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ADRENOCHROME AND ADRENOLUTIN AND THEIR
RELATIONSHIP TO MENTAL DISEASE*

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INTRODUCTION

Since the age of Hippocrates, philosophers, and since Galileo, scientists as well as philosophers, have examined the problem of the relationship of mind to body. Even today, the solution is not in sight. This basic dichotomy has continued to perplex the research worker in psychiatry, especially in the subject of etiology. Psychological theories of cause have changed little over the centuries in that they ascribe etiology to forces of either a spiritual or physical external world. The ancient devils have been replaced by modern devils such as the bad environment, the hostile accepting-rejecting mother, weaknesses of personality or ego, etc. And in an era when the concept of the whole man has been deified so that even classification is abhorrent, all mental disease is ascribed to two or three psychological propositions applied in ever more mysterious complexity. In sharp contrast, biological theories have undergone an interesting refinement from the crude vague humoral theory of the past when chemical structure and the molecule were not known, to the exogenous indoles and amines of the early twentieth century notably supported by BUSCAINO[5] and others, until the recent focus on indolic substances derived from natural body chemicals such as tyrosine and tryptophan. Over the years, the theory has sharpened its focus and has reduced the number of potential biochemical factors from the hundreds of thousands of the humors, to the tens of thousands of the amines and indoles, to the tens of the endogenous mammalian indoles related to epinephrine and to serotonin.

The greatest and most difficult problem has been to find a way of narrowing the search among the thousands of potential substances. For this reason, research psychiatrists tried to develop models of the psychoses. The discovery of even one substance which was psychotomimetic immediately would vastly reduce the possible number of compounds (on the assumption that there might be a similarity between the natural schizophrenic substance and the psychotomimetic substance). The brilliant pioneer, DE JONG[6], no doubt had this in mind when he examined a series of compounds related to mescaline and to epinephrine in his search for a catatonizing nucleus. Unfortunately, his discovery that many dissimilar substances induced catatonia in animals caused him to give up this concept. Had he sharpened his criteria and looked for the unity of all catatonizing substances or their derivatives in the body,

he might have come to the epinephrine derivatives for especial examination. More recently, OSMOND AND SMYTHIES[29] re-emphasized the chemical similarity between mescaline and epinephrine and suggested that this observation be used in the search for the biochemical abnormality. Both epinephrine and mescaline potentially may form indoles either *in vitro* or *in vivo*, and many interesting hallucinogens are indoles.

HOFFER, OSMOND AND SMYTHIES[19] began a series of studies with one of the known derivatives of epinephrine, *i.e.* adrenochrome, and more recently, adrenolutin. They found that in normal volunteers, especially those skilled in the use of psychotomimetic drugs, adrenochrome induced changes in thought and mood and even personality often with no insight in the volunteer that change had occurred. In addition, SZATMARI, HOFFER AND SCHNEIDER[37] reported that intravenous administration of adrenochrome markedly increased the EEG abnormality of deteriorated epileptic patients. More recent studies with adrenolutin have confirmed and amplified these earlier investigation[16, 17]. It was therefore hypothesized that as many hallucinogens were indoles, one might begin to search for natural indolic substances related to epinephrine. This was intended to guide the search. At no time did we enunciate an indole theory of hallucinogenic activity. No competent biochemist could suggest that all indoles are hallucinogens, or conversely that all hallucinogens are indoles. The indole theory, if it must so be labelled, applies only to schizophrenia. The working hypothesis was established that indole derivatives of epinephrine were implicated in the production of schizophrenia.

REVIEW OF EPINEPHRINE METABOLISM

The metabolism of epinephrine has recently been reviewed[18]. Epinephrine produced *in vivo* may be absorbed and stored within the erythrocytes[1, 2], within myocardial tissue[33], and perhaps in other cellular elements. After absorption into the erythrocytes, it may be slowly released when the cells are placed in serum containing little epinephrine or it may be recovered by hemolyzing the cells[1]. The erythrocytes may therefore act as a buffer against epinephrine over-concentration. The deamination of epinephrine by amine oxidase is another possible pathway and has been considered one of the major detoxification routes. It is suggestive of the relationship of epinephrine to mental disease that substances that are active inhibitors of amine oxidase will induce euphoria when given in small dosages and psychosis when given in high dosages for extended periods of time. The indolization of epinephrine is another pathway. This has been strongly supported by BACQ[1]. This route would lead to the formation of adrenochrome or adrenolutin or both and perhaps other still unidentified substances. Finally, some of the epinephrine may be excreted as the sulfate ester. When large quantities of epinephrine are administered by mouth, this does occur. No doubt other changes occur but they are not known as yet. Recently, ELMADJIAN[8] has shown, using radioactive tracers, that a very small fraction of administered epinephrine can be accounted for in the urine. The more recent secretion rates of epinephrine may be close to 25 mg per day[3].

