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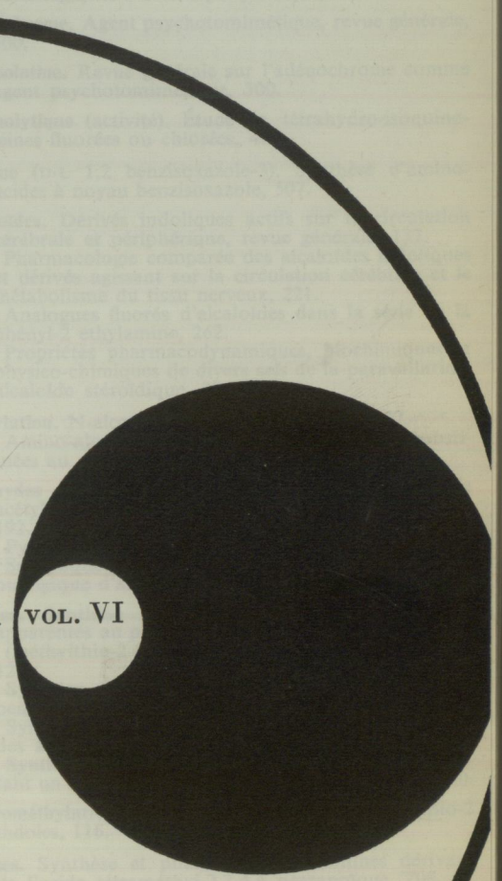

TABLES MATIÈRES ET AUTEURS - 1971 VOL. VI

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Adrenochrome as a psychotomimetic agent. A review of the literature(*)

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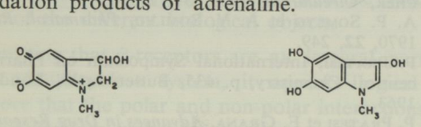
The potential physiological importance and pharmacological activity of catecholamine oxidation products, such as adrenochrome **1**, has attracted the attention of research workers for many years. However, it is only in recent years that pure and stable samples of these compounds have become readily available and this has facilitated the development of pharmacological work in this field. However unless certain precaution are taken, adrenochrome **1**, prepared by the usual procedures, will contain variable amounts of its rearrangement product adrenolutin **2**, insoluble melanin-like products and some residual silver (1).

In instances where solutions of oxidised adrenaline **3** have been used for pharmacological studies, without preliminary isolation of adrenochrome **1**, some of the results obtained may be open to question since such solutions probably contained some unchanged adrenaline, as well as other unidentified oxidation products of adrenaline.



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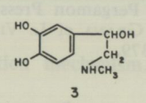

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Fig. 1.

A study was carried out by HEACOCK *et al.* in 1963 on the stability of adrenochrome in the dry state and in solution and on the purity of various commercial samples of this compound. The results reported by these authors indicated that caution should be employed when interpreting results of biological studies using either adrenochrome samples that are more than one year old, or some of the commercially available samples of this substance (2). It was further pointed out that pharmacological results could be invalidated if the adrenochrome solutions being examined were contaminated by trace quantities of metallic ions (2).

KISCH was one of earlier workers to be interested in the physiological activity of « oxidised adrenaline », which he referred to in 1930 as « omega » substance (3). The possible pharmacological role of « omega », now known to be adrenochrome, was later considered in detail by KISCH (4) and BACQ (5). The general pharmacology of adrenochrome has been reviewed by several workers including : KISCH (4), MARQUARDT (6), BACQ (5), TATAI (7), SOBOTKA *et al.* (8), HOFFER (9), and HOFFER and OSMOND (10).

The psychotomimetic effects ascribed to adrenochrome and the possible role of this compound in the aetiology of some forms of mental illness, particularly schizophrenia, have been the subjects of some controversy since the adrenochrome hypothesis of schizophrenia was originally proposed by HOFFER, OSMOND and SMYTHIES in 1954 (11). This hypothesis resulted in part from the suggestion made two years earlier by OSMOND and SMYTHIES that schizophrenia might result from an aberration in the normal metabolism of adrenaline in the body resulting in the formation *in vivo* of a psychotoxic metabolite of adrenaline (12). OSMOND and SMYTHIES referred to this hypothetical substance as « M-substance » since it was considered to have « mescaline-like » physiological activity (12). These authors were impressed with the relative similarity of the chemical structures of adrenaline and mescaline and there appeared to be some reasonable possibility that the unknown adrenaline derivative might be endowed with mescaline-like psychotoxic activity (12). In the later paper HOFFER *et al.* hypothesised that adrenochrome was a suitable candidate for « M-substance » (11). This suggestion was based on the results of self-administration of adrenochrome and on reports that psychotic reactions had occasionally resulted when « deteriorated » or « pink » adrenaline was used in anesthesia or by chronic asthma sufferers (cf. 10, 11). OSMOND and HOFFER later documented a specific case in which one subject experienced a prolonged psychotic reaction after inhaling a « coloured » adrenaline solution for a month (13). In 1957 HOFFER reported that adrenolutin, in doses of 25-50 mg, also produced psychological changes in human volunteers (9, 10, 14-16). MELANDER and MARTENS also showed that adrenolutin at a dose level of 100 mg produces catatonia in cats (17).

