I believed nothing had happened and that I had been normal.

"At home I decided not to tell my friends anything. I slept well. The next morning I was tired but my head was clear. I was able to figure out the math problem in my head easily [the one she could not solve the previous night]. I realized I had been uncommunicative last night but was able to talk freely now. I realized that I had not reacted normally last night but today I'm thinking more clearly and critically."

Two weeks later, she was again given 50 mg adrenolutin. She was more relaxed this time. The first half hour, she discussed the three things which had impressed her about the first experience. These were (*a*) her feeling she must not communicate; (*b*) her feeling of suspiciousness; (*c*) her difficulty in thinking. At 6:30, she again felt she must not talk, became suspicious, and felt again that we were looking down at her. She also felt quiet. She described one observer's face as having cruel eyes, an accentuated mouth and eyebrows. At 6:45, she again saw words move but less than the first experiment, and they were blurred. At 6:50, these visual changes were gone. At 7:00, she felt more relaxed and was more sure of herself. She tried the serial seven test four times and failed each one but it did not disturb her. On proverbs and on the Wechsler-Bellevue test, she was somewhat better. At 8:00, there was no tension. She felt quiet. There was less paranoid feeling about the observers this time. At 10:00, she was relaxed and felt she had done much better this evening. There was actually very little difference on the scores.

The next day she reported:

"At 5:15 p.m. I was not apprehensive, and was looking forward to the evening. I was curious to know what would happen. After the first test, I took the drug. After a few minutes, we went back to the first room—repeating the first test to which I felt I responded fairly well. After this, Dr. Hoffer gave me a book and asked me if I saw the same thing as last week (movement in page)—I did not. I then experienced the feeling of being looked down upon by A. more than Dr. Hoffer. A.'s eyes appeared somewhat cruel, his eyebrows were pronounced as was his mouth; just Dr. Hoffer's eyes and eyebrows were pronounced. This lasted only momentarily and was not as intense as last week. After this we went out to do the "distance test." At this time, I realized that my mood was definitely calm, that I was not suspicious as on the previous test and that I would probably be more truthful in my comments but still not too talkative. My reaction towards the resident psychiatrist was friendly and not critical realizing he knew his work. The test passed quickly; I was sure of my measurement and did not feel as though I was underestimating myself. Interest did not seem to fade during the test. I believe at this time I was somewhat relieved to think I was not having the same reactions. Dr. Hoffer began his

math quiz again. I thought I could do better than I did, however. I did have several different answers to the 93-7 test; felt I did better on the math but the fact that I had made some errors did not greatly concern me. I felt that Dr. Hoffer and A. were friendly and kindly towards me; also was not as worried about not being able to answer questions but felt perhaps could still do better. During the EEG, I felt very relaxed and calm—could easily have gone to sleep. The time of the test did not annoy me, the hyperventilation part of the test—had some headache, but not as severe as last week. I was finding the evening more interesting even though the tests were the same—perhaps I enjoyed the calm, relaxed feeling I was experiencing in contrast to the previous evening. The Rorschach test also was more enjoyable—I still saw some bats and crawling animals although not as sinister or frightening; and I was able to see more pleasant things—clouds, melting snow, rock and tree reflections in water, just modern art painting for my imagination could not see anything but color. The colors were softer, warmer blue.

"February 25. This morning I was still tired—somewhat more than usual. Talked to the Director—was not the least bit annoyed with her this morning either—a feeling which is different from the annoyance I have felt towards her (p.s., this is a feeling that is experienced not only by myself but also my fellow workers). I still feel relaxed and calmer I believe than what I normally am.

"February 26. I believe the calming effect lasted well into Saturday evening. I was going out Saturday evening and had none of my usual apprehensive manifestations—an excessive perspiration in axilla and palms of the hands. I am still somewhat tired this morning but I am unable to be definitely certain that this is a result of the medication. The experience still remains enjoyable and is beginning to repress the first evening from my mind."

3. *Subjects Receiving Placebo Twice*

Miss B. C. This subject received riboflavin twice. There was no change evident during either experiment; this was typical of the placebo runs. The following account was submitted by the subject on the day following the first session:

"I can remember everything that happened last night quite clearly. I think I was at ease all evening and not exceptionally nervous. I recall that my eyes seemed to be jumping with the lights flashing on and off and flickering but I had no headache. While walking to the EEG lab, I did feel slightly unsteady and not too sure of how I was walking. When I was being asked questions at EEG, I felt a little slow in my thinking partly because of the work being done on my head. It didn't annoy me much but did distract me some. I felt quite relaxed and sleepy after the questioning and when the EEG first started. With the light flashing in my eyes, I saw various colors and designs—all symetrical and moving but no images of any kind. For a while I was dizzy, with my eyes closed. The bed seemed to be turning under me and I was turning around in the opposite direction—similar to a ride at the Exhibition. But it did not last too long, cleared some when I opened my eyes. It stopped without leaving any different feeling—no headache or nausea. After the EEG and the lights, I felt

rather tired and not interested in any more problems. But on walking back to the office, I wakened up again and felt quite normal. However, I was beginning to get hungry. I think I did and said the same things on the tests then as I would have without any drug. After I returned home, I felt quite normal, ate and went to bed and to sleep right away."

