

# Some Relations Between Indoles and Psychiatry

Mark D. Altschule, M.D., and Zoltan L. Hegedus, Ch.E., M.S.

## Introduction

When clinicians encounter a new, or least previously unrecognized syndrome they may either content themselves merely with being able to recognize it, or they may want, in addition, to understand the mechanisms of its manifestations. In the latter case, they must look to other branches of knowledge for data to elucidate the clinical findings. This situation now obtains with respect to the clinical phenomenon of mental disorder produced by the ingestion of certain indoles.

It must not be concluded that all hallucinogenic substances are indoles. Although many belong to other chemical groups, the actions of the indoles are best understood and will be discussed here. The term "hallucinogenic" will be retained because it is generally used to designate the substances under discussion. However, in most cases feelings of depersonalization, illusions and delusions occur earlier and are more prominent than hallucinations.

There are now many biochemical studies which show that some indoles or their derivatives inhibit brain-tissue enzymes, including those that contain nicotinic acid (Allvisatos, et al.<sup>1</sup>; DeLaey, et al.<sup>2</sup>;

## The Role of Indoles

Hochstein and Cohen<sup>34</sup>). Some indoles are toxic to nerve cells in tissue culture (Silberberg<sup>5</sup>). The toxic effects of indoles on the brain in intact animals is evidenced by their induction of seizures (Feinberg and McCullough<sup>6</sup>). Hence there is good reason to study the possible role of indoles in clinical syndromes of brain dysfunction.

## Hallucinogenic Indoles

The indole hallucinogens most prominently in the public eye today are lysergic acid (Fig. 1B), and dimethyl tryptamine and its derivatives bufotenine (Fig. 1C) and psilocybin. However, harmine (Fig. 1D) and yohimbine (Fig. 2E) are also hallucinogens, the latter being closely related to and found in nature with reserpine (Fig. 2F).

The aminochromes, which are oxidized indoles derived from epinephrine and other catecholamines, are also under study as hallucinogens. One of them, adrenochrome (Fig. 1A), has received most attention owing to its central position in the adrenochrome hypothesis of schizophrenia (Osmond and