The basic assumptions upon which the adrenochrome hypothesis of schizophrenia are based, and which would have to be proved to be true before

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the hypothesis could be accepted are : (*i*) adrenochrome (or some readily derivable compound, such as adrenolutin) is psychotomimetic in man; (*ii*) adrenochrome and/or adrenolutin could be metabolites of adrenaline in man under certain circumstances, and (*iii*) adrenochrome formation and metabolism is disturbed in schizophrenia [cf. HOFFER and OSMOND (10), HOFFER (18), OSMOND and HOFFER (19)]. With reference to the last point HOFFER has suggested that adrenochrome is a normal metabolite of adrenaline and that it can be metabolised in two ways. One pathway leads to the formation of adrenolutin **2** (*), which is considered to be a toxic substance and the other pathway leads to the production of 5,6-dihydroxy-*N*-methylindole **5** which is reported to be non-toxic (18).

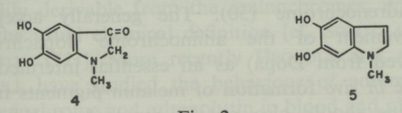

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Fig. 2.

Schizophrenia results when the normal balance between these two pathways is upset (18). There is evidence to suggest that two such metabolic pathways exist in certain animals for adrenochrome, one involving rearrangement to adrenolutin **2** and the other reduction, leading to the formation of 5,6-dihydroxy-*N*-methylindole **5**. As a result of studies involving the use of labeled adrenochrome, NOVAL *et al.* reported in 1962 that adrenochrome **1** is metabolised in rats to give what is probably a sulphate conjugate of adrenolutin (this product is highly fluorescent and relatively unstable) and two derivatives of 5,6-dihydroxy-*N*-methylindole, probably sulphate and glucuronide conjugates (21). Similar products can also be detected in the urine of rats which have been fed adrenolutin or 5,6-dihydroxy-*N*-methylindole in place of adrenochrome (21). These findings effectively substantiated the earlier work of FISCHER and LECOMTE (22); BACQ, FISCHER and LECOMTE (23); and FISCHER and LECOMTE (24). However both NOVAL *et al.* (21) and the earlier Belgian workers (22, 23, 24) found that there were certain species differences. For instance FISCHER and LECOMTE reported that in the cat and the dog much of the administered adrenochrome was excreted unchanged, whilst in rabbits the man product was adrenolutin, both free and as a sulphate conjugate (24). SCHAYER and SMILEY also reported that adrenochrome was metabolised by rats to an unstable yellow pigment (25). It is most probable however that extensive decomposition of this pigment occurred in the solvent systems used during the course of chromatographic investigations [cf. NOVAL *et al.* (21)].

The adrenochrome hypothesis of schizophrenia is discussed at length in a series of publications by HOFFER and OSMOND (10, 11, 14-16, 18, 19, 26-30). Some workers, including BENJAMIN (31), SMYTHIES (32, 33), KETY (34) and SOURKES (35, 36), have however been critical of this hypothesis.

HOFFER *et al.* in 1954 were the first to report that adrenochrome gave rise to psychotomimetic effects in man (11). These workers observed effects from doses (s.c. or i.v.) in the 0.5 to 10 mg range including marked effects from doses as low as 0.5 mg. In the same year RINKEL *et al.* reported that adrenochrome monosemicarbazone **6** does not produce behavioural changes in man (37). RINKEL *et al.* (1954) concluded that the toxic factor in « oxidised » adrenaline was not adrenochrome, but some ill-defined further oxidation product of adrenochrome known as « adrenoxine » and originally described by HEIRMANN in 1937 (38) [cf. MARQUARDT (39)]. However, there is no evidence that adrenochrome is regenerated from its monosemicarbazone *in vivo*. In fact, little work appears to have been carried out on the metabolism of adrenochrome monosemicarbazone in animals or in man. Over twenty years ago FISCHER and LECOMTE reported that in man about 20-30 % of the semicarbazone is excreted unchanged, and whilst there was some evidence for conjugate formation, another 20 % was excreted as an indole derivative which had lost its semicarbazone moiety (40). More recently it has been reported by SOHLER *et al.* that in rats at a dose level of 10 mg/kg, approximately half the administered dose could be accounted for by urinary excretion within 6 hours of administration (41). Tracer studies indicated that 85-90 % of the urinary product was unchanged adrenochrome monosemicarbazone **6**. The remaining 10-15 % consisted of three minor metabolites, one was not identified and the others were considered to be the sulphate ester of 5-amino-6-hydroxy-*N*-methylindole **7** and the zwitterionic indole compound **8**, which retains the semicarbazide function [SOHLER *et al.* (41)].