4. *Summary*

A summary of the fourteen subjects who received adrenolutin and placebo is shown in Table V.

A score was derived by giving the subject one point for an abnormality and zero for normality under the headings shown in the table. Thus the presence of changes in thought is scored one. I consider it normal for the subject to have had anxiety during these experiments. Its absence is scored as one. The mean score of 14 adrenolutin runs was 4.43, with a range of 1 to 7. For placebo, it was 0.93 with a range of 0 to 3. In 11 pairs of results the scores for placebo were less.

The subjective accounts were then examined for the presence of residual changes in the days following the experiments. Out of 18 subjects given adrenolutin, there were 9 prolonged reactions. Out of 32 placebo experiments, only 4 were prolonged (Chi-square = 6.4, $P < 0.01$).

The subjects were not asked regularly what they thought they had received. But several spontaneously remarked that they had had something active or inactive. Of 9 subjects each of whom received both adrenolutin and a placebo, only 1 subject erred by calling adrenolutin inactive; in all instances the placebo was termed inactive. (For this distribution, with one *d.f.*, the value of chi-square is 10; therefore $P < 0.001$.)

This sample of series is of course biased in that people guessing what they had may have been different, and it is possible that if all subjects had been asked to make these predictions, the results would have been different. The work reported by Grof *et al.* (1961) makes this suggestion quite unlikely. Their subjects were able to detect adrenochrome very well.

B. Prolonged Reactions to Adrenochrome and Adrenolutin

1. *Adrenochrome*

Some of the changes produced by adrenochrome may persist several days, and in some cases the effects nearly led to disastrous

results. Two cases of prolonged reactions will be discussed. These experiences with adrenochrome have made us quite cautious with this drug which seems to be so mild in its action but which can be so dangerous because of the lack of insight it induces in some subjects.

a. *Miss F. M.* This young female, age 16, had been well until age 8. For the next 2 years, she had unusual sensations in her chest and nose every night. A few weeks before this investigation, she developed changes in perception (her mother's face seemed strange and altered as she watched; the visual field was covered with a checkerboard pattern, her body image was different, time moved very slowly, and houses looked like cornflake boxes). There was no thought disorder but she was very apprehensive. For several years, she had been given dilantin and phenobarbital for mixed petit and grand mal epilepsy. At the time of investigation, she was normal. The EEG showed a very marked left anterior temporal focus characterized by high voltage, slow waves, and an occasional saw-tooth wave with single spikes (Szatmari *et al.*, 1955, p. 607). The left temporal focus increased with hyperventilation.

At the beginning of the EEG test, she was happy, cheerful and friendly. She was given 50 mg of adrenochrome by vein. After 10 minutes, she developed a feeling of estrangement and fear and her nose itched. The pathological activity of the temporal focus increased and dysrhythmia became generalized. She was now morose, quiet, and depressed. When she was urged to describe how she felt she cried. Then she reported that the strange feelings and disturbances in body image which had been present 2 weeks before had returned. She was given 500 mg of nicotinic acid by vein. Within 15 minutes, the focus was less intense, the dysrhythmia had disappeared, and she was mentally normal.

That evening at home, she was moody and quiet. One week later, she was very disturbed and 2 weeks after the treatment required committal to a mental hospital.

On admission, she suffered from perceptual changes (all faces were strange; there were marked *déjà vu*, feelings of estrangement and unreality, and visual hallucinations). She had thought disorder (her present life was merely a show and a replay of a previous period in her life; she was confused, rambling, and almost incoherent) and referential ideas with delusions of guilt, and she was paranoid. Her mood was flat. The staff were not aware she had received adrenochrome. On admission, the diagnosis of schizophrenia was entertained but with her history of epilepsy, she was finally diagnosed as having an epileptic psychosis.

A few days after admission, her psychosis cleared and a few weeks later, she had typical grand mal convulsions. These were controlled by anti-convulsant medication. She was in the hospital about 6 months. Over the next 6½ years, she has shown no schizophrenic-like symptoms.

b. *Mr. D. S.* This patient, age 18, was first treated June 7 to September 29, 1957. He was diagnosed as having a neurotic hysterical reaction with marked depression. Schizophrenic features were present. He was given regular psychotherapy and 20 ECT and was discharged much improved. Two weeks

TABLE V

COMPARISON OF SUBJECTS RECEIVING ADRENOLUTIN (A) AND PLACEBO (P)

Subject and treatment		Headache	Perception	Thought	Mood	Anxiety	Personality change	Residual	Score
A:	A	yes	yes	yes	yes[a]	no	yes	yes	7
	P	no	no	no	no	yes	no	no	0
B:	A	no	no	no	no	no	yes	no	2
	P	no	no	no	no	no	no	no	1
C:	A	no	yes	yes	no	no	no	no	3
	P	no	no	yes	no	yes	no	no	1
D:	A	yes	yes	yes	yes[a]	no	no	yes	6
	P	no	no	yes	yes[b]	yes	no	no	2
E:	A	no	no	no	no	no	yes	no	2
	P	no	yes	yes	no	yes	no	no	2
F:	A	yes	yes	yes	yes[b]	no	yes	no	6
	P	no	no	no	no	yes	no	no	0
G:	A	no	no	no	no	no	no	yes	2
	P	no	yes	no	no	yes	no	no	1