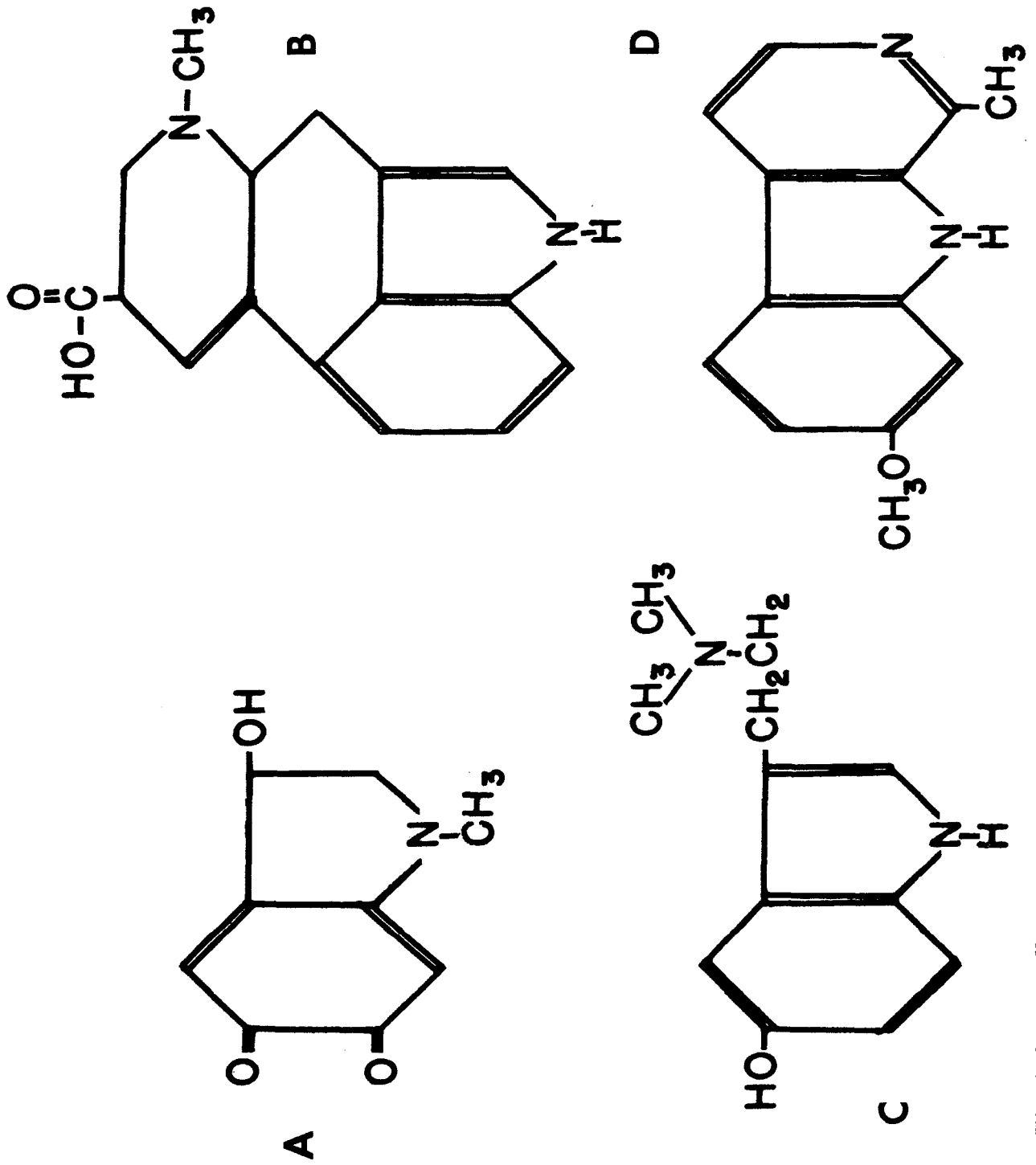


Fig. 1. Some Hallucinogenic Indoles; A. Adrenochrome; B. Lysergic acid; C. Bufotenine; D. Harmine

Smythies<sup>7</sup>; Hoffer, et al.<sup>8</sup>).

The hallucinogenic indoles occur widely distributed in plants and also are found in some animals. What purpose is served in these organisms by their changing tryptophan and tyrosine into these indoles is completely unknown. However, the phenomenon of their occurrence in many biologic organisms raises the possibility of their synthesis in the tissues of man. If this does occur, additional questions arise:

- 1) Can they be present in human tissues, in sufficiently high concentrations to cause symptoms?
- 2) If the answer is affirmative, what circumstances lead to this occurrence?
- 3) Can they be detected in blood or urine?

#### Endogenous Indoles

The available clinical data establish the psychosis-inducing effects of ingested indoles. However, the data that might define the role, if any, of *endogenous* indoles, is fragmentary. For example, recent work by excellent biochemists who studied bufo-tenine in human urine, showed that this hallucinogenic indole occurs in the urine of patients diagnosed as having schizophrenia (Tanimukai, et al.<sup>9</sup>). Another hallucinogen, harmaline (a close relative of harmine), has also been discussed as a possible cause of endogenous psychosis (Mclsaac<sup>10</sup>).

The suggestion has been made that this hallucinogen develops in humans owing to an abnormal metabolism of the pineal-gland hormone melatonin. Although harmaline is readily made from melatonin in

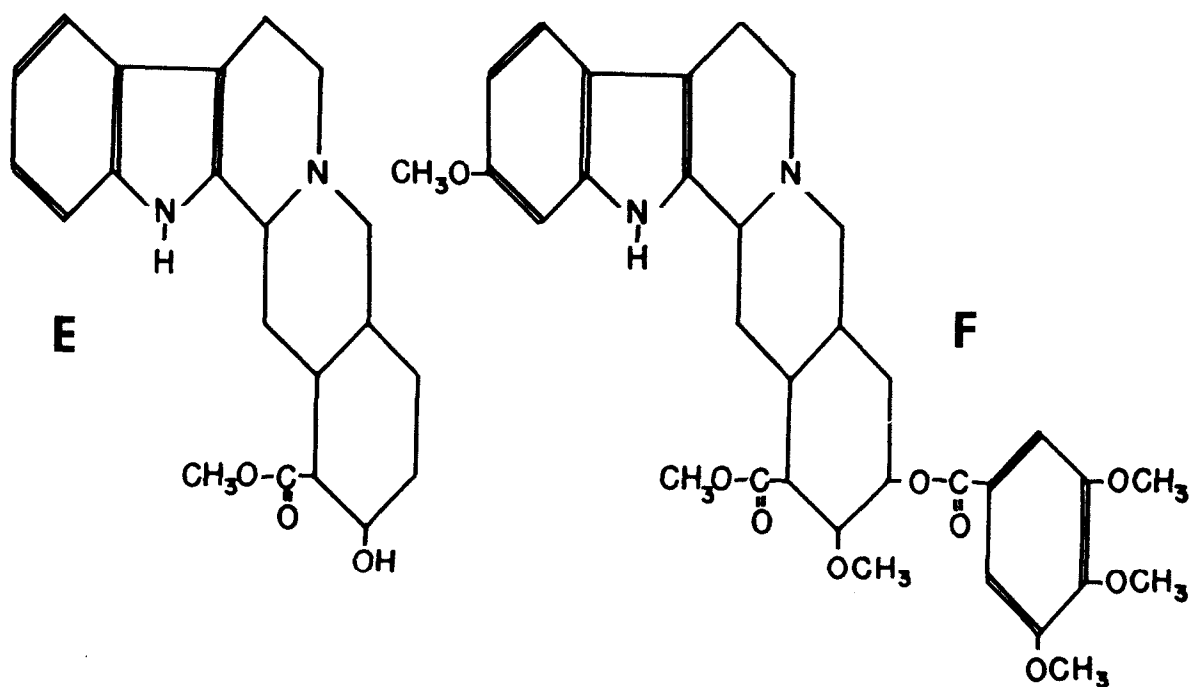


Fig. 2. Some Indole Alkaloids: E. Yohimbine; F. Reserpine.

## RELATIONS BETWEEN INDOLES AND PSYCHIATRY

vitro, there is as yet no evidence of this transformation in vivo.