Adrenochrome and adrenolutin are very active chemically. *In vitro*, adrenochrome markedly interferes with carbohydrate metabolism[39] but *in vivo* studies have been inconclusive. It is a very strong inhibitor of glutamic acid decarboxylation[21] by cerebral tissue. Microgram quantities per gram of tissue produce nearly complete inhibition. Glutamic acid, according to recent studies of HIMWICH[14], may play an im-

portant role in cerebral metabolism. Adrenochrome completely uncouples oxidative phosphorylation in hamster liver mitochondria ($5 \cdot 10^{-4} M$). This is not reversed by magnesium, but is increased by ten-fold in the presence of thyroxine[30]. Uncoupling is counteracted by glutathione and EDTA[31]. Decomposed epinephrine (which contains among other things adrenochrome) is antimitotic for certain rapidly growing tissues[25, 10]. *In vivo*, it inhibits mitosis in mouse epidermis, and *in vitro*, inhibits epidermal mitosis[4]. Schizophrenic serum also markedly inhibits the growth of L strain cells[9]. Adrenochrome blocks acetylcholine esterase[38] and is cholinergic *in vivo*[36]. In large doses relative to epinephrine it blocks synaptic transmission[28] but prevents muscle fatigue *in vitro*[7]. *In vivo*, it has an effect on electrical activity of brain of rats similar to LSD, epinephrine, and serotonin[35]. Both adrenochrome and adrenolutin are hypothermic for rats[22]. When administered into the ventricular system of cats, both adrenochrome and adrenolutin produce trance-like states for up to twenty-four hours with marked change in the EEG[34]. By this route, it is more active than in LSD but less active than mescaline. This recalls the different and anesthetic action of epinephrine when administered intraventricularly.

THE CONVERSION OF EPINEPHRINE INTO ADRENOCHROME

The mammalian body contains all the conditions essential for the formation of both adrenochrome and adrenolutin. These are (1) *the substrate* – epinephrine – which is produced in fairly large quantities per day. Early estimates based upon concentration in the serum and excretion of known metabolites in urine were much too low. Recent studies using radioactive tracers and perfused excited adrenal glands give estimates of a much higher order, between 10 and 25 mg per day. (2) *the enzymes* – which catalyze the conversion to indoles. This has been suspected for some time. LEACH AND HEATH[23] have shown that epinephrine is converted more rapidly in schizophrenic serum than
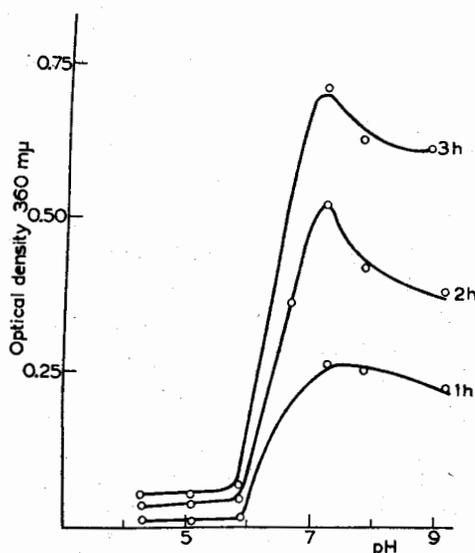

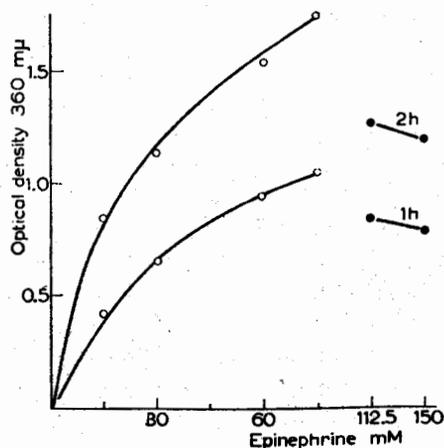Fig. 1. Effect of acidity on conversion of epinephrine to adrenochrome semicarbazide.

Fig. 2. Effect of epinephrine (substrate) on conversion to adrenochrome semicarbazide.