H:	A	no	yes	yes	no	no	yes	no	4
	P	no	no	no	no	no	no	no	1
I:	A	yes	yes	yes	yes[a]	no	yes	no	6
	P	no	no	no	no	yes	no	no	0
J:	A	yes	no	yes	yes[a]	no	yes	yes	6
	P	no	no	no	no	yes	no	no	0
K:	A	yes	no	yes	yes[a]	yes	yes	yes	6
	P	no	no	no	no	yes	no	no	0
L:	A	yes	no	yes	yes[a]	no	yes	yes	6
	P	no	no	no	yes[b]	yes	no	no	1
M:	A	no	no	yes	no	yes	no	no	1
	P	no	no	no	no	no	no	no	1
N:	A	yes	yes	yes	no	no	no	yes	5
	P	no	yes	no	no	no	no	yes	3

[a] Depressed.
[b] Euphoric.

later, he remained well. He was readmitted February 21 to March 21, 1958, in the same condition as on his first admission. A better history was taken and he was found to have had perceptual changes. He felt people were staring at him, thought his nose was getting bigger; he felt small in stature compared to others, and he had visual hallucinations of shadows and people. He had thought disorder and paranoid delusions, and was extremely tense. He restlessly paced up and down in his room for many hours. He was diagnosed as an early schizophrenic. Three days after admission, he was given 10 mg of *d*-adrenochrome by vein. Almost immediately he became more relaxed but developed vivid hallucinations. He could see his hands growing larger and smaller, he could no longer estimate distance of people from himself, and pictures appeared very vivid. One hour later, while looking in a mirror, he saw his face divided into two halves, one white and one black. For the next 6 days, this recurred whenever he became very tense.

2. *Adrenolutin*

There have been many prolonged reactions to adrenolutin. Some of these changes have already been described in the case histories (cf. Section IX, A). Other reactions lasted more than 1 day after a single administration of adrenolutin, and reactions up to 1 week have occurred.

Mr. I. K. Mr. I. K. was given 25 mg of adrenolutin at 6:00 PM on January 27, 1955. Over the next few hours, a few visual changes were present; he was relaxed and felt his mind was clear but his thinking was altered. He had difficulty in following conversation and felt other people about him were unimportant to him. Between 8:30 and 10:00 PM voices seemed unnaturally loud. The next day he suffered from a slight headache all morning, and he was listless and tired.

On March 3, 1955, he was given 50 mg of adrenolutin at 6:00 PM. There was little change in him. Two hours later, he was quieter and spoke with difficulty. Later, he developed an irritating headache over his left eye. We concluded that there had been no reaction and he was allowed to go home at 10:00 PM. His wife reported he looked drawn and tired. He was unusually unresponsive and did not tell his wife anything about the evening. That night he slept fitfully and he was less responsive to the fussing of his two young children. The next morning, he was irritable and seemed disinterested in his mail. Episodes which normally did not bother him were causes for irritation. That night, he was angry about his car being stuck in the snow near his house.

The second morning, he seemed more normal. When he could not start his car, he came rushing in and shouted at his wife that he could not start the car and that it was all her fault. This degree of anger and this type of accusation was most unusual for him. When asked how it was her fault, he stated "if she had not wakened him yesterday, he wouldn't have been able to help her sister get her car out and therefore she wouldn't have had to drive home again and so get stuck in the same hole and that therefore he wouldn't have had to drive

his car around to the front and leave it there to freeze on the road and ruin the starter."

That evening when Mrs. I. K. was feeding a young child, he suddenly without warning shouted her name in a violent manner and then said she was harming the child by her concern over the feeding. When Mrs. K. asked him why he shouted instead of just quietly telling her, he glowered and muttered something. That evening, he appeared haggard and ill. He was unreasonable and uncommunicative. The third day, he awoke cheerful and normal until late in the afternoon when his irritability, restlessness, and peevishness returned. The rest of the day he was alternately normal and withdrawn and irritable.

Much has been made of placebo reactions, and they are indeed very powerful. But the incidence of prolonged reactions was very unusual with our placebo subjects. Most of them stated they were normal on the day following the experiment. The records of 25 subjects were reexamined and only their subjective accounts used. In these accounts they described how they felt the following day. Thirty-two subjects had placebo. Four stated there was some residual effect which consisted of some dizziness in three and euphoria in one. Most subjects received Tuinal 200 mg at bedtime. Eighteen subjects received adrenolutin. Of these, nine had prolonged reactions. Chi-square for this is about 6.4. There is less than 2% chance that this difference is due only to chance. Furthermore, not a single placebo subject had any residual reaction lasting more than one-half a day. Yet many adrenolutin subjects were not normal by noon and some were clearly abnormal for several days; there was one reaction that lasted 2 weeks.

C. Effect of Adrenochrome on Humans as Reported by Other Laboratories

In order that investigators can judge a report, it must include a description of the subjects used, the nature of the chemical, and the results which were found. Using these criteria, there have so far been recorded corroborative results from three independent investigators; there are no adverse papers, although apparently sporadic trials by some have proven negative. Rinkel *et al.* (1954) showed that adrenochrome semicarbazone did not produce changes in human volunteers. This is the derivative of adrenochrome which is used for hemostasis. It is not hydrolyzed in the body to adrenochrome; neither is it active in producing changes in spiders.