We have studied the possibility of the transformation of catecholamines in human blood and plasma to hallucinogenic indoles or their derivatives (Hegedus and Altschule<sup>11,12,13,14,15,16</sup>). The studies were simulated by the fact that:

- (a) epinephrine plays an important part in stress reactions,
- (b) a relation between epinephrine-derived indoles and endogenous psychosis has been postulated (Osmond and Smythies<sup>7</sup>; Hoffer et al.<sup>8</sup>)

Our studies have followed two directions:

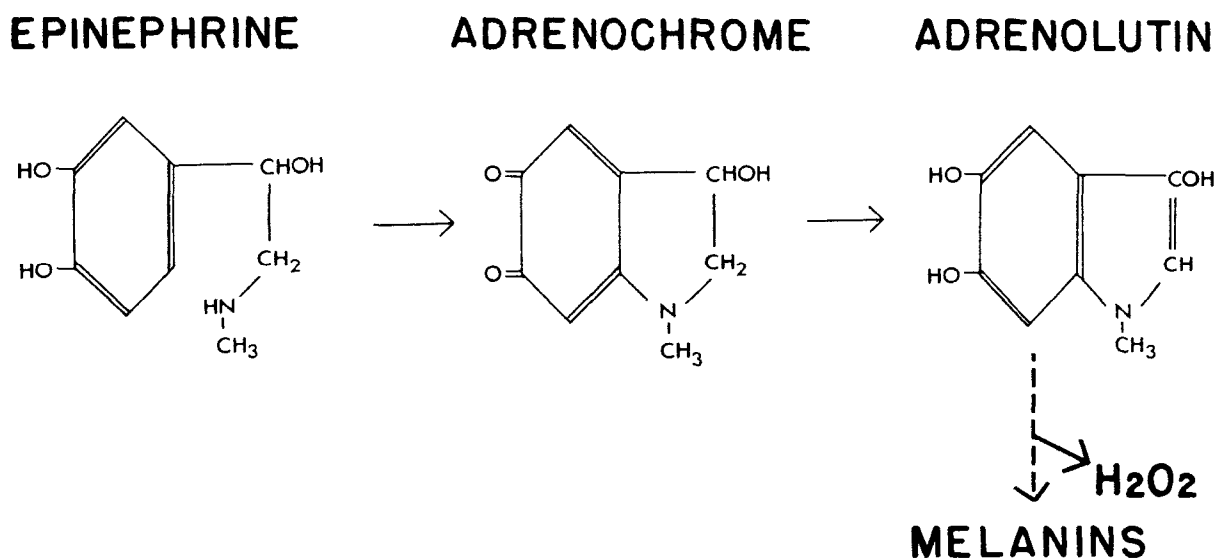
- (1) proving or disproving the transformation of catecholamines to indoles in living tissues,
- (2) searching for these indoles or their derivatives in the blood and urine of patients with endogenous psychoses.

The first approach has already yielded convincing data (Hegedus and Altschule<sup>13</sup>).

Epinephrine incubated in blood plasma can follow the pathway that leads to the formation of aminochromes and their derivatives (Fig. 3). It should be noted that the transformation of one catecholamine, dopamine, into indoles and then melanin in tissues is widely accepted as established, but this has not been true in the case of epinephrine.

However a few years ago Kaliman,<sup>17</sup> and Kaliman and Koshlyak<sup>18</sup> showed that various rat and rabbit tissues cyclize epinephrine. Pastan, et al.<sup>19</sup>, showed the same with respect to dog and calf thyroid tissue. Axelrod<sup>20</sup> showed that most cat tissue cyclize epinephrine to adrenochrome. Sweat and Bryson<sup>21</sup> showed that rat adrenal tissue has the same action. The reaction is catalyzed by an enzyme, often called adrenalin oxidase. Axelrod<sup>20</sup> showed that human tissue contains the enzyme.

It is also evident from many studies that animal and human blood plasma or serum



**Fig. 3. Transformation of Epinephrine to Adrenochrome, then Adrenolutin, and then Melanin.**

can also transform epinephrine into an indole, adrenochrome (Angel, et al.<sup>2</sup>; Axel-rod<sup>2m</sup>; Billiewicz-Stankiewicz, et al.<sup>23</sup>; Gel-ler, et al.<sup>24</sup>; Hoffer<sup>25</sup>; Hoffer and Kenyon<sup>26</sup>; Leach and Heath<sup>27</sup>; Leach, et al.<sup>28</sup>; Payza and Hoffer<sup>29</sup>; Payza and Zaleschuk<sup>30</sup>; Yu-wiler, et al.<sup>31</sup>). In fact this may be the only pathway available to epinephrine in the blood, because human blood contains no O-methyltransferase, an enzyme required for metabolizing epinephrine to vanillyl-man-delic acid (Berthiaume, et al.<sup>32</sup>; Cohen, et al.<sup>33</sup>).

Although adrenochrome can be forced in human blood, there is little likelihood of its being detected there. When adrenochrome is incubated in human blood or in blood plasma it rapidly changes to adrenolutin (Hegedus and Altschule<sup>1115</sup>).

Thus Fig. 4 shows A, the spectrum of adrenochrome dissolved in blood plasma. It rapidly changes to B, a curve almost identical with D, the curve of adrenolutin dissolved in blood plasma. The reaction is catalyzed by an enzyme.