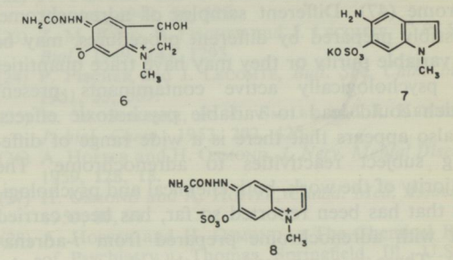

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Fig. 3.

RINKEL and SOLOMON have reported on unsuccessful attempts to demonstrate the psychotomimetic effects of free adrenochrome in man (42). SCHWARZ *et al.* reported that doses of 50-75 mg of adrenochrome produced behavioural effects in their subjects (43). In 1957 TAUBMANN and JANTZ reported that they observed definite behavioural changes from sublingual doses of 3 mg of the samples of adrenochrome available to them (44). However, these

(*) Although adrenolutin is usually depicted as a 3,5,6-trihydroxyindole derivative, it exists, in the solid state at least, mainly in the keto form (i.e. **4**) (20).

authors believed that the psychotoxic agent was probably not adrenochrome, but a small quantity of a very active impurity or decomposition product of adrenochrome (44). SMYTHIES has also referred to unpublished and essentially negative results of attempts by HEATH and PFEIFFER to obtain psychotomimetic effects from adrenochrome (33).

The most definitive studies on the psychotomimetic properties of adrenochrome in man, which have been carried out so far are those of GROF, VOJTECHOVSKY, VITEK and their co-workers in Czechoslovakia. Following on from the work of CAPEK *et al.*, who reported in 1960 that adrenochrome in doses of 1-2 mg evoked changes in the behaviour of cats which would be expected for a psychotomimetic drug (45), GROF *et al.* concluded, as a result of an extensive «double-blind» study, that adrenochrome, especially in higher doses, caused transitory psychotic reactions in some subjects, whilst at lower doses, neurotic and uncertain reactions were more frequently observed (46, 47). From a total of twenty-four human experiments these workers observed nine definite psychotic reactions to adrenochrome (seven from sublingual doses of 30 mg and two from sublingual doses of 15 mg) (46, 47). It was further reported by GROF *et al.* (1963) that both qualitatively and quantitatively different results were observed when they used adrenochrome synthesised by the procedure described by FELDSTEIN (48) and when they used a commercially available preparation of adrenochrome (47). As a result of their investigations, GROF *et al.* concluded that the adrenochrome psychosis represents an approximate model of subtle schizophrenic alteration in the area of associative thinking (47).

GROF *et al.* have discussed several of the factors which could possibly account for some of the confusion and contradiction in the literature concerning the psychotomimetic properties of adrenochrome (47). Different samples of adrenochrome, possibly prepared by different procedures, may be of variable purity or they may have trace quantities of psychologically active contaminants present which could lead to variable psychotoxic effects. It also appears that there is a wide range of differing subject reactivities to adrenochrome. The majority of the work, both chemical and psychological that has been reported so far, has been carried out with adrenochrome prepared from *l*-adrenaline. There is some evidence that the sign of the rotation is altered during the oxidation procedure (8, 49), consequently aqueous solutions of the usual form of adrenochrome would be dextrorotatory. The commercial sample used by GROF *et al.* in their investigations was apparently prepared from *dl*-adrenaline, whereas the material synthesised by this group was obtained from *l*-adrenaline (47). HOFFER has reported that adrenochrome prepared from *d*-adrenaline shows somewhat more pronounced psychological effects than that prepared from the other optical isomer of adrenaline (9, 18).

A considerable amount of work has been carried out on the general pharmacology [cf. Reviews by BACQ (5), TATAI (7), SOBOTKA *et al.* (8)] and psychopharmacology [HOFFER (9)] of adrenochrome in animals. There appears to be less controversy over the results of the animal studies and it is more or less generally accepted that adrenochrome does produce behavioural changes in animals, although the effects produced appear to be both dose and species dependent.

