Central Monoamine Metabolism in Depressions. I. Serotonin and Related Compounds

H. M. van Praag

IN THE PAST 15 years, much research has been done into the significance of disorders of central monoamine (MA) metabolism in the pathogenesis of depressions, and more specifically in pathogenesis of vital depressions. MAs are compounds that act as neurotransmitter in the central nervous system (CNS). The principal MA in the brain are serotonin (5-hydroxytryptamine; [5-HT]), noradrenaline (NA), and dopamine (DA). A vital depression is defined as a particular depressive syndrome that is etiologically nonspecific, shows a marked tendency to relapse, and develops with or without (hypo)manic phases (bipolar and unipolar vital depression, respectively). The syndrome has been defined previously.[1]

This research led to the formulation of the so-called MA hypothesis, which states that a central 5-HT and/or NA deficiency, or hypofunction of serotonergic and/or NA-ergic systems, plays a role in the pathogenesis of vital depressions of a certain subcategory of vital depressions.

The question of a possible relationship between MA and depression was raised by the finding that the two principal groups of antidepressants—tricyclic antidepressants and monoamine oxidase (MAO) inhibitors—show similarities on two levels: on the psychopathological level in that they exert a beneficial influence on vital depressions, and on the biochemical level in that they increase the amount of MA available at the central postsynaptic receptors, thus enhancing the neuronal activity of these systems.[2] This prompted the question of whether depressions responsive to antidepressants involve a MA deficiency. This question became more urgent when the antidepressants were found to have a counterpart: reserpine. Reserpine lowers the central MA levels and, on the other hand, provokes vital depressions in a by no means negligible number of (hypertensive) patients.

RESEARCH STRATEGIES

The human central MA metabolism has been studied with the aid of several strategies.[3]

Study of MA Metabolism in the Periphery

This measures (1) the renal excretion of MA metabolites, (2) the plasma concentrations of enzymes involved in MA metabolism, and (3) the uptake of 5-HT in blood platelets, a structure which to some extent is acceptable as a model of a serotonergic nerve ending in the brain. This strategy is of limited

---

From the Department of Psychiatry, Utrecht University Hospital, Utrecht, The Netherlands.
Address reprint requests to H. M. van Praag, M.D., Ph.D., Utrecht University Hospital, Utrecht, The Netherlands.
 0010-440X/80/2101-0004$02.00/0

significance as long as there is no evidence indicating that a peripheral variable is representative of the situation in the brain.

Postmortem Studies

This method involves postmortem studies of the central MA metabolism in suicide victims. This strategy has its justification in the fact that an estimated 50% of all suicides are committed in a state of vital depressiveness.[4]

Cerebrospinal Fluid

Another method is measurement of the concentration of MA metabolites in the cerebrospinal fluid (CSF). This strategy postulates a relation between MA degradation in the CNS or CNS components and the concentration of MA metabolites in the CSF. This relationship, if not very pronounced, has been established for some metabolites.[5] The instructive value of CSF studies can be enhanced by giving probenecid in advance.[3] Probenecid inhibits the transport of acid MA metabolites from CSF to bloodstream. These metabolites consequently accumulate in brain and CSF, and their accumulation is a (gross) indicator of the rate of degradation of the mother substances in the CNS. In the so-called probenecid test, the concentration of certain MA metabolites in the lumbar CSF is measured before and after probenecid loading. Marked accumulation of a given metabolite is regarded as an indicator of marked degradation of the mother substance, and vice versa.

Pharmacologic Manipulation of Central MA

If a central deficiency in one or several MA is involved in the pathogenesis of vital depressions, then the pharmacologic reduction of its (or their) availability can be expected to have a depressogenic effect, while enhancement of its (or their) availability should have an antidepressant effect.

Neuroendocrine Strategy

The neuroendocrine strategy is the most recent.[6] The release of hormones by the anterior pituitary lobe is regulated by the so-called releasing and inhibiting factors from the hypothalamus. The production of these "factors" is at least partly determined by MA-ergic nerve cells. Disorders in the function of these neurons should therefore "translate" themselves into an altered release of anterior pituitary hormones; and this can be measured from a change in their concentration in the blood.

DESIGN OF THIS STUDY

The following is a brief outline of 5-HT research in depressions. For economy of space, the catecholamine (CA) research in these patients is discussed in a separate treatise, even though this might seem to suggest that the two systems do not interact (which, emphatically, they do). No effort has been made to ensure comprehensiveness, nor does the available space permit comments on all the observations mentioned. My concern is with the main lines of approach and with the (tentative) conclusions that (in my opinion) the findings

so far warrant. References to the literature cannot be comprehensive either. Whenever possible, therefore, I intend to refer to reviews.