The adrenolutin then changes further to C, an unidentified substance related to rheomelanin which in turn changes to rheomelanin. Epinephrine, adrenochrome and adrenolutin, when incubated individually in human heparinated or oxalated blood plasma or blood all change to soluble mela-nins that have similar properties (Hegedus and Altschule<sup>1315</sup>). They appear to be soluble in blood plasma for a long time. The name rheomelanins has been given to these plasma-soluble compounds. They may represent transport forms of melanin.

The inherent toxicity of some indoles for brain was discussed previously. Some indoles (including the aminochromes) may be toxic in another way. All indoles that have free OH side groups at position 5 and 6 readily polymerize to form melanin. Hydrogen peroxide is released during this process (Fig. 3). Hydrogen peroxide damages the lipids of cells.

The blood contains two enzymes, cata-lase and

glutathione reductase, which destroy hydrogen peroxide. The brain is deficient in these enzymes and hence is very vulnerable to the damage produced by the hydrogen peroxide that may be formed when indoles polymerize to melanin (Cohen and Hochstein<sup>34</sup>).

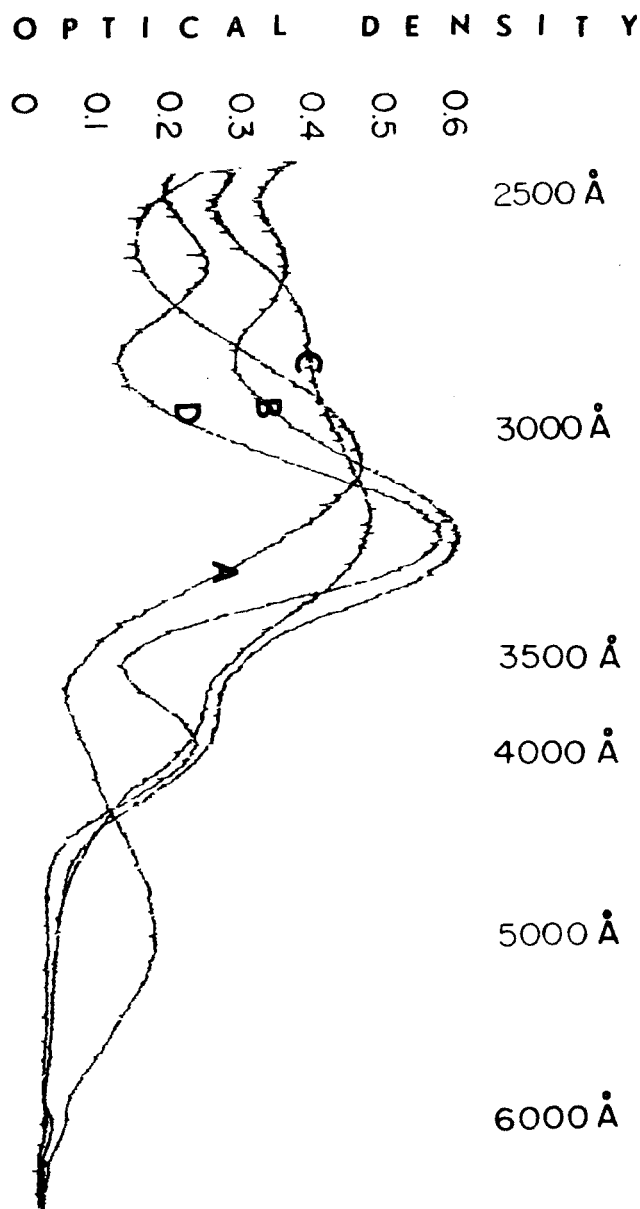


Fig. 4. Spectra showing transformation in human plasma of added Adrenochrome (A) to Adrenolutin (B) and then to unknown intermediate of Rheomelanin (C). Curve (D) is that of Adrenolutin freshly added to plasma.

There is good evidence that this polymerization results in damage to erythrocytes (Hegedus and Altschule<sup>15,16</sup>; Hochstein and Cohen<sup>3</sup>) and also brain tissue (Hochstein and Cohen<sup>4</sup>). In fact, in vitro, the hydrogen peroxide damages the melanin also, producing a pale brown instead of the usual deep brown or black form (Fig. 5), (Swan and Wright<sup>35,36</sup>).

**Toxic Indoles**

It is evident that toxic indoles can form during the metabolism of epinephrine in at least some human tissues. The next question to be answered is whether these indoles or their derivatives can be detected in human blood or urine. At the moment no firm answer can be given, although suggestive evidence has been accumulated (Altschule<sup>37</sup>; Koch<sup>38</sup>; Veech, et al.<sup>39</sup>). The brief existence of the epinephrine-derived aminochromes in blood plasma (Hegedus and Altschule<sup>11</sup>) suggests that it might be useful to measure some other manifestation of their possible presence. One approach might be to measure the amount of circulating rheomelanins. Efforts in this direction are in progress. However, the specificity