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in normal serum into a substance shown to be adrenolutin by HOFFER AND KENYON[20]. The conversion is undoubtedly enzymic. Auto-oxidation plays a minor role in the serum because of the presence of anti-oxidants such as ascorbic acid, glutathione, cysteine and albumin. In our laboratory, we have found that the conversion is enzymic and much greater th ancan be accounted for by auto-oxidation. PAYZA[32] has found that (a) there is an optimum acidity for the conversion to adrenochrome trapped with semicarbazide (to prevent conversion to adrenolutin) (Fig. 1); (b) there is a relationship between substrate and degrèe of conversion (Fig. 2); (c) the enzyme is inactivated by heat (Fig. 3); (d) the rate of change is accelerated by copper ion and
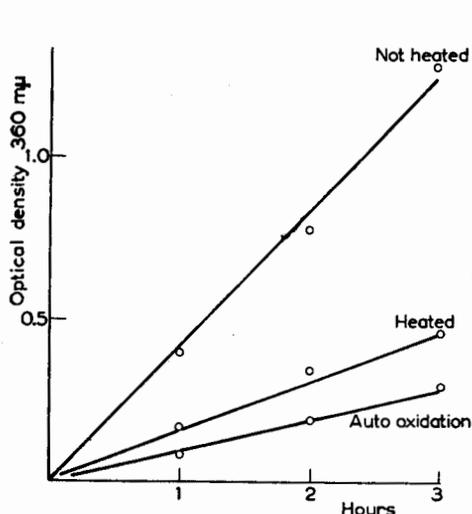

Fig. 3. Effect of heat-treated serum on conversion of epinephrine to adrenochrome semicarbazide.
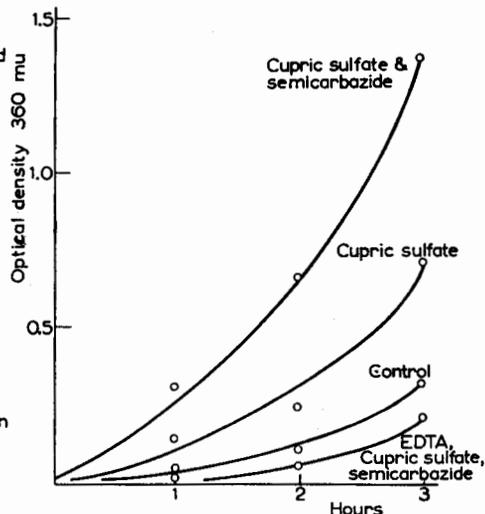
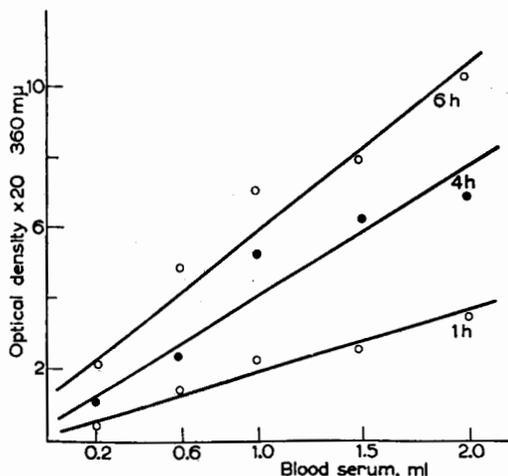Fig. 4. Effect of some substances on conversion of epinephrine to adrenochrome semicarbazide.

Fig. 5. Effect of enzyme concentration.

inhibited by the chelating substance EDTA (Fig. 4); (e) there is a relationship between enzyme concentration (amount of serum) and conversion. This may be used to compare various sera.

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According to LEACH *et al.*[24], one of the enzymes is ceruloplasmin. It produces mild behavioral changes in monkeys[12]. In further isolation studies, they isolated another substance, taraxein, probably an enzymes, which injected into volunteers produces a remarkable picture of catatonia[12]. Similar results were obtained in monkeys. At the same time, the typical spike and wave appears in the septal area. When given to schizophrenic patients in remission, the psychosis was reactivated. At the same time, there was as reactivation of the schizophrenic EEG abnormality.

There is a relationship between the concentration of enzyme present in volunteers and the intensity of the psychological experience induced by LSD and mescaline. HOFFER[15] found that at the height of the hallucinogenic experience, the rate of conversion of epinephrine to adrenolutin was increased (Fig. 6). This confirms the report of LEACH AND HEATH[13]. PAYZA[32] found in one case more than a three-fold increase in enzyme concentration after administration of 100 μg of LSD. The activity two hours after administration was much greater than has been seen for any schizophrenic patient so far (Fig. 7).
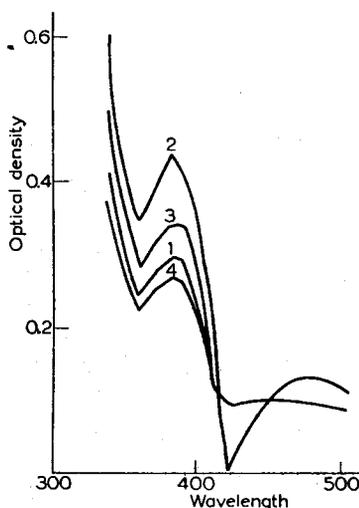