CENTRAL 5-HT METABOLISM IN DEPRESSIONS

Three series of data indicate the plausibility of a central 5-HT deficiency in vital depressions. They derive from postmortem, CSF, and peripheral research, respectively.

Postmortem Research

This research has been done in suicide victims as well as in depressive patients who died from other causes. I only mention the two studies that focused on distinct parts of the brain rather than on the brain as a whole.

Lloyd et al.,[7] studying suicide victims, found that the concentration of 5-HT and of 5-hydroxyindoleacetic acid (5-HIAA, the principal 5-HT metabolite) was decreased, specifically in certain raphe nuclei. These nuclei are the sites of predilection of cell bodies of serotonergic neurons. Birkmayer and Riederer[8] reported similar findings obtained in the brain in depressive patients who died from causes other than suicide.

CSF Research Without Probenecid

Studies of baseline CSF 5-HIAA concentrations have not produced unequivocal results. The most important study in this context, by Åsberg et al.,[9] did reveal a decrease in vital depressive patients—not in all patients, but only in a certain subcategory. Vital depressive patients with and without a decreased baseline 5-HIAA concentration were indistinguishable in terms of psychopathologic symptoms.

I consider this study important because the number of patients examined was large, the sample tended towards psychopathologic homogeneity, 5-HIAA was measured by the best method now available (gas chromatography/mass spectrometry), and the study was repeated in an independent sample in which the results were confirmed.

Åsberg et al.[9] measured 5-HIAA in lumbar CSF. The 5-HIAA concentration in that CSF compartment is determined by the 5-HT degradation in brain and spinal cord. The 5-HIAA concentration in ventricular CSF reflects largely the 5-HT degradation in the brain. In psychiatric patients who underwent psychosurgery, Bridges et al.[10] found that the average concentrations of 5-HIAA and tryptophan (the mother substance of 5-HT) in ventricular CSF were lower in vital depressive patients than in other categories of psychiatric patients and in a neurologic control group.

CSF Research After Probenecid Loading

The abovementioned findings of Åsberg et al.[9] confirmed the findings we obtained a few years earlier with the probenecid technique.[11,12] In about 40% of the patients examined, the postprobenecid 5-HIAA accumulation was decreased prior to treatment; these findings have meanwhile been corroborated elsewhere.[13] This phenomenon can be regarded as an indication of a diminished 5-HT degradation in the brain. Low and normal 5-HIAA responders were

indistinguishable in terms of psychopathologic findings. For this reason we formulated a working hypothesis, the postulate of the biochemical classifiability of depressions. The group of the vital depressions should be classifiable, not only on the basis of the three traditional criteria (symptomatology, etiology, and course) but also on the basis of the criterion pathogenesis. I define the term pathogenesis as denoting the complex of cerebral functional disorders that is instrumental in the causation of certain behavior disorders.[14] There are believed to be vital depressions with and without demonstrable disturbances in central 5-HT metabolism.

Free Tryptophan in Plasma and Mood Level

The amino-acid tryptophan is the mother substance of 5-HT. The plasma concentration of free tryptophan (i.e., tryptophan not bound to albumin) correlates with the tryptophan concentration in the brain.[15] The tryptophan concentration in the brain largely determines the rate of 5-HT synthesis.[16] If serotonergic systems are involved in mood regulation, then there is some justification for the hypothesis that a certain relationship can be expected to exist between the free tryptophan concentration in plasma and the mood level. There are in fact indications in support of this hypothesis. For example, a relation between plasma free tryptophan level and mood level was demonstrated during the first week after parturition, a period known to be often characterized by emotional instability and despondency.[17,18]

Moreover, the vital depression group includes a subgroup of patients in whom the plasma concentration of free tryptophan is decreased in relation to that of other neutral amino acids such as valine and (iso)leucine.[19,20] Since these amino acids compete for the same mechanism to enter the CNS, it is plausible that the entrance of tryptophan into the CNS is diminished. In these patients, large doses of L-tryptophan had a therapeutic effect (see Tryptophan Medication).

These findings are by no means definitive. Still lacking is longitudinal research, studying mood level and free tryptophan concentration over longer periods in the same individual under relative standard conditions. As it is, we can only observe that the tryptophan data are not at odds with the hypothesis that a central 5-HT deficiency can be a factor in the pathogenesis of certain types of pathological despondency.

Conclusion

The group of vital depressions includes a group of patients with disorders of the central 5-HT metabolism. The nature of these disorders is not inconsistent with the existence of a central 5-HT deficiency.