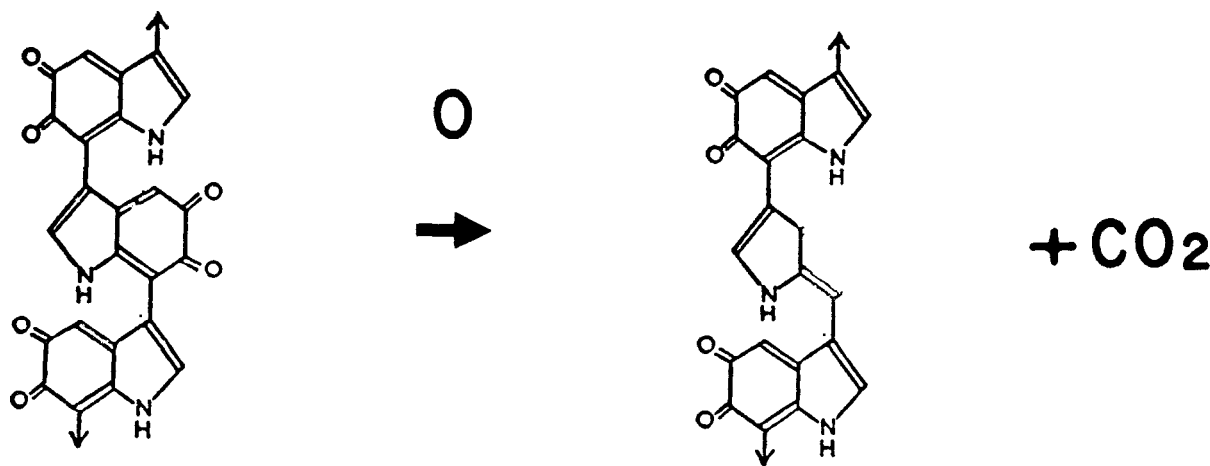
of any such measurement is impaired by the fact that norepinephrine, dopa and dopamine also give rise to rheomelanins in the blood plasma (Hegedus and Altschule<sup>14</sup>).

Another approach currently in use here was suggested by the fact that aminochromes damage red blood cells, producing increased fragility (Hochstein and Cohen<sup>3</sup>) and also the probable formation of porphyrins (Hegedus and Altschule<sup>15</sup>).

It is known that the erythrocytes of schizophrenic patients are abnormally fragile by some tests (Hoffer<sup>40</sup>). Our studies



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**Fig. 5. Normal Melanin (on left) showing its structure as an Indole Polymer. At right is incomplete melanin formed in the presence of Hydrogen Peroxide.**



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suggest that schizophrenic  
patients' blood forms  
porphyrins abnormally

easily during the formation of rheomelanins (Hegedus and Altschule<sup>16</sup>).

This phenomenon is now being studied by means of another approach (Altschule and Hegedus<sup>41</sup>) and preliminary results indicate that the blood of patients with endogenous psychoses, or the close blood relatives of these patients, form porphyrins at an abnormally rapid rate when mixed with

