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.

Furthermore, however one interprets the lack of effect of tryptamine reported by Coppen *et al.* (4), evidence that peripheral or exogenous tryptamine alters mood in man is tenuous. Thus, the therapeutic action of methysergide upon mania taken by Dr. Dewhurst (5) to substantiate his tryptamine hypothesis was not apparent in a double-blind trial (6), and could have been equally interpretable in terms of 5-hydroxytryptamine antagonism.

The 'hypomanic patient (secreting) large amounts of tryptophan' is patient number 1 of reference (7). Interpretation is difficult because he was also secreting large amounts of 5-hydroxytryptophan and because it was thought impossible to distinguish between biochemical and psychiatric factors in his mood swings between depression and elation (Ashcroft, personal communication).

The suggestion that mood is simply a function of net brain level or turnover of any single amine would be naïve, and was not made in my paper. Dr. Dewhurst states correctly that low CSF 5-hydroxyindole-acetic acid (5HIAA) has been found in both depression and mania. However, in a recent confirmation of this (8) it was also found that there was a negative correlation between 5HIAA and degree of depression on the MMPI scale, but a positive correlation between 5HIAA and degree of mania (approaching 5 per cent significance).

2. One cannot reasonably argue with Dr. Dewhurst's use of 'primary' to indicate that mood changes are principal symptoms in depression. I used 'primary' and 'secondary' to indicate a temporal order of biochemical changes, and did not, I hope, imply that secondary changes were necessarily of unique or dominating importance.

3. In thyrotoxicosis, MAO activity is low and tryptamine excretion high (9). While phasic excretion of amines may well occur, this was not investigated in the paper to which Dr. Dewhurst refers, albeit indirectly (9). Apart from this, his third point usefully comments upon various factors which might influence amine metabolism.

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PSYCHIATRIC SEQUELAE OF CHILDHOOD BEREAVEMENT

Dear Sir,

Might I be permitted to respond to some of the points raised by Professor Munro in reply to my recently published letter.

It *is* important to differentiate between parent death and parent loss from other causes, and quite unhelpful to deliberately confound them as Munro claims he and Griffiths did (1969). We are at present in no position to say whether the two forms of loss are identical in their effects, and, Munro himself contends, though without justification, that the one is a more potent cause of psychopathology. Hill's (1969) remark that loss due to cause other than death may denote a higher index of psychiatric disturbance in this group of parents is not a 'theory' but a serious methodological consideration. Parent death is a valuable experimental opportunity, for it is as close as one can get in the human situation to lowering a hand into the cage and removing the parent animal. Loss from other causes may be preceded and succeeded by discord between the parents and within their families, which may be of greater aetiological significance than the separation experience itself.

This confusion between the two forms of loss is related to the next point. To explain a high incidence of parental bereavement in depressed patients on the grounds of contamination by cases of personality disorder, psychopathy, delinquency and attempted suicide is unreasonable. As it happens, an interesting point in itself, the majority of studies of depression