Brit. J. Psychiat. (1970), 116, 569–75

Correspondence

FEARS AND PHOBIAS

DEAR SIR,

In his review of Isaac Marks' *Fears and Phobias* Dr. Aitken raises an interesting point when he says (with approval) that the author 'makes it clear that any explanation must account for all the facts'. Thus, we are told, is he able 'to castigate for their *naïveté* both the classical psychoanalytic and the behaviourist models'. Dr. Marks (or should it be Dr. Aitken?) must be congratulated on discovering an entirely new law in the logic of scientific methodology; one moreover, which at one stroke would rule out of court practically all the scientific laws, theories and generalizations ever proposed. If indeed any explanation must account for all the facts then poor old Newton could never have proposed his theory of universal gravitation; didn't he fail, in spite of his most anguished endeavour, to make his law account for such a simple thing as the movements of the moon? And did not the French physicists continue to point out phenomena clearly not explained by his laws? It is perhaps fortunate that he and other working scientists were ignorant of the Marks/Aitken rule, as otherwise, their *naïveté* shattered, they would have refused to commit their theories to paper.

It is of course quite customary in science, and indeed universal, to propose theories which cover some of the phenomena, in the hope that eventually, after much research and with many modifications, they may cover all; such hopes are usually asymptotic, but they are the lifeblood of science. This is precisely what the behaviourist model is doing at the present time; to call it naïve for not encompassing every known fact (and alleged or imaginary facts as well) is simply to put it on a par with Newton's, Einstein's or any other scientist's theories. It does differ in one essential respect from the psychoanalytic theory in that it is clearly falsifiable. In so far as specific predictions are falsified, the theory will have to be changed; this too, is not unusual in science. May I suggest that the Aitken proposal for only accepting theories which account for all the facts is a defence mechanism useful for retaining theories which account for none of the facts.

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TRYPTOPHAN PYRROLASE—A BIOCHEMICAL FACTOR IN DEPRESSIVE ILLNESS?

DEAR SIR,

Dr. Curzon's interesting paper (4) provides a succinct review of the evidence incriminating tryptophan pyrrolase in depression and the part played by adrenocortical hormones. With much of his views I am in agreement, but I must take issue with him on three things.

1. Dr. Curzon suggests that it is tactically 'more reasonable' to study 5HT rather than tryptamine in depressive illness. I contend that exactly the reverse is true. Dr. Curzon first cites the well-established presence of 5HT in brain, whereas tryptamine detection requires administration of tryptophan and/or monoamine oxidase inhibitors (MAOI). To infer from this that the presence of tryptamine is 'abnormal' entails the belief that the tryptophan decarboxylase disappears in the absence of MAOI and is present only after such drugs have been given; strange chemistry indeed, and I am sure not seriously entertained by an experienced biochemist like Dr. Curzon; in fact existing data suggest that if anything MAOI inhibit decarboxylases. If tryptamine is still thought 'suspect', the only alternative is to suppose that tryptophan is not normally present in the brain as a substrate. This can be refuted also, for ten years ago Price and West (13) not only demonstrated the presence of tryptophan throughout the brain stem but also pointed out with much perspicacity that its concentration did not follow that of 5HT; in the pons the ratio of tryptophan to 5HT was at least ten times that found in other regions. It must be recognized that the administrations of tryptophan and/or MAOI are no more than convenient devices which compensate for the insensitivity of detection techniques for tryptamine, and such devices have been used to aid detection of other amines in the past for exactly the same reasons. Recently, Björklund *et al.* (1) have devised a highly sensitive and specific technique for tryptamine and have already demonstrated its presence in the pituitary. Tryptamine, then, is no more an artefact than 5HT, and this being so neither the susceptibility to current measuring techniques which 5HT possesses nor quantitative differences hold relevance for functional significance. To study 5HT on these grounds is not 'tactically more reasonable', just technically much easier.

'Reasons' must therefore be sought in the other

category of evidence quoted by Dr. Curzon, namely the diminution in 5-hydroxyindoles found in the CSF and brain of depressed patients. I do not dispute these findings at all (although the low 5HT reported by Shaw *et al.* (14) was not confirmed in the later study of Bourne *et al.* (2)). But to interpret these findings sensibly it is important to know that 5-hydroxyindoles are low not only in schizophrenia (10) but also in disseminated sclerosis (11) and mania (5), to which no reference is made. Whilst mood can only be conjectural in the first two conditions, the findings in mania have particular significance, for they indicate that 5HT changes are *not* correlated with mood, although it is not unlikely that they are related to other phenomena such as sleep. The lack of correlation with mood is also borne out by a variety of other evidence which is not mentioned by Dr. Curzon but which has been considered in detail elsewhere (9).