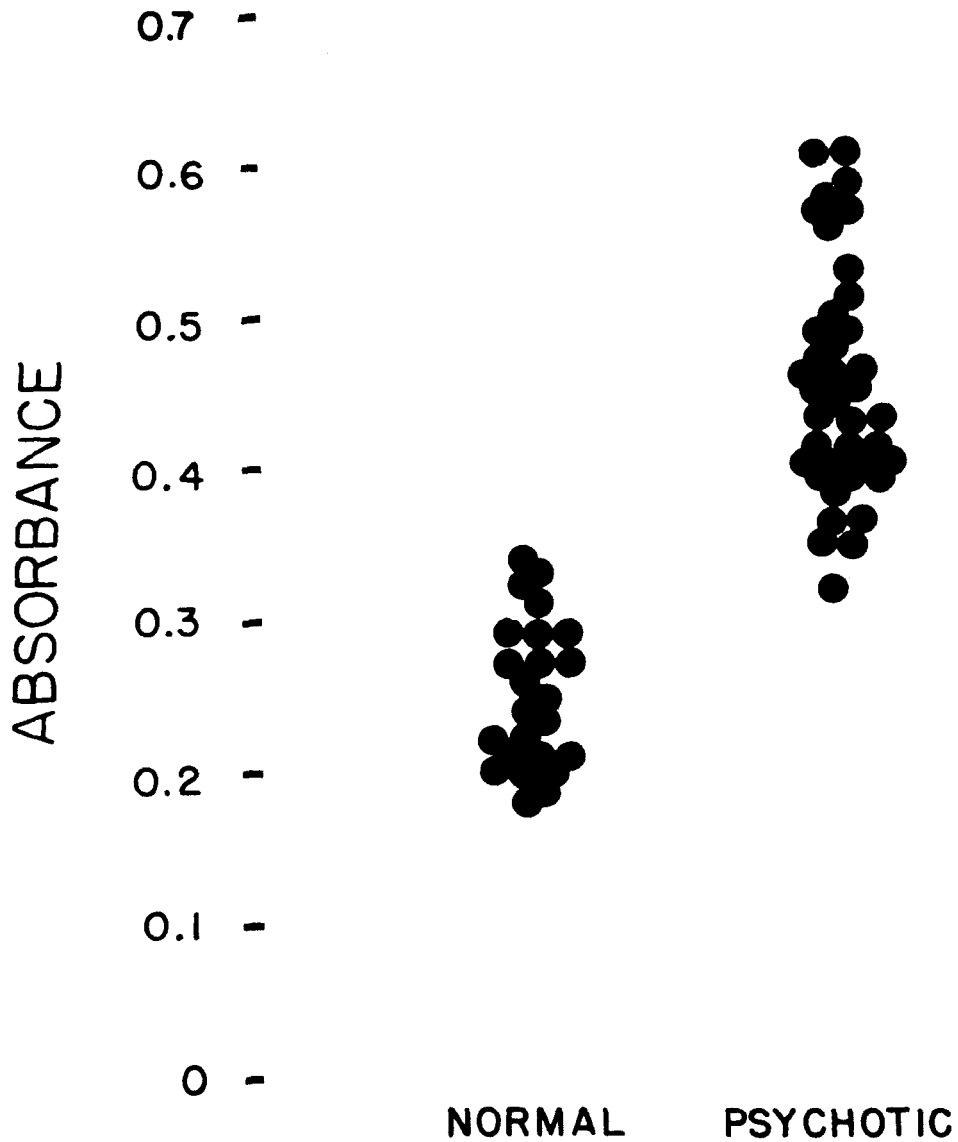


Fig. 7. Results of the Bisulfite test.

a porphyrin-inducing substance such as sodium bisulfite (Fig. 7). This test is far from specific because other factors, e.g., tocopherol deficiency, hemolytic disorders, may have the same effects.

**The Indole Pathway**

It is now evident that epinephrine can be metabolized in humans via two pathways (Fig. 6). One, the VMA pathway, perhaps accounts almost entirely for what normally happens to epinephrine in the body.

The other, the indole pathway, ordinarily accounts for relatively little of what happens to epinephrine. The circumstances that lead to suppression of the first and potentiation of the second are largely unknown. Ascorbic acid blocks the indole pathway but corticosteroids potentiate it (Sweat and Bryson<sup>21</sup>). Cyclopropane may block the VMA pathway (Gardier, et al.<sup>42</sup>) and thereby may enhance the indole pathway. It is highly probable that genetic factors are important as regards the potential activity of the indole pathway.

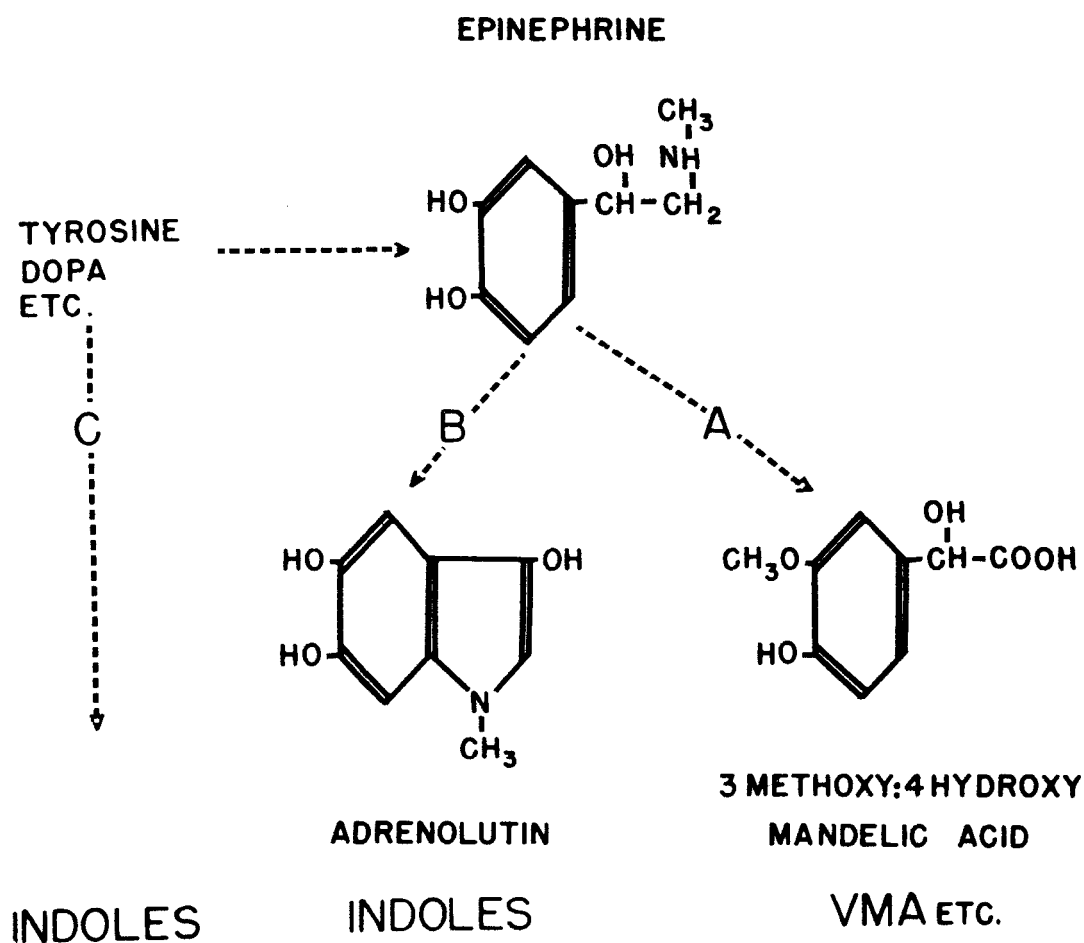


Fig. 6. The pathways of degradation of Epinephrine and its precursors.