5-HT DISORDERS AND PATHOGENESIS OF VITAL DEPRESSIONS

Research Strategy

If the abovementioned observations are indeed indicative of a 5-HT deficiency in the brain, then the question arises whether this deficiency (1) contributes to the pathogenesis of the depression; (2) is secondary to it; or (3) is

unrelated to the depression. There is only one research strategy that can lead to an answer to this question for the human: attempt to abolish the postulated 5-HT deficiency by optimally selective means and investigate the consequences on the behavioral level. If the 5-HT deficiency plays a causative role, then 5-HT potentiation can be expected to alleviate the (or some) depressive symptoms, particularly in patients with a demonstrable 5-HT disorder. If no alleviation is observed, then a causative relation of the 5-HT disorder to the depression is unlikely.

An increase of the amount of 5-HT available in the brain has so far been effected mainly by administration of the 5-HT precursors tryptophan and 5-hydroxytryptophan (5-HTP). Two enzymes involved in 5-HT synthesis—tryptophan hydroxylase and 5-HTP decarboxylase—are not saturated with substrate; consequently, an extra supply of 5-HT precursors enhances 5-HT synthesis (Table 1).

Tryptophan Medication

The first trials with tryptophan in depressions were carried out by Pare and Sandler[21] and Van Praag.[22] The results were on the whole negative, but the doses given were relatively small. Research in subsequent years did not provide an unequivocal answer to the question whether L-tryptophan has an antidepressant effect. The numbers of studies with negative results more or less equal those with positive results.[23] Today, however, we are aware of a number of factors that may have contributed to this discrepancy. So far there has been no tryptophan study in which the patients were biochemically classified in advance (on the basis of the presence or absence of central 5-HT disorders). Most studies concerned a limited number of patients, and tryptophan was given during a limited period of time (less than 3 weeks). Only sporadically was tryptophan given in combination with nicotinamide and pyridoxine, compounds that probably enhance the effect of the tryptophan dose. Nicotinamide does this by inhibiting the conversion of tryptophan to nicotinamide; and pyridoxine (coenzyme in the decarboxylation of 5-HTP to 5-HT) by facilitating the conversion of tryptophan to 5-HT. Finally, most studies disregarded the fact that there is probably a critical range of tryptophan concentration in plasma (and in the brain), above and below which the therapeutic efficacy diminishes.

The methodologically best designed study[24] compared this amino acid double-blind with the tricyclic antidepressant amitriptyline. The two compounds were found to be therapeutically equivalent. There is little doubt, moreover, that L-tryptophan enhances the therapeutic efficacy of MAO inhibitors and various tricyclic antidepressants.[23,25]

These facts warrant the contention that L-tryptophan is more than just a

Table 1. Simplified Diagram of 5-HT Metabolism

Tryptophan	→ 5-Hydroxytryptophan (5-HTP)	→ 5-Hydroxytryptamine Serotonin (5-HT)	
		↓	
		5-Hydroxyindoleacetic Acid (5-HIAA)	

placebo: To determine its value more exactly, however, studies that take the abovementioned factors into account are required.

5-HTP Medication

Since 1970 we have mainly studied the second 5-HT precursor: 5-HTP.[26] Our preference for 5-HTP was for three reasons: (1) Unlike tryptophan, 5-HTP is almost exclusively converted to 5-HT. (2) Our group had demonstrated in rats that 5-HTP given orally is (partly) converted to 5-HT in central serotonergic neurons. (3) We had found indications that conversion of tryptophan to 5-HT can be impaired in depressive patients, whereas that of 5-HTP to 5-HT remains undisturbed.

In 1972 we published the results of a double-blind placebo-controlled study of 5-HTP in vital depressive patients, which warranted the conclusion that 5-HTP (1) can exert an antidepressant influence, and (2) is most likely to do so in patients with indications of a central 5-HT deficiency.[11] In the same year, Sano[27] published an open study, also leading to the conclusion that 5-HTP has antidepressant properties. In a number of controlled[1,28,29] and uncontrolled[30,31] studies, the antidepressant potency of 5-HTP was confirmed. Its effect proved not to differ significantly from that of the tricyclic antidepressants clomipramine[32] and imipramine.[28] The combination of 5-HTP and clomipramine proved to be more effective than each of its components separately (Fig. 1).[32] The antidepressant effect of MAO inhibitors is likewise potentiated by 5-HTP.[33]

So far, only two studies have produced negative results: one open and one placebo-controlled study. The former (Takahashi et al.[34]) involved brief medication (7 days) with small doses of 5-HTP. The latter (Brodie et al.[35]) involved only 7 patients who were likewise medicated briefly (1–15 days).