Whilst reasons are lacking for the continued study of 5HT in relation to mood disturbance, there is much more evidence implicating tryptamine than one might suppose from Dr. Curzon's statement:

'Furthermore, while tryptamine may conceivably influence mood (Dewhurst, 1968), it was found not to enhance the effects of MAOI on depression (Coppen, 1967).' I cannot repeat this positive evidence in detail here, and must hope that interested readers will consult references (7) (8) (9) and will judge for themselves whether the rather considerable body of data presented can be given such light dismissal. I must, however, deal with the objection raised that tryptamine has no effect in depression. In the work cited (3), apparently large doses of tryptamine were given intravenously to patients previously given MAOI. I have stressed elsewhere (7) (8) that amines in solution are unstable and even though sealed in ampoules under nitrogen are none the less susceptible to destruction by light, heat and changes of pH. Unfortunately, to ensure that solutions are safe for human intravenous use other precautions must be taken about sterility, toxicity and so on, which will provide conditions (as well as time) favourable to amine destruction. These points are not mentioned in the paper, and there is no description of precautions taken to avoid such destruction, nor any account of checks to monitor such destruction, and for these reasons considerable reservations must be held about the amine content at the time the solution reached the patient. Empirical substantiation of this was unwittingly provided by the authors themselves, for pulse rate and blood pressure were recorded during the infusions. In animals tryptamine has a considerable depressor effect, and a similar mechanism occurs as part of the response to L-tryptophan in normal humans without MAOI (6). Assuming an arbitrary patient weight of 70 kilogrammes, the supposed amounts of tryptamine infused range from six to twenty-three times those producing vascular responses in animals. Yet, despite potentiation by MAOI, no effects on blood pressure or pulse rate were recorded. The conclusion therefore seems inescapable that the infusions were pharmacologically inactive. Nor would I counsel anyone to repeat these studies without full consideration of possible dangers. There is, however, evidence from another source. Patients with carcinoid tumours customarily produce large amounts of 5HT, but some varieties of neoplasm show atypical metabolic features, and one such case reported by Ashcroft (at the meeting of the Section of Psychiatry, Royal Society of Medicine, November, 1968) secreted large amounts of tryptamine, which (unlike 5HT) passes the blood brain barrier; the patient suffered from hypomania.

2. I agree that 'temporally the secondary biochemical factors may be important in the preservation of the depressed state'. But it is surely still important to distinguish primary from secondary. In depressive illnesses one envisages a variety of genetic and environmental factors which although widely differing in nature may lead to a common clinical entity (or two entities if one follows Roth's school). Whether one is unimodal or bimodal in persuasion, I believe that most clinicians would accept the basic fact that the primary change is in mood, and other phenomena such as the disturbances of sleeping, eating, motility and so forth whilst common are neither essential nor constant accompaniments. There is practical importance in recognizing the primacy of mood change for if it is understood remedial measures may then be devised and applied whatever the causes. And presumably if this is done early enough secondary phenomena will also recede. If delayed, the autonomy which some secondary phenomena may develop does not negate the importance of understanding the chain of events. In chronic pulmonary tuberculosis the secondary fibrosis of lung is certainly autonomous, but recognition of its origin is none the less important, and no surgeon would resect without ensuring that tubercle bacilli are dealt with first. Autonomy is an argument for the earliest possible treatment of the causative event, not its neglect.

3. Whilst I agree that a good case can be made for changes in tryptophan pyrrolase and adrenocortical disturbances in some cases of depression, these mechanisms must be placed in proper context. I also drew attention to other hormonal and enzyme interactions, such as the role of the thyroid and the

phasic excretion of amines which occurs in thyrotoxicosis (6). Since then the effects of oestrogens on tryptophan metabolism have been examined by Price *et al.* (12), and it has been suggested that they produce a relative pyridoxine deficiency. Pyridoxine is an essential co-factor both for amino-acid decarboxylases (which produce the amines) and transaminases (which produce acids), and consequently variations in amine formation may well underly menstrual fluctuations of mood as well as the depressive episodes reported on 'the pill' to which attention has recently been drawn by Winston and others (15). The role of ascorbic acid in the hydroxylation of tryptophan, and the importance of NAD and ATP, are other aspects of the matabolic picture which may on occasion require consideration. All this, together with possible deficiencies of tryptophan intake, either in diet or through anorexia, indicate that tryptophan pyrrolase is one of a number of possible points where amino-acid metabolism may be disturbed with reflected consequences on amines.

Whichever biochemical road one takes in depressive illness, it certainly seems that most lead to amine disturbance as the final common pathway. And when all the evidence and proposals on amines are carefully weighed, I believe that the roles I have proposed for tryptamine and other amines stand up to critical evaluation, whilst criticisms of the other views have remained unanswered. Apart from clarifying ways in which amine production can be effective at various metabolic points, it even provides explanations for the low 5-hydroxyindoles found in both mania and depression, without invocation of that awkward postulate that mania is simply the most severe form of depression. Tryptamine certainly seems more deserving of further scrutiny than either the catecholamines or 5HT, and has already proved more rewarding.

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Dear Sir,

Commenting on Dr. Dewhurst's three points in order:

1. While tryptophan and decarboxylase are necessary for tryptamine synthesis, their presence in brain does not prove tryptamine to occur physiologically therein to a significant extent. This must depend upon the kinetic parameters of the decarboxylase, upon compartmentation, and upon the rate at which brain monoamine oxidase (MAO) destroys tryptamine. As the latter has only been detected in brain after giving very large doses of tryptophan *plus* MAOI (1) (not 'and/or' MAOI), and as infusion of tracer amounts of C^{14}-tryptophan does not lead to detectable C^{14} in a brain extract which would have contained any tryptamine present (2), evidence is against tryptamine formation or presence in brain under physiological conditions. The histofluorimetric detection of a tryptamine-like substance in the pituitary (3) is consistent with the long accepted presence of tryptamine outside the brain, and though the sensitive method used may in the future provide evidence for brain tryptamine a physiological role for tryptamine in brain is at present conjectural.