**Summary**

Hallucinogenic indoles are formed by a number of plant and animal species. Their role in metabolism is unknown.

Recent studies show that the indole pathway of epinephrine metabolism is available in humans. The pathway comprises products and processes that are toxic to brain and to blood cells.

It is evident that in humans epinephrine has two available pathways of degradation:

- (1) the VMA pathway
- (2) the indole pathway

The first ordinarily predominates. The factors that might lead to the dominance of the second have been studied incompletely.

**APPENDIX**

**Method of Measuring Bisulfite Susceptibility of Red Blood Cells**

The procedure is carried out in a space with no direct sunlight and away from strong artificial illumination.

1. Collect blood with heparin as anticoagulant. Place in refrigerator if not used immediately.
2. Place 5 ml. of blood in a 50 ml. Erlenmyer flask. Add 50 mg. sodium bisulfite.
3. Place in horizontal shaker and shake for 20 minutes precisely at room temperature (20°—25° C).
4. Stop shaker and pour in 15 ml. freshly prepared 10% trichloroacetic acid solution.
5. Shake for two additional minutes.
6. Filter through Whatman No. 42 fluted filter paper.
7. Collect the first 10 ml. of filtrate.
8. Dilute with equal volume of distilled water.
9. Read absorbance in spectrophotometer at 395 mμ., using water as the blank.

**REFERENCES**

1. Allivisatos, S. G. A., Mourkides, G. A. and Jibril, A.: Enzymic reactions of indoles with coenzyme. I. *Nature* 186:718, 1960.
2. DeLaey, P., Hoft, C., Timmerman, J. and Snoeck, J.: Biochemical aspects of the Hart-nup disease. II. Some observations on rats about tryptophan metabolism. *Ann. Paediat.* 202:17, 1964.
3. Hochstein, P. and Cohen, G.: The cytotoxicity of melanin precursors. *Ann. N.Y. Acad. Sci.* 100:876, 1963.
4. Hochstein, P. and Cohen, G.: The inhibitory effects of quinones and dihydric phenols on glucose metabolism in subcellular systems of brain. *J. Neurochem.* 5:370, 1969.