Even though the number of controlled studies comparing 5-HTP with a

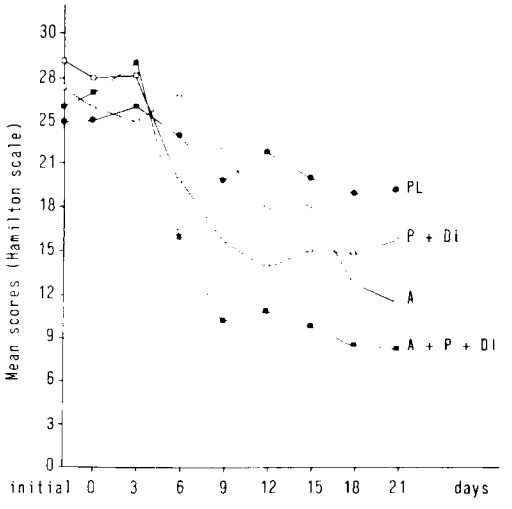

Fig. 1. Depression scores (Hamilton scale) in 4 groups of 10 vital depressive patients each, before and after medication with placebo (PL) or with 5-HT-potentiating compounds: clomipramine alone (Anafranil; A 225 mg/day), 5-HTP alone (P; 200 mg/day, combined with 150 mg of the peripheral decarboxylase inhibitor MK 486), or a combination of these compounds. The design was double blind. 5-HTP equalled clomipramine. The combination of 5-HTP with clomipramine was superior to each of the separate compounds.[5]

placebo or a standard antidepressant is still too small to warrant definite conclusions, the results so far obtained do indicate that 5-HTP has antidepressant properties. Two other facts point in the same direction. 5-HTP has a euphorizing effect on normal test subjects,[36,37] and in myoclonus patients, 5-HTP, when used therapeutically, was reported to cause (hypo)manic disinhibition as a side effect.[38]

Our study showing that the group of depressive patients with a disturbed 5-HT metabolism have a preferential indication for 5-HTP medication has not yet been repeated (Fig. 2). Nearly all investigators conclude, however, that no more than 40%–60% of patients with vital depressions benefit from 5-HTP. This percentage approximates that of the 5-HT-deficient subgroup within the group of vital depressions.

Does 5-HTP Act via Enhancement of 5-HT Synthesis?

The pharmacotherapeutic effect of 5-HTP need not necessarily be based on potentiation of 5-HT in the brain, for 5-HTP does not exclusively influence the central 5-HT metabolism. This compound is taken up in DA-ergic and NA-ergic as well as in serotonergic neurons. In these neurons, too, there is conversion to 5-HT, which might locally start to function as a so-called false transmitter. A false transmitter is a substance that occupies the postsynaptic receptors but fails to activate them. Consequently the neuronal activity in DA-ergic and NA-ergic would diminish. In my opinion, this is not a plausible explanation. To begin with, suppression of DA-ergic and NA-ergic activity is more likely to provoke depression than to alleviate it (see Part II of this article). Secondly,

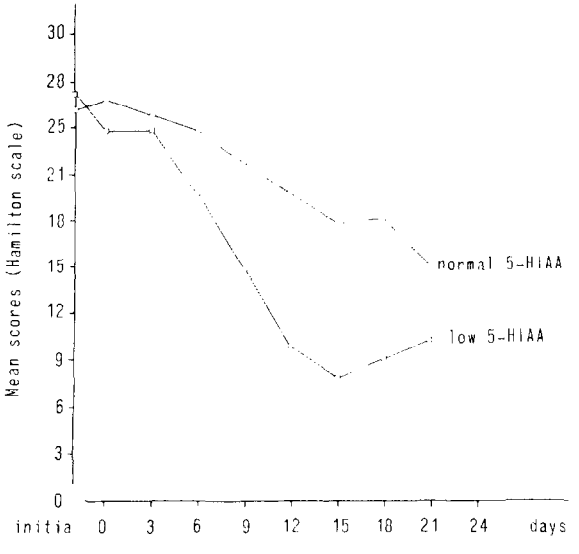

Fig. 2. Hamilton scores in 30 patients with unipolar or bipolar vital depressions before and during a 3-week period of medication with serotonin-potentiating compounds; clomipramine alone, 5-HTP alone (together with a peripheral decarboxylase inhibitor), and a combination of these two compounds. The lower curve indicates therapeutic results in patients with a subnormal pretreatment 5-HIAA response to probenecid ($N = 13$); the upper curve indicates those in patients with a normal pretreatment 5-HIAA response ($N = 17$). *The therapeutic result in the former group was significantly better than that in the* latter.[5]

agents are being developed that potentiate 5-HT in the brain, not by enhanced synthesis but by a different mechanism. One of these compounds is zimilidine, a selective 5-HT reuptake inhibitor. Preliminary reports indicate an antidepressant effect of this compound.[39]