Fig. 6. Effect of LSD on conversion of epinephrine to adrenolutin (1) before, (2) 2 h, (3) 5 h, (4) 6 h.
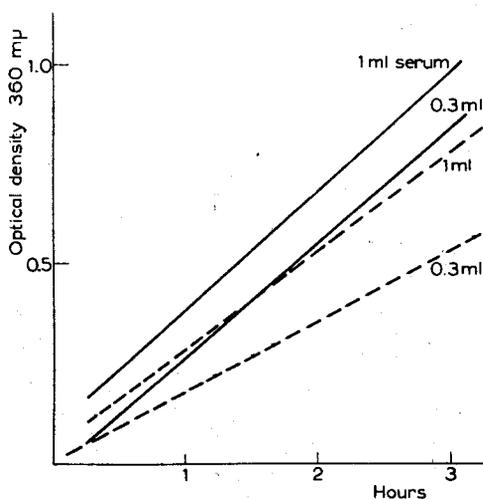
Fig. 7. Effect of LSD on enzyme concentration (broken line) before, (solid line) after 2 h.

After the intensity of the experience begins to wear off, the concentration of enzyme as determined by the conversion to adrenolutin returns to normal. LIDDELL AND WEIL-MALHERBE[26] found an increase in epinephrine concentration early after giving LSD. This was later followed by a decrease in epinephrine. It is likely that the rapid increase in enzyme quickly reduces the free levels of epinephrine. Perhaps the formation of the adrenolutin plays a role in the LSD experience, especially after the early acute and intense experience begins to wane. At this time, one often finds thought disorder, paranoid thinking, etc.; (3) *the formed substances* – there are adrenochrome, adrenolutin or leuco adrenochrome. Indirect evidence for the presence of adrenochrome in serum has been reviewed by HOFFER[18]. More recently, adrenochrome has been isolated from rat brain and adrenal cortex when the animal was convulsed by high oxygen tension[11].

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RELATIONSHIP OF ADRENOCHROME AND ADRENOLUTIN TO HEMOGLOBIN

In repeating the epinephrine conversion studies of LEACH AND HEATH[23], it soon became apparent that many normal subjects had high conversion rates, especially when the serum had a pink tinge due to the presence of hemolyzed erythrocytes. Instead of obtaining a conversion curve as shown in curve 1, Fig. 6, one obtains a type of curve like curve 2 in Fig. 6. PAYZA[32] has found that 10 to 100 μg of freshly hemolyzed hemoglobin markedly accelerates the conversion of epinephrine to adrenolutin (Fig. 8). This may account for some of the overlap between the conversion
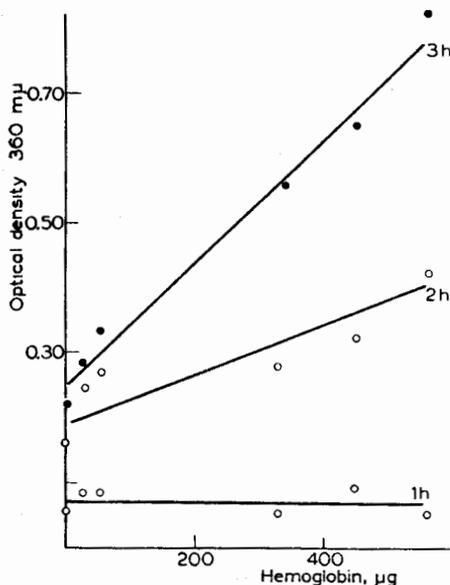

Fig. 8. Effect of fresh hemoglobin on conversion of epinephrine to adrenochrome trapped with semicarbazide.
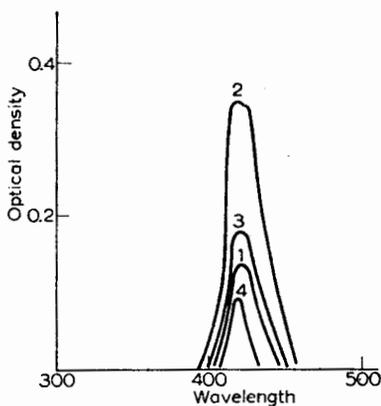
Fig. 9. Effect of LSD on ascorbic acid bleaching of serum (1) before, (2) 2 h after, (3) 5 h, (4) 6 h.

rates for normals and for schizophrenics, since it is most difficult to prevent hemolysis in some instances owing to mechanical trauma. It may also explain the increased conversion rates found in conditions like high fever and allergic states where the fragility of the erythrocytes may be high. In one experiment, blood was drawn from the right arm of a normal volunteer using a small needle and faulty technique and a small syringe. The conversion rate from this sample was high. Blood drawn a few seconds later from her left arm using a large bore needle, a large syringe, and good technique, yielded a sample of blood which showed a lower conversion rate. The visual estimate of the degree of hemolysis is not reliable. There is a good relationship between degree of pinkness measured by the DU spectrophotometer and conversion rates. For this reason, it is preferable not to use serum with any tinge of pink.