The first group of workers to corroborate our work was Schwarz

et al. (1956a). On three occasions, they gave 50, 60, and 75 mg of adrenochrome by vein to subject 1 in their series. He suffered body image disturbances and had a loosening of associations. Subject 2 was given 50 and 60 mg. He developed a pleasant smile and marked relaxation. He experienced catalepsy on both occasions which persisted for more than 30 minutes. At these times, he held his arms in unnatural positions for periods of time which could not be matched by controls. He had never shown this before, and it was not induced by mescaline or LSD. The epileptic patient was very relaxed and drowsy after adrenochrome but there were no other changes. Szatmari *et al.* (1955) also reported that little change occurred in chronic deteriorated epileptics until 50 mg of adrenochrome was given. This is not surprising; apparently, they react minimally to mescaline (Denber and Merlis, 1955c).

The second group of workers to find activity in adrenochrome was Taubmann and Jantz (1957). Taubmann explained the increased toxicity of Novocain when applied sublingually to venous anastomosis between the buccal mucosa and the cerebral cortex. Man, for many years, has taken his euphorients by his buccal mucosa, e.g., coca, betel, hashish, tobacco (snuff), and cocaine. By this route, decomposition of the active principle by blood or liver is avoided. These authors therefore gave adrenochrome sublingually and reported marked psychological activity in their subjects.

Grof (1960) and Grof *et al.* (1961) summarized a year's research with adrenochrome. The adrenochrome was synthesized by Dr. V. Vitek according to Feldstein (1958) or purchased from L. Light and Company. They carried out double blind studies on 15 volunteers using subjects very similar to those used in our studies in Saskatchewan, i.e., intelligent, educated, normal subjects as well as some psychiatric patients. Many of their subjects were sophisticated in psychological experiments, having taken LSD, mescaline, or psilocybine. The placebo was a red dye; the dose of adrenochrome varied between 15 and 30 mg sublingually. In the double blind design, out of 15 subjects given placebo, only one thought he had received an active compound. Out of 15 subjects given adrenochrome, only 4 believed they had received placebo. [Chi-square for 1 *d.f.* is over 11 ($P < 0.001$).]

Clinical Changes

Perception. There were no perceptual changes in 6 subjects.

Changes in body image including depersonalization and derealization occurred in 4 subjects. Of these one had a disorder of body image and derealization and felt his legs were short. Visual perceptual changes occurred in 5 subjects and ranged from increased sensitivity to color, to illusions, pseudo-hallucinations, and hallucinations. Auditory changes were reported by 4 subjects and included increased acuity for sound to clear auditory hallucinations of mysterious messages in telegraphic code coming from the universe. Tactile hallucinations occurred in 3 subjects. Taste and olfactory hallucinations were not reported. Eight had alterations in perception and estimation of time. Very few and vague changes were reported by 3 placebo subjects. They included transitory derealization, and minor undulations in the visual field.

Thought. There were no clinical changes in thought in 5 subjects. Some of these showed marked changes on association tests. Paranoid and other delusions were present in 7 subjects. Changes in tempo of thinking such as flight of ideas, difficulty in concentrating, blocking, and speech alterations occurred in 5. One showed negativism, ambivalence, and splitting of personality. Another developed inappropriate behavior such as sitting in a wastebasket or creeping along the floor. Two subjects had no insight into the fact that their condition had been changed. None of the placebo subjects showed any pathological changes in thinking.

The most sensitive method for demonstrating the central effects of adrenochrome was the word-association experiment. There was a high frequency of disturbed associations compared to the placebo experiments. It was significantly different, at the 1% level at 30 minutes, 2–5% level at 60 minutes, and at the 5% level at 120 minutes. The latency period, i.e., the time between stimulus word and response, was prolonged significantly by adrenochrome at the 5% level at 2 hours. In 11 subjects given 330 verbal stimulus words, there were 81 disturbed associations (25%). The most frequent were clang associations. There were only 6 to 7% disturbed associations with placebo. The quantity of disturbed associations is about the same as for schizophrenic patients. The authors concluded that in many cases the subjects formed answers before they understood the meaning of the stimulus word. But for other cases, the origin of the disturbed association was not known. In a few subjects disturbed associations carried on until the next placebo experiment although they had been normal before. This they had never observed with

LSD, mescaline, or psilocybine. They finally concluded that the changes in thinking induced by adrenochrome were similar to those observed in schizophrenia. Adrenochrome caused an elective inhibition of the process which determines the content of associative thinking. This occurred in doses which did not heighten lability of basic processes, did not reduce excitation, and did not loosen temporary connections as was the case with LSD.

Sommer *et al.* (1960) used the Kent-Rosanoff word-association test for testing the hypothesis that schizophrenics had a specific language which had been suggested by some psychoanalytic writers. They found that a group of 49 schizophrenic patients gave about 15% uncommon responses. This degree of unusual responses is very similar to the 25% disturbed associations found by Grof *et al.* (1961). The nonschizophrenic group of 69 subjects gave only 7% uncommon responses. Furthermore, schizophrenics were less stable on repetition of the test ($P < 0.02$) and fewer patients "thought alike" ($P < 0.001$).