The question as to whether or not adrenochrome is formed *in vivo* from adrenaline, is still a somewhat controversial one, although AXELROD has reported that a soluble enzyme is present in the salivary glands of the cat and certain other animals which brought about the *in vitro* oxidation of adrenaline to adrenochrome (50). The generally accepted involvement of the aminochrome dopachrome (derived from Dopa) as an essential intermediate in the *in vivo* formation of melanin pigments from tyrosine should also not be overlooked. VANDER WENDE and SPOERLEIN have described the presence of an enzyme system in rat brain that is capable of oxidising DOPA to melanitic pigments and this same enzyme oxidises adrenaline to adrenochrome (51). WANDER WENDE and JOHNSON have recently shown that serotonin is an effective inhibitor of the oxidation of dopamine (both enzymic and autoxidation) (52). These authors have further demonstrated that adrenochrome formation from adranaline can either be accelerated or inhibited by serotonin, the nature of the effect being dependent on the relative concentrations of the two amines (53). INCHIOSA has also recently demonstrated the presence of an adrenaline-oxidising enzyme in mammalian tissues (54-56). KALIMAN and KOSHLYAK have also shown that some animal tissues possess similar activity (57, 58).

In view of its high chemical reactivity [cf. Reviews by HEACOCK (59, 60)] it is doubtful if free adrenochrome could have more than a transient existence *in vivo*. However this does not entirely rule out the possible existence of adrenochrome *in vivo*; its concentration being maintained by some form of dynamic equilibrium. There is also the possibility of « stabilising » adrenochrome by its potentially reversible association with some other species, e.g. a naturally occurring thiol [cf. HEACOCK and MATTOK (61), MATTOK and HEACOCK (62), POWELL, HEACOCK, MATTOK and WILSON (63)].

DENISOV (64) and INCHIOSA (54) have suggested that the inhibition of certain enzymes, such as actomyosin ATPase, by oxidation products of adrenaline is due to interaction of these products with the SH groups in the enzyme. KRALL *et al.* (65) have suggested that the adrenochrome inhibition of oxidative phosphorylation by rat brain mitochondria is due to the binding of free SH groups in the enzyme.

A number of workers have reported the presence of fluorescent derivatives of adrenaline in body

fluids or tissues. In no cases were the fluorescent products unambiguously identified, although they could be considered to be formed by an oxidative cyclisation of adrenaline in the first instance. The relevant references are listed in the book by HOFFER and OSMOND (Ref. 10, pp. 339 and 340).

ALTSCHULE and his colleagues have reported an increased urinary excretion of adrenolutin-like substances in patients suffering from certain mental diseases (66-68). These findings have been questioned by YUWILER (69). ALTSCHULE has proposed the term « hyperaminochromia » to describe the condition [ALTSCHULE (70, 71)]. These workers are using the term aminochrome in a broad sense to include certain compounds, such as the lutins (i.e. 3,5,6-trihydroxyindoles), which whilst being readily derivable from the aminochromes, do not fit the usual chemical definition [cf. SOBOTKA and AUSTIN (72)]. More recently HEGEDUS and ALTSCHULE have studied the behaviour of adrenaline, adrenochrome and adrenolutin in blood and plasma of normal persons and subjects with psychiatric diseases and concluded that adrenaline, adrenochrome and adrenolutin are all converted to the same plasma-soluble compounds on incubation in humain plasma at 37° for 24 h for which they proposed the term « rheomelanin ». These workers concluded that their results indicate a possible metabolic pathway for adrenaline in man which would lead to indolic products [HEGEDUS and ALTSCHULE (73-77)].

GALZINGA has demonstrated that a reaction occurs between acetylcholine and noradrenochrome (78). This reaction could be responsible for the apparent inhibition of acetylcholinesterase by noradrenochrome. Reactions of this type might help to explain the hallucinogenic activity of the aminochromes (78). Recent experiments by GALZINGA have suggested that certain mental illnesses may be mediated by the formation of complexes between cholinergic transmitters and catecholamine oxidation products, such as the aminochromes (79, 80).

A considerable amount of interest has developed in the last decade in the mechanism of aminochrome formation from catecholamines and in the probability of short-lived but physiologically important intermediates being formed during the early stages of catecholamine oxidation, which subsequently cyclise to the aminochrome or some other product. A detailed consideration of this aspect of the problem is however outside the scope of this review. However this important aspect of the subject is extensively covered in the following references : [cf. WALAAS and WALAAS (81), WALAAS (82), WALAAS *et al.* (83), HARRISON (84, 85), HARRISON and WHISLER (86), HARRISON *et al.* (87, 88), HAWLEY *et al.* (89)].

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