Hemoglobin is very active as a catalyst for the oxidation of epinephrine, perhaps by acting as a hydrogen acceptor. Because of the acceleration induced by fresh hemoglobin and because epinephrine is avidly taken up and held by erythrocytes, it is essential to examine them for the presence of the products of epinephrine degradation. When ascorbic acid is added to serum, it bleaches the serum after a few minutes so

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that when the original serum is read in the DU Spectrophotometer against the ascorbic acid-treated serum as the blank, a peak appears with a maximum at 420. Hemoglobin has a peak absorption at about 420 and hemoglobin is bleached by ascorbic acid. The quantity of this 420 factor can be increased in serum by the addition of hemoglobin, adrenochrome, adrenolutin, or epinephrine (as in the Leach and Heath conversion test). It thus appears likely that ascorbic acid changes some of the components of this complex. It will be shown later that ascorbic acid changes adrenochrome to leuco adrenochrome which is colorless. This might be a partial explanation for the bleaching effect seen in serum. The relationship of the quantity of fresh hemoglobin to the conversion of epinephrine to adrenolutin and upon the 420 factor are shown in Table I.

TABLE I

THE RELATIONSHIP OF HEMOGLOBIN CONCENTRATION OF SERUM TO THE CONVERSION OF EPINEPHRINE TO ADRENOLUTIN (395) AND THE 420 FACTOR

Hemoglobin O.D.	Number	Mean O.D.* at 395	Mean O.D.** at 420
0.1 to 0.19	14	0.29	0.07
0.2 to 0.29	14	0.29	0.12
0.3 to 0.39	4	0.36	0.16
over 0.40	4	0.31	0.24

* Conversion to adrenolutin.
** Bleaching effect of ascorbic acid on serum.

With an increase in hemoglobin, there is an increase in the quantity of adrenolutin formed and a marked increase in the quantity of 420 factor (of which hemoglobin is one component). In Table II, some relationships are shown of diagnostic groups to the conversion of epinephrine into adrenolutin as measured by the height of the peak at 395, of adrenochrome as measured by the height of the curve at 460, and the 420 factor.

TABLE II

THE RELATION OF DIAGNOSTIC GROUPS TO THE CONVERSION TO EPINEPHRINE, ADRENOLUTIN, ADRENOCHROME, AND THE PRESENCE OF 420 FACTOR

Diagnostic group	Number	O.D.* at 395	O.D.** at 460	O.D.*** at 420
Normal	18	0.30	0.10	0.10
Neurotic	16	0.31	0.10	0.09
Surgical – pre-operation	28	0.36	0.12	0.13
Surgical – during operation	12	0.43	0.19	0.22
Schizophrenic	13	0.35	0.12	0.21
Schizophrenic – after treatment	11	0.35	0.13	0.06

* Conversion to adrenolutin.
** Conversion to adrenochrome.
*** Bleaching effect of ascorbic acid on serum.

It is seen that the conversion to adrenolutin in serum drawn from normals and neurotics is less than for the other four groups. The greatest quantity of adrenochrome was

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formed by the surgical patients when blood was drawn during the operation. Here one would expect much hemolysis due to the trauma of the operation. This is shown by the height of the 420 peak for these surgical patients. However, the schizophrenic patients before treatment had as much 420 factor as the surgicals. After treatment, their 420 factor was within normal range although the enzyme concentration was the same as before treatment. Thus schizophrenic patients have a great deal of 420 factor. Since the hemoglobin content of these patients was within normal range, this can be due only to the presence of other substances adsorbed on the hemoglobin that are bleached with ascorbic acid, perhaps adrenochrome or similar substances. The effect of the LSD experience upon this 420 factor is shown in Fig. 9.

FLUORESCENT SUBSTANCES IN ERYTHROCYTES

Acetone, which is a good solvent for adrenolutin, can be used as a solvent for adreno-lutin from biological material. When erythrocytes washed several times in saline are extracted with acetone, a fluorescence develops in the acetone which can be measured in the Farrand Recording Spectrofluorometer. The acetone precipitates the hemo-globin and leaves a clear supernatant which is filtered from the hemoglobin. Nine ml of acetone is added to 1 ml of erythrocyte suspension containing 1 ml of solution with saline or with ascorbic acid.

Adrenochrome has a fluorescence maximum at 480 when excited at 475 and at 400 in acetone. Adrenolutin has one major excitation maximum at 400 with fluores-cence maximum at 480.