Mood. Eight subjects reported or demonstrated no changes in affect. Euphoria and silly laughter or giggling occurred in six. Three subjects had anxiety, one was fearful and one became hostile and depressed. Very often early tension or anxiety was replaced by euphoria and relaxation.

Comparison to Other Psychotomimetic Experiences. Most of the subjects had not taken other hallucinogens and so had no basis for comparison. Of the group that did, two compared it to mild psilocybine experiments and three to mild LSD reactions but in each instance without the autonomic changes.

General. The other tests used were in agreement with the clinical observations. The changes in 3 subjects varied from no reaction to severe schizophrenic-like states. Nine subjects received doses of 30 mg sublingually. Four suffered endogenous Bonhoeffer type psychosis, 3 schizophrenic-like psychosis, and in one the reaction was doubtful. One failed to react. There were thus 7 out of 9 reactors, or nearly 80%. When 15 mg was given, there were 6 definite reactions (1 toxic, 1 schizophrenic-like, and 4 neurotic), i.e. nearly 40%. Five subjects had uncertain reactions and 5 were without reaction.

I have reviewed this work in some detail because of its importance. It is the first double blind study with adrenochrome on humans and fully corroborates the Saskatchewan findings.

D. Adrenochrome Given Sublingually

The Taubmann and Jantz method for giving adrenochrome seems most useful. We therefore ran a few trials with crystalline adrenochrome. Since two adrenochromes are known, made from either *d*- or *l*-epinephrine both forms and the *dl* mixture were tested.

1. *Adrenochrome from l-Epinephrine*

In several studies 6 mg of *d*-adrenochrome given sublingually produced no change. In one instance, 10 mg produced a change which was very clear and obvious for about 2 days. This case is unusually well documented.

The usual adrenochrome changes in perception and thinking resulted. The subject was depressed and irritable, and suffered a marked change in personality. In another case, 3 mg did produce a marked change. After 30 minutes, there was a flush. One and a half hours later, the subject developed strong feelings of isolation. The room became unclear visually and there seemed to be much movement about him. The rest of the day passed without having any sensation of time. In the evening, while in bed, he momentarily hallucinated the face of a person close to him and he became very anxious. In the morning, he was normal.

2. *Adrenochrome from d-Epinephrine*

This was synthesized by R. A. Heacock in 1958. Three mg was given sublingually to two subjects.

Subject 1 observed some difficulty in reading and focusing at 7 minutes. At 10 minutes, he was light-headed. At 12 minutes, far objects seemed very far away. At 24 minutes, he was euphoric and could not estimate time. At 35 minutes, time had seemed almost stationary. At 45 minutes, colors were very bright and vivid. At 80 minutes, he was very active in speech and movements and abrupt with people. At 5½ hours, he felt normal. However, for the next 24 hours, people's faces and other objects would become alternately small and large in size. In one instance, a speaker's face appeared to move away and toward him. Objects moving toward him increased in size too quickly.

Subject 2 also received 3 mg. At 4 minutes, printing on a page became blurred and he had difficulty grasping the meaning of words. At 9 minutes, he became tired and his vision was blurred. At 30 minutes, his thinking was fuzzy. He was apathetic and could not concentrate. The outline of his hand seemed blurred. At 39 minutes, curtains in the room appeared to shimmer. At 52 minutes, he was withdrawn. For the next 30 hours, he was depressed, withdrawn, and disinterested.

3. *Adrenochrome from dl-Epinephrine*

The same subject who had taken 3 mg *d*-adrenochrome (from *l*-epinephrine) took 3 mg *dl*-adrenochrome sublingually.

Slight changes in perception (dizziness, light-headedness, increased brightness of room, changes in size of far objects) occurred. There was no change in thought and there was slight euphoria. After 2 hours, he found the experience unpleasant and took 1 gm of nicotinic acid by mouth. That evening, he was irritable, restless, and without ambition. He was bothered by the odor of new wax on the floor, and later by insomnia.

The following subjects received 6 mg of *dl*-adrenochrome sublingually.

Subject 1 took his adrenochrome at 4:00 PM. Ten minutes later, he had an anesthetic area over both cheeks and he had difficulty in focusing. At 4:15, he was very quiet and appeared sad but denied this. He underestimated the size of objects about 20%. Three minutes later, he was dizzy as if he would faint. At 4:25, he could no longer estimate passage of time. He thought he had been in all afternoon. His limbs became very light. His hands changed in size as he looked at them and the observer's face changed in size. The rest of the hour, he found paintings unusually vivid. At the end of the hour, he had a headache in the occipital area and felt indifferent. Because of his discomfort, he was given 1 gm of nicotinic acid. In 10 minutes as he began to flush, the perceptual changes vanished and he felt normal. That night, he slept lightly and was not sure whether he had been awake or asleep (twilight sleep). The next morning, he was very tired and considered not coming to work. At work, he was irritable all day.