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## RELATIONS BETWEEN INDOLES AND PSYCHIATRY

5. Silberberg, D. H.: Phenylketonuria metabolites in cerebellum culture morphology. *Arch. Neurol.* 17:524, 1967.
6. Feinberg, I. M. and McCullough, W. S.: Site of action of indole in the central nervous system. *Proc. Soc. Exper. Biol. and Med.* 56: 1963, 1944.
7. Osmond, H. and Smythies, J.: Schizophrenia: a new approach. *I. J. Ment. Sci.* 98:309, 1952.
8. Hoffer, A., Osmond, H. and Smythies, J.: Schizophrenia: A new approach. II. Result of a year's research. *J. Ment. Sci.* 100:29, 1954.
9. Tanimukai, H., Grinther, R., Spaide, J., Bueno, J. R. and Himwich, H. E.: Occurrence of bufotenine (5-hydroxy-N-dimethyltryptamine) in urine of schizophrenic patients. *Life Sciences* 6:1697, 1967.
10. Melsaac, W.: A biochemical concept of mental disease. *Postgrad. Med.* 30:111, 1961.
11. Hegedus, Z. L. and Altschule, M. D.: Studies on aminochromes. I. Behavior of adrenochrome added to human plasma. *Arch. Internat. Bio-chim. Physiol.* 75:690, 1967.
12. Hegedus, Z. L. and Altschule, M. D.: Studies on aminochromes. II. Behavior of added adrenolutin in blood of normal and psychotic persons. *Arch. Internat. Biochim. Physiol.* 75: 697, 1967.
13. Hegedus, Z. L. and Altschule, M. D.: Studies on aminochromes. III. Transformation of epinephrine, adrenochrome and adrenolutin into plasma-soluble melanins during incubation in human blood plasma. *Arch. Biochem. Biophys.* 126:388, 1968.
14. Hegedus, Z. L. and Altschule, M. D.: Studies on rheomelanins. I. The formation of rheo-melanins in human plasma from catecholamines, from L-dopa and from some of their derivatives. *Arch. Internat. Physiol. Biochim.* (in press).
15. Hegedus, Z. L. and Altschule, M. D.: Studies on aminochromes. IV. Hemolysis associated with the transformation of epinephrine, adrenochrome and adrenolutin into rheomelanins in human whole blood. *Arch. Internat. Pharma-codyn.* (in press).
16. Hegedus, Z. L. and Altschule, M. D.: Studies on aminochromes. V. Excessive hemolysis associated with the formation of rheomealanins during incubation of adrenochrome and adrenolutin in the bloods of chronic schizophrenic patients. *Arch. Internat. Pharmacodyn.* (in press).
17. Kaliman, P. A.: Enzymic oxidation of adrenaline, noradrenaline, and tyramine in the liver and heart of rabbits. *Biokhimiya* 26:284, 1961 (*Chem. Abst.* 55:16732, 1961).
18. Kaliman, P. A. and Koshlyak, T. V.: Adrenaline oxidation on the tissues of white rats. *Biokhimiva* 26:729, 1961 (*Chem. Abstr.* 55: 27582, 1961).
19. Pastan, I., Herring, B., Johnson, P. and Fields, J. B.: Studies on the mechanism by which epinephrine stimulates glucose oxidation in the thyroid. *J. Biol. Chem.* 237:287, 1962.
20. Axelrod, J.: Enzymatic oxidation of epinephrine to adrenochrome by the salivary gland. *Biochem. et Biophys. Acta* 85:147, 1964.
21. Sweat, M. L. and Bryson, M. J.: Stsroid 11-B oxygenation, ascorbic acid, epinephrine and adrenochrome interrelations in the adrenal gland. *Endocrinology* 76:773, 1965.
22. Angel, C, Leach, B. E., Martens, S., Cohen, M. and Heath, R. G.: Serum oxidation tests in schizophrenic and normal subjects. *Arch. Neurol. Psychiat.* 78:500, 1957.
23. Billiewicz-Stankiewicz, J., Szczekala, Z. and Tyburczyk, W.: Beeinflusse ung der "Adrenalin-oxydasen" des Blutplasmas in vivo durch bio-gen Monamine und Neuropharmaka. *Experientia* 20:85, 1964.
24. Geller, E., Eiduson, S. and Yuwiler, A.: Oxidation of p-phenylenediamine and adrenaline in enzymic and copper-catalvzed reactions. *J. Neurochem.* 5:73, 1959.
25. Hoffer, A.: Ceruloplasmin, adrenaline oxidase and schizophrenia. *Dis. Nerv. Syst.* 26:25, 1965.
26. Hoffer, A. and Kenyon, M.: Conversion of adrenaline to adrenolutin in human blood serum. *Arch. Neurol. and Psychiat.* 77:437, 1957.
27. Leach, B. and Heatii, R. G.: The in vitro oxidation of epinephrine in plasma. *Arch Neurol, and Psychiat.* 76:444, 1956.
28. Leach, B. E., Cohen, M., Heath, R. G. and Martens, S.: Studies on the role of Ceruloplasmin and albumin in adrenaline metabolism. *Arch. Neurol, and Psychiat.* 76:635, 1956.
29. Payza, A. N. and Hoffer, A.: Study of adrenaline oxidation by human plasma. *Bull. Fac. Med. Istanbul* 22:1096, 1959.
30. Payza, A. N. and Zaleschuk, J.: The properties of human plasma p-phenylenediamine oxidase. *Bull. Fac. Med. Istanbul* 22:1523, 1959.
31. Yuwiler, A., Jenkins, I. M. and Dukay, A.: Serum oxidase tests and schizophrenia. *Arch. Gen. Psychiat.* 4:395, 1961.
32. Berthiaume, M., Leduc, J. and DTorio, A.: Metabolism of dl-epinephrine-beta-C" in plasma of schizophrenics. *Arch. Gen. Psychiat.* 2: 468, 1960.
33. Cohen, G., Holland, B. and Goldenberg, M.: The stability of epinephrine and arerenol (norepinephrine) in plasma and serum. *Arch. Neurol, and Psychiat.* 80:485, 1958.
34. Cohen, G. and Hochstein, P.: Enzymatic mechanisms of drug sensitivty in brain. *Dis. Nerv. Syst.* 24 Supp.:44, 1963<sup>^</sup>

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## SOME RELATIONS BETWEEN INDOLES AND PSYCHIATRY'

## REFERENCES continued

35. Swan, G. A. and Wright, D.: A study of the evolution of carbon dioxide during melanin formation, including the use of 2-(3:4-dihydroxy-phenyl) [1-<sup>14</sup>C]- and 2-(3:4-dihydroxy-phenyl) [2-<sup>14</sup>C]-ethylamine). *J. Chem. Soc.* 381, 1954.
36. Swan, G. A. and Wright, D.: A study of melanin formation by the use of 2-(3:4-dihydroxy [3-<sup>14</sup>C] phenyl)K and 2-(3:4-dihydroxy [4-<sup>14</sup>C] phenyl)-, and 2-(3:4-dihydroxy [5-<sup>14</sup>C] phenyl-ethylamine). *J. Chem. Soc.* 1549, 1956.
37. Altschule, M. D.: Preliminary observations on the measurement of amiochromes in the blood. Walaas, O. (Ed.): *Molecular Basis of Some Aspects of Some Mental Activity, Volume 2.* London, Academic Press, 1967.
38. Koch, E.: The in vivo detection of some oxidation products of adrenalin and noradrenalin (coming from adrenochrome and noradreno-chrome by fluorimetric, spectrophotometric and paper chromatographic analysis). *Internat. J. Neuropsych.* 2:227, 1966.
39. Veech, R. L., Bigelow, L. B., Denckla, W. D. and Altschule, M.D.: Urinary aminochromes in schizophrenia. *Arch. Gen. Psychiat.* 5:127, 1961.
40. Hoffer, A.: Erythrocytes from schizophrenic patients. *Dis. Nerv. Syst.* 20:87, 1959.
41. Altschule, M.D. and Hegedus, Z. L.: Sensitivity of erythrocytes to porphyrin producing effect of bisulfite. In preparation, 1970.
42. Gardier, R. W., Endahl, G. L. and Hamelberg, W.: Cyclopropane: effect on catecholamine biotransformation. *Anesthesiology* 28:677, 1967.

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