When ascorbic acid is added to adrenochrome solutions in water, it is decolorized. According to LUND[27], adrenolutin is formed in the presence of alkali. However, this is not the case with ascorbic acid alone, since the colorless compound has a much higher fluorescence when excited at 475 and does not develop the characteristic
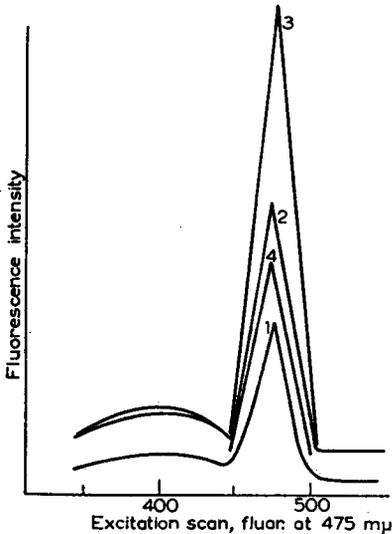

Fig. 10. Effect of ascorbic acid on adrenochrome fluorescence (1) 0, (2) 5, (3) 10, (4) 20 mg.
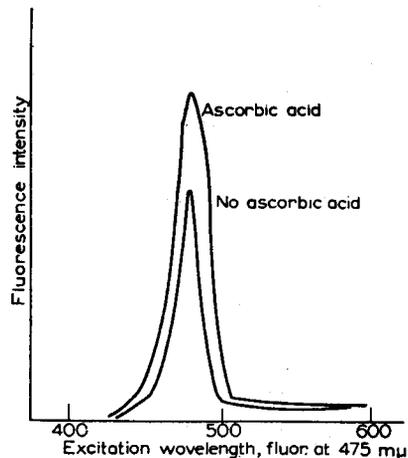
Fig. 11. Effect of ascorbic acid on fluorescence of schizophrenic erythrocyte extract.

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adrenolutin excitation maximum. It is more likely that leuco adrenochrome is formed. Sulfhydril compounds will also effect this transformation. The effect of various quantities of ascorbic acid upon a solution of adrenochrome is shown in Fig. 10.

Adrenochrome isonicotinic hydrazide also increases in fluorescence when treated with ascorbic acid but we have not found any other substance as yet which will do so. On the contrary, ascorbic acid quenches the fluorescence of most fluorescent substances. There is an optimum concentration of ascorbic acid for pure adrenochrome which is about 10 mg per ml of solution.

When erythrocytes are extracted with acetone, they also develop the same excitable maxima as are present for adrenochrome. The addition of ascorbic acid increases the fluorescence of schizophrenic erythrocytes but decreases the fluorescence of non-schizophrenic erythrocytes. This may be seen in Table III and Fig. 11.

TABLE III

EFFECT OF ASCORBIC ACID ON FLUORESCENCE FACTOR IN ERYTHROCYTES,
EXCITATION AT 475, FLUORESCENCE AT 480

Diagnostic group	Number	Mean fluorescence	Range
Schizophrenic			
No ascorbic acid	33	0.82	0.38 to 1.12
With ascorbic acid	13	1.08	0.66 to 1.70
Surgical and normal			
No ascorbic acid	11	1.04	0.82 to 1.40
With ascorbic acid	8	0.65	0.36 to 1.20

It will be seen that non-schizophrenic erythrocytes contain more fluorescent substances than do schizophrenic erythrocytes. However, after the addition of ascorbic acid, the schizophrenic erythrocytes contain more fluorescent substances.

These observations may be explained with the assumption that normal erythrocytes contain fluorescent substances similar in structure to adrenochrome but with higher initial fluorescence, perhaps leuco adrenochrome. Ascorbic acid quenches the fluorescence. However, schizophrenic erythrocytes contain adrenochrome. Thus, the initially lower fluorescence is markedly increased by the addition of ascorbic acid by its conversion into leuco adrenochrome.

Since adrenochrome or some of its derivatives show the increased fluorescence it is therefore possible that these are the substances present in the schizophrenic erythrocytes. However, I shall call these schizophrenic fluorescent factor (SFF) in contrast to the normal fluorescent factor (NFF) present in non-schizophrenic persons. None of the following substances show these maxima in acetone-tryptophan, indole acetic acid, eserine, and adrenochrome semicarbazide.

Apparently, there are at least two closely related substances derived from epinephrine. One of them is present in schizophrenic cells and may be responsible for the symptomatology of this illness. Preliminary calculation lead to the estimate that about 25 mg of SFF expressed as adrenochrome is present within the erythrocytes, in the body. The other substances, perhaps leuco adrenochrome or other derivatives as yet unknown, are present within the normal cell.

It is therefore possible that the disease schizophrenia is due to the overproduction

of adrenochrome within the erythrocyte, from which it is released slowly over long periods of time. This may be due to the increased production of adrenochrome, to the inability to convert it to non-toxic substances quickly enough, to some lack of absorptive ability of the schizophrenic erythrocyte, or to some increase in erythrocyte fragility. Most likely, schizophrenic erythrocytes contain an abnormal enzyme which is adaptive (perhaps taraxein), which transforms epinephrine into adrenochrome rather than into leuco adrenochrome or some similar non-toxic substance. It is not known whether leuco adrenochrome is less toxic than adrenochrome but this is under investigation.