Subject 2 had had much experience with LSD and was skilled at introspective observation. At 2:00 PM, he received the adrenochrome. In 5 minutes, he became aware that colors and detail were more distinct. People in pictures seemed more lifelike and larger. In 10 minutes, he had a marked frontal headache. He was able to read but could not make sense out of what he read. At 20 minutes, the visual changes were very clear. He estimated 30 seconds as 45 seconds (mean of 3 trials). At 25 minutes, he looked older in the mirror. He was relaxed and disinterested. His headache was almost gone but he felt clumsy when moving. One hour after starting he was depressed and irritable. His face was flushed. He was withdrawn and indifferent. While lined up in a cafeteria for coffee, the other people appeared to be puppets. When he drank his coffee, he complained about the noisiness. He felt the people around him were puppetlike, lacked understanding. They annoyed him but he stated he was superior to them. They seemed empty people. At 3:15, his facial flush was gone. The white uniforms of nurses in the cafeteria annoyed him. At 3:40, he thought 2 hours had elapsed since taking adrenochrome. He markedly overestimated size of objects (12 trials). At 2 hours, he felt music was being played at half speed. He likened the experience to the initial symptoms of LSD. It

seemed like 3½ hours since taking it. His headache was now gone. He reported that the most pleasant part of the experience was that it was wearing off. The next hour, he was easily confused and still could not estimate time correctly. After that he was normal.

E. Potentiation of the Action of Adrenochrome

Melander and Mårtens (1958) found that lysergic acid diethylamide (15 to 30 μg/kg) and taraxein when given ahead of adrenolutin markedly potentiated its effect. Thus 20–25 mg/kg when given by vein produced only slight changes in cats. But pretreated cats showed a marked response of drowsiness and muscle relaxation after 2–3 mg/kg. Acetyl-LSD also was a potentiator but bromo-LSD was not. Mårtens *et al.* (1959c) reported that LSD and taraxein sensitized cats to acetylcholine, epinephrine, atropine, chlorpromazine, histamine, mescaline, and serotonin. They therefore made the sensible suggestion that taraxein, LSD, and *dl*-acetyl lysergic acid diethylamide (ALD) increase the permeability of these substances through the blood-brain barrier, i.e., they "have the property of enabling certain intravenously injected drugs to act on selected brain centers not normally accessible to them."

Hoffer (1959b) and Hoffer and Osmond (1960) found that humans reacted to the combination of LSD followed by adrenochrome or adrenolutin in the same way. There was a marked potentiation of the adrenochrome effect. This was especially notable in human subjects who reacted to LSD primarily by the production of severe tension and anxiety. Visual and psychedelic changes were minimal if present at all. In these subjects, the injection of 10 mg adrenochrome or adrenolutin produced a certain relaxation from tension and the usual LSD experience of marked visual and other changes. Adrenochrome can be used in this way to help break across the tension barrier into the psychedelic experience, which is helpful in treating alcoholics.

Heath *et al.* (1958) postulated that ceruloplasmin formed part of a protective system. Its function would be to protect the body against amines or their metabolites liberated during stress. Mårtens *et al.* (1959a, b) provided powerful evidence in support of this idea. Ceruloplasmin irreversibly binds adrenolutin (Melander, 1957) and histamine (Mårtens *et al.*, 1959c). When animals were pretreated with ceruloplasmin, they were protected against the psychotomimetic properties of LSD alone or LSD followed by other com-

pounds listed by these authors above. It also decreased the toxicity of histamine. Further support for the protective role of ceruloplasmin were the interesting therapeutic responses of schizophrenic patients to ceruloplasmin, reported by Mårtens *et al.* (1959a, b).

F. Discussion

The basic issue is whether or not adrenochrome and compounds which can be derived from it *in vivo*, perhaps adrenolutin and 5,6-dihydroxy-*N*-methylindole, are active hallucinogens in man. The evidence that these compounds exist in the body is growing more substantial. The fact that these compounds are active in producing changes in animals can no longer be denied, and indeed it was concluded by Kety (1959) that there was no doubt it did produce changes in animals. Adrenochrome will therefore be most interesting to physiologists who are following the properties of metabolic products of epinephrine.

The fact that adrenochrome and adrenolutin have produced changes in the perception, thinking, and feeling of humans makes them very interesting for psychiatrists and physiological psychologists. Although Smythies (1960) denies that adrenochrome is active in humans, the literature reviewed in this paper, as well as the detailed outline of new data from our research, makes clear that it is no longer sufficient merely to state that adrenochrome is not active. If it were true that adrenochrome is indeed inactive in humans, we would then have the curious situation of a chemical which is active in many species of animals, including the monkey, being inactive in man.

In general, it seems to be true that when more sophisticated tests of animal behavior are used, smaller quantities of adrenochrome are effective in producing change. This is most clearly established for monkeys. Thus, Heath, giving 100 mg of adrenolutin to monkeys fixed in a chair, and using the animal's rage as an index of activity, saw no effect unless the animal was pretreated with taraxein. In sharp contrast, Iordanis and Kuchino (1959) using very refined conditioned reflex techniques showed that 1 mg of adrenochrome abolished sequential conditioned responses. The monkey reacted appropriately to the sight of food but did no longer respond to the symbols signifying food. It, in effect, became very concrete in its thinking. Similarly for rats, the refined experiments of Weckowicz

(1961) clearly showed a remarkable effect of adrenochrome in decreasing learning and in increasing extinction of acquired conditioned reflexes.