SUMMARY

The relationship of epinephrine to mental disease, especially schizophrenia, is currently under investigation owing to the similarity in the structure of two oxidized derivatives, adrenochrome and adrenolutin, to some active indolic hallucinogens. Epinephrine may be metabolized *in vivo* in several ways: (1) by storage within cells and its gradual release unchanged, (2) by de-amination to aldehyde by amine oxidase, (3) by indolization to adrenochrome by phenolases, (4) by esterification with sulfate. In general, known metabolites from epinephrine account for a minor proportion of administered epinephrine using radio active tracers.

Adrenochrome has the following properties — (1) it interferes with carbohydrate metabolism *in vitro* by inhibiting consumption of oxygen in Warburg and by uncoupling oxidative phosphorylation, (2) it inhibits decarboxylation of glutamic acid by brain tissue, (3) it is antimitotic for cells *in vivo* and *in vitro* for mouse epidermis, and *in vitro* for L strain cells, (4) it blocks acetylcholine esterase *in vitro* and thus is cholinergic *in vivo*, (5) it increases EEG abnormality in humans when administered intravenously, and in cats when administered intraventricularly, (6) it has some effect on synaptic transmission of stimuli, and (7) it prevents muscle fatigue *in vitro*.

The question remains whether adrenochrome is present *in vivo* and if it is related to the schizophrenic psychosis. The conditions essential for its formation are present, *viz.* (1) a substrate, *i.e.* epinephrine, (2) oxidizing enzymes (auto-oxidation is unlikely owing to presence of glutathione, ascorbic acid and albumin in serum), *i.e.* cytochrome indophenol oxidase present in all cells, ceruloplasmin (a copper-containing oxidase), and taraxein (a psychotomimetic substance extracted from schizophrenic serum).

Indirect evidence for adrenochrome is obtained from the effect of epinephrine on the mitotic rate of the epidermis of mice, from toxicity of schizophrenic serum, and from delayed hemostatic action of epinephrine. Direct evidence is obtained by extracting adrenochrome from the brain of animals convulsed by increased oxygen.

Because of the psychological properties of adrenochrome and adrenolutin in humans, given orally and by vein, and in cats, administered intraventricularly, the relationship of these results to schizophrenia, either quantitatively or qualitatively, is interesting.

Evidence will be given to show the high affinity of adrenochrome for hemoglobin and for the presence of adrenolutin in schizophrenic red blood cells.

REFERENCES

[1] Z. M. BACQ, *J. Pharmacol. Exptl. Therap.*, 95 (1949) 1.
[2] W. A. BAIN, W. E. GAUNT and S. F. SUFFOLK, *J. Physiol.*, 91 (1937) 233.
[3] F. BISCHOFF AND C. L. GRAY, *Federation Proc.*, 15 (1956) 221.
[4] W. B. BULLOUGH, *J. Endocrinol.*, 8 (1952) 265.
[5] V. M. BUSCAINO, *Proc. 1st Intern. Congr. Neuropathol.*, (1952) 31.
[6] H. H. DE JONG, *Experimental Catatonia*, The Williams and Wilkins Co., Baltimore, 1945.
[7] A. DEROUAUX AND J. ROSKAM, *J. Physiol. (London)*, 108 (1949) 1.
[8] F. ELMADJIAN, *Hormones, Brain Function, and Behavior*, edited by H. HOAGLAND, Acad. Press Inc., New York, 1957.
[9] S. FEDOROFF, *J. Lab. Clin. Invest.*, 48 (1956) 55.

[10] J. FREDERIC, *Ann. N. Y. Acad. Sci.*, 58 (1954) 1085.

[11] Z. S. GERSHENOVICH, *Ukrain. Biokhim. Zhur.*, 27 (1955) 3.

[12] R. G. HEATH, S. MARTENS AND B. E. LEACH, *A.P.A. Regional Meeting*, Montreal, November, 1956.

[13] R. G. HEATH AND B. E. LEACH, *Changing Concepts of Psychoanalytic Medicine*, Grune and Stratton, Inc., New York, 1956.

[14] W. A. HIMWICH AND W. T. SULLIVAN, *J. Nervous Mental Disease*, 124 (1956) 21.

[15] A. HOFFER, *Meeting Boston Soc. Psychiat. and Neurol.*, March 21, 1957.

[16] A. HOFFER, *Hormones, Brain Function and Behavior*, edited by H. HOAGLAND, Acad. Press Inc., New York, 1957.

[17] A. HOFFER, *Tranquilizing Drugs*, edited by H. E. HIMWICH, *Publ. Assoc. Advance. Sci.*, No. 46, Washington, D.C., 1957.

[18] A. HOFFER, *J. Clin. Exptl. Psychopath. & Quart. Rev. Psychiat. Neurol.*, 18 (1957) 27.

[19] A. HOFFER, H. OSMOND AND J. SMYTHIES, *J. Mental. Sci.*, 100 (1954) 29.

[20] A. HOFFER AND M. KENYON, *A.M.A. Arch. Neurol. Psychiat.*, 77 (1957) 437.

[21] P. HOLTZ AND E. WESTERMANN, *Naturwissenschaften*, 43 (1956) 37.

[22] D. E. HUTCHEON, J. LOWENTHAL AND N. R. EADE, *Acta intern. pharmacodynamie*, 106 (1956) 90.

[23] B. E. LEACH AND R. G. HEATH, *A.M.A. Arch. Neurol. Psychiat.*, 76 (1956) 444.

[24] B. E. LEACH, M. COHEN, R. C. HEATH AND S. MARTENS, *A.M.A. Arch. Neurol. Psychiat.*, 76 (1956) 635.

[25] R. LETTRE, *Ann. N. Y. Acad. Sci.*, 58 (1954) 1085.

[26] D. W. LIDDELL AND H. WEIL-MALHERBE, *J. Neurol. Neurosurg. Psychiat.*, 16 (1953) 7.

[27] A. LUND, *Acta. Pharmacol. Toxicol.*, 5 (1949) 231.

[28] A. S. MARRAZZI, *Ann. N. Y. Acad. Sci.*, 66 (1957) 496.

[29] H. OSMOND AND J. SMYTHIES, *J. Mental. Sci.*, 98 (1952) 309.

[30] J. H. PARK, B. P. MERIWETHER AND C. R. PARK, *Federation Proc.*, 15 (1956) 141.

[31] J. H. PARK, B. P. MERIWETHER, C. R. PARK, S. H. MUDD AND F. LEPMANN, *Biochim. Biophys. Acta*, 22 (1956) 403.

[32] N. PAYZA, Personal communication, 1957.

[33] W. RAAB, *Advances in Cardiology*, S. Karger, New York, 1956.

[34] B. E. SCHWARZ, K. G. WAKIM, R. G. BICKFORD AND F. R. LICHTENHELD, *A.M.A. Arch. Neurol. Psychiat.*, 75 (1956) 83.

[35] A. G. SLOCOMBE, H. HOAGLAND AND L. S. TOZIAN, *Am. J. Physiol.*, 185 (1956) 601.

[36] V. SRINIVASAN, P. I. GEORGE AND D. V. S. REDDY, *Current Sci. (India)*, 22 (1953) 176.

[37] A. SZATMARI, A. HOFFER AND R. SCHNEIDER, *Am. J. Psychiat.*, 111 (1955) 603.

[38] H. WAELSCH AND H. RACKOW, *Science*, 96 (1942) 386.

[39] V. WOODFORD, *8th Scientific Session, Western Regional Group*, N.R.C., Canada, 1954.

DISCUSSION

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A proposito della relazione di HOFFER, il fatto che l'azione schizogena dell'adrenocromo non trovi conferma in ricerche di qualche altro A. è da ritenere probabilmente in dipendenza dalla circostanza che l'azione allucinogena dell'adrenocromo è dovuta (TAUBMANN) non alla detta sostanza ma a prodotti di disintegrazione di essa, Sulla natura di questi prodotti non è stato fatto alcun accertamento. C'è da ricordare la comparsa di 5–6 dioxindoli (RAPER) tra i prodotti di disintegrazione dell'adrenocromo.

Ma che sostanze a derivazione indolica possano avere importanza per la genesi della schizofrenia (visto che la LSD, come ha fatto notare BUSCAINO V.M. nel 1951, contiene un aggruppamento indolico, un aggruppamento chimico cioè presente anche nell'organismo umano) è dimostrato dalle ricerche fatte (1955, 1956) nella *Clinica neurologica di Napoli* (BUSCAINO, KEMALI ROMANO, BALBI). Risulta infatti accertato con·i metodi cromatografici un vero e proprio dismetabolismo indolico nelle orine e nel sangue di schizofrenici. I primi accertamenti documentano in schizofrenici, in contrasto con i controlli, la presenza tra l'altro di triptamine (enteramina o serotonina esclusa), la presenza di derivati ossindolici, la presenza di acido indolacetico e indolaceturico (derivati questi acidi dall'indoletilamina).

Questi reperti hanno un indubbio significato, quando si tengano presenti l'azione catatonigena (DE JONG) della indoletilamina e l'azione psicopatogena di triptamine (bufotenina, dietil- e dimetiltriptamina – secondo le ricerche per queste due ultime di SZARA –). Aggiunti poi agli altri reperti dismetabligeni accertati in schizofrenici (basi imidazoliché e basi xantiniche) confermano ancora una volta l'importanza, segnalata ed illustrata ormai da 25 anni da chi parla, delle tossicosi aminiche per la genesi delle sintomatologie schizofreniche e confusionali della patologia umana.