X. Mode of Action of Adrenochrome

Theoretically, chemicals could affect the mind by interfering with its media of input or output. If perceptual stimuli were distorted by some defect in the retina of the eye, then there might be some disorder of those aspects of mind which depend upon the accurate reception of sensory data. In fact, Fogel and Hoffer (1961) have produced a large series of models of psychiatric syndromes merely by producing simple alterations in perception. Psychological methods only were used.

Adrenochrome and adrenolutin are chemically very reactive substances and react with an amazing variety of constituents of the body. They could therefore somehow interfere with sensory perception. However, the evidence gathered in this review suggests clearly that the brain is the chief target. This evidence is that (1) given into the ventricles of the brain, the compounds are much more active than when given by vein; (2) pretreatment with taraxein, LSD, and ALD potentiates their action; (3) pretreatment with ceruloplasmin protects the animal against their toxic effect; (4) adrenochrome produces hypothermia in normal and adrenalectomized rats (Hutcheon *et al.*, 1956) without decreasing the consumption of oxygen (Eade, 1954); and (5) anxiety increases the susceptibility of normal human subjects to adrenolutin (Hoffer, 1957c). In contrast, however, is our finding that severely tense alcoholics and endogenous depressives react very little to adrenochrome given by vein. Braines *et al.* (1959) found that fear potentiated the reaction of dogs to adrenochrome. Recently, Mazel and Bush (1961) found that epinephrine brought about a great increase in the rate of entry of barbital into mouse brain. Norepinephrine had little effect. The concept of the blood-brain barrier has been reviewed by Aird (1956). (6) Adrenochrome alters the EEG pattern from the depths or from the surface in animals and on the surface in man. Adrenochrome may affect the brain by interfering with the blood-brain barrier. Thus, Greig and Gibbons (1959) found that adrenochrome decreased the penetration of glucose, labeled with C^{14}, into mouse brain; bulbocapnine, bufotenine, and mescaline were much more

active. The effect of LSD was variable, while adrenolutin and iproniazid had no effect. They further found that human serum pseudocholinesterase was inhibited 50% by the following concentrations of LSD, bulbocapnine, bufotenine, adrenolutin, and adrenochrome: 9×10^{-7}, 2×10^{-5}, 4×10^{-4}, 3.8×10^{-3}, and 3.3×10^{-3} *M*. They therefore suggested that hallucinogens could act by decreasing transfer of glucose into brain.

In the brain substance there are many enzyme systems which would be inhibited. These include (1) hexokinase (Bullough, 1952; Gelfant, 1960; Walaas and Walaas, 1956; Takahashi and Akabane, 1960) and in general (2) the glycolytic cycle (Cohen and Hochstein, 1960; Hochstein and Cohen, 1960; Korzoff and Kuchino, 1959; Meyerhof and Randall, 1948; Radmsa and Golterman, 1954; Randall, 1946; Woodford, 1959). Cohen and Hochstein found that adrenochrome as well as some other quinones inhibited the production of lactic acid from glucose by mouse-brain homogenate. They suggested that these compounds might have an *in vivo* role in regulating energy production from glucose in the central nervous system. Hochstein and Cohen found that brain tissue was more sensitive to adrenochrome than was liver tissue. The mitochondria seemed to be most sensitive. Liver supernatant protected brain tissue against inhibition by 10^{-5} *M* adrenochrome. Liver mitochondria were sensitized by brain supernatant. Frederic (1954) had shown that mitochondria of living cells were inhibited by adrenolutin. (3) Oxidative phosphorylation is uncoupled by adrenochrome (Park *et al.*, 1956a, b). (4) ATPase is inhibited (Inchiose and Freedberg, 1961). (5) Glutamic acid decarboxylase is inhibited (Holtz and Westermann, 1956). (6) Coenzyme A is deactivated (Roston, 1960).

The effect of adrenochrome on neurons (Geiger, 1960) has already been described. It also has some inhibitor action on synaptic transmission (Marrazzi, 1957; Hart *et al.*, 1956) and some antifatigue effect on sympathetic nerves (Derouaux and Roskam, 1949).

The pigments in the cells of the central nervous system are apparently not derived from tyrosine. Foley and Baxter (1958) examined the brains of 2 albino human subjects. In both cases, the intensity and pigmentation in the cells of the locus caeruleus and substantia nigra appeared normal. One patient also had several pigmented cells in the dorsal motor nucleus of the vagus. In contrast neither brain had any melanin pigment present in the pial melano-

phores. They therefore concluded that "melanins" of the brain stem differ fundamentally from the melanin of skin, choroid, and pia in that they are not formed by the action of the tyrosinase complex. Albinos lack tyrosinase. Other sources of melanin-like pigment include epinephrine, norepinephrine, hydroxytyramine, dopa, and tryptophan. Fellman (1958) found that substantia nigra contained enzymes which oxidized epinephrine. He observed argentophilic granules not unlike those seen in the adrenal medulla and in other chromaffin tissue.

Epinephrine and norepinephrine might be the main source of these pigments. The evidence for this view is as follows: (1) Brain tissue is very rich in epinephrine oxidases (Payza and Hoffer, 1959) and contains argentophilic cells (Fellman, 1958). (2) Brain contains inhibitors of epinephrine oxidation (Walaas and Jervell, 1958). One would expect both activators and inhibitors to be present in tissue in which epinephrine is oxidized to adrenochrome. Brain is rich in ascorbic acid, which tends to inhibit oxidation of epinephrine to adrenochrome. (3) The increase in density of brain pigments parallels closely the increase in secretion of epinephrine during fetal and postnatal development. The medulla contains chiefly norepinephrine at a late stage of intrauterine life. After birth there is a rapid reorganization of the medulla and the proportion of epinephrine increases rapidly for about 2 years. After 3 years the Zuckerkandl bodies show very little activity (West *et al.*, 1951, 1953). Foley and Baxter found brown-black granules in cells of the locus caeruleus as early as the fifth month of gestation, after which their number increased rapidly. Similar granules were not present in the substantia nigra until 18 months, after which they increased. But the locus caeruleus always had had more until puberty. Since epinephrine is oxidized to adrenochrome more readily than norepinephrine is to noradrenochrome, it is possible, that the formation of the pigment depends upon the production of epinephrine. (4) Although methoxylation of phenolic hydroxyls may be a main pathway of epinephrine and norepinephrine degradation, it is not yet clearly established whether or not this is also the main pathway in brain. Thus, Weil-Malherbe *et al.* (1961) found that pyrogallol, an inhibitor of catechol-O-methyl transferase, does not affect concentration of brain norepinephrine unless it is combined with an amine oxidase inhibitor. Borovitz and Merritt (1961) reported that the

usual studies of epinephrine metabolism refer to liver metabolism. They found that heart, brain, and liver handled epinephrine in different ways. Spector *et al.* (1960) provided evidence that methoxylation is not the main enzyme for inactivating norepinephrine in brain. Pyrogallol did not block metabolism of brain amines released by reserpine. They suggested that monamine oxidase was responsible for metabolism of norepinephrine in tissues where it regulates levels of stored amines, while catechol-O-methyl transferase inactivated catechol amines after they were released into the circulation. (5) In Wilson's disease, there is an excess accumulation of copper combined with a deficiency of ceruloplasmin (Denny-Brown, 1953). The excess of copper would favor the oxidation of epinephrine to adrenochrome and the lack of ceruloplasmin would intensify the pathological effects. The chief pathological changes are in the brain and liver. Clinically, there are severe neurological changes including tremor and marked mental changes. Barbeau (1960) found evidence for an abnormality of catechol amine metabolism in basal ganglia diseases, and Domer and Feldberg (1960) found that minute quantities of epinephrine placed in the brain ventricles had marked antitremor properties. I postulate that in Wilson's disease a rapid conversion of epinephrine to adrenochrome occurs (due to copper deposition). This would account for the tremor (due to a lack of epinephrine), progressing to increased deposition of brain pigment (a copper adrenochrome melanin complex), psychosis (due to excess adrenochrome and adrenolutin combined with lack of ceruloplasmin), and finally destruction of neurons by adrenochrome as was found by Geiger (1960). These ideas are highly conjectural; perhaps newer techniques for staining adrenochrome and adrenolutin-like pigments will reveal whether they are indeed present.

If ceruloplasmin does play a role in protecting the brain against toxic amines and indoles as has been suggested, then serum ceruloplasmin levels need to be considered as a factor determining the response of animals given adrenochrome and adrenolutin. Pregnant animals, especially just before term, when the production of ceruloplasmin by the placenta is at a maximum, should be quite resistive to the action of LSD or adrenochrome, but Peck (1960) indicates that no papers are available which report tests of this hypothesis. A woman 6 months pregnant reacted in the usual way to a large dose

of LSD but at this stage ceruloplasmin levels have not increased very much. It is perhaps more than coincidence that toxemia of pregnancy is more common in schizophrenics than in controls (Wiedorn, 1954), and that epinephrine levels are elevated just before parturition (and apparently do little harm) but decrease very quickly during labor (Ritzel *et al.*, 1957). Puerperal psychosis came on most frequently in the few weeks after delivery. During this time, ceruloplasmin levels decrease very quickly. Linn (1941) reported that 59 cases of *post partum* psychosis out of a series of 76 developed within 2 weeks. Of these, 42 occurred within 7 days. The third day was apparently a critical one. Paffenbarger *et al.* (1961) found that from a series of 125 women developing puerperal psychosis, 96 came on in the first month and 109 in the first 2 months (87%).

XI. Conclusions

Adrenochrome and adrenolutin produce marked changes in behavior in spiders, pigeons, rats, cats, dogs, and monkeys. The finer aspects of behavior appear to be altered first. Gross changes are produced by larger quantities.

Activity is also seen in human subjects. The types of change produced mimic in many ways the changes seen in schizophrenia. The kind of visual hallucinations seen with mescaline, LSD, psilocybine, and other substances is not produced. The findings of our group have been corroborated in man by three independent research centers, while no research paper has reported details of failure to corroborate.

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