Practical Notes

5-HTP is usually given in combination with a peripheral decarboxylase inhibitor. Compounds of this type inhibit the conversion of 5-HTP to 5-HT exclusively in the periphery because they do not penetrate to the brain. This means that the supply of 5-HTP to the brain is increased, and the efficacy of the dose therefore enhanced. Moreover, we have started to give the 5-HTP capsules a coating which does not dissolve until pH 8.6 (i.e. in the intestine); this was done because uncoated tablets cause many gastrointestinal side effects and we obtained information indicating that this was due to a direct effect of 5-HTP on the gastric wall. These side effects have since been observed only occasionally.

Conclusion

On the basis of the therapeutic findings obtained with the 5-HT precursors tryptophan and 5-HTP, it seems more likely that 5-HT disorders play a role in the causation of depressions than that they are secondary or totally unrelated to them. Quite apart from this, the possibility of treating certain types of depression with physiologic substances can be regarded as an advance in psychopharmacology.

5-HT DEFICIENCY IN DEPRESSIONS: CAUSATIVE OR PREDISPOSING FACTOR?

Research Strategy

Assuming that (1) the reported disorders of central 5-HT metabolism have been correctly interpreted as indicative of a 5-HT deficiency and (2) it has been correctly concluded that this deficiency plays a role in the pathogenesis of depressions, the following question arises. Is the 5-HT deficiency a real causative factor—condition sine qua non for a depression to become manifest—or a predisposing factor, which increases the risk of depression but is not an absolute prerequisite for its manifestation.

The only strategy by which insight into this question can be gained is that of longitudinal studies or, more precisely, repetition of the determination of 5-HIAA accumulation in the CSF after regression of symptoms.[3,26] If at that time the metabolic disorder is no longer demonstrable, then a causative relation seems plausible. If it proves to be persistent, however, then a predisposing factor is the more likely.

Longitudinal 5-HT Studies

In over 50% of the patients examined, a subnormal postprobenecid 5-HIAA response was still observed after clinical recovery (Table 2).[6] This finding supports the predisposition hypothesis. Should this hypothesis be correct, then a long-term increase of the cerebral 5-HT concentration might be expected to

Table 2. Number of Depressive Patients After Probenecid Loading With Low or Normal Response of CSF 5-HIAA and CSF Homovanillic Acid Before Treatment and After Clinical Recovery

	Before Treatment		After Recovery	
	5-HIAA	HVA	5-HIAA	HVA
Low response	19	15	10	1
Normal response	31	35	40	49

have a prophylactic effect, particularly in recurrent vital depressions with persistent disorders of the central 5-HT metabolism.

5-HTP as Prophylactic

In a controlled study of vital depressive patients with a high relapse rate, we found indications that seemed to confirm the above hypothesis. During chronic 5-HTP medication the relapse rate was lower than that during placebo periods (Table 3). The open study described by Van Hiele and coworkers[30] points in the same direction. The prophylactic effect was most pronounced in patients with a persistently diminished CSF 5-HIAA level (Table 4), but the relatively small number of patients studied precludes a definite conclusion on this point.

Assuming that these data will be corroborated, 5-HTP prophylaxis would be the first form of aimed chemoprophylaxis to be introduced in psychiatry. "Aimed" connotes focusing on a suspected factor in the pathogenesis of certain types of depression. 5-HTP and lithium prophylaxis have not yet been compared with each other.

Table 3. Patients With Unipolar and Bipolar Vital Depressions and High Relapse Rate Given 1 Year of 5-HTP Medication (With a Peripheral Decarboxylase Inhibitor) and 1 Year of Placebo Medication

	Number of Test Subjects†	Number of Patients who Developed Relapses		Number of Relapses	
		Placebo Period	5-HTP Period	Placebo Period	5-HTP Period
Group A*	10	9	3	14	3
Group B**	10	8	3	10	4

*One year of 5-HTP medication followed by 1 year of placebo medication.

**One year of placebo medication followed by 1 year of 5-HTP medication.

†The number of patients who relapsed and the total number of relapses were significantly larger during the placebo than during the 5-HTP periods.

Table 4. Normal and Subnormal Postprobenecid CSF 5-HIAA Response

Patient Group*	No. of Patients	Relapse During 5-HTP	No Relapse During 5-HTP
Persistently subnormal postprobenecid CSF 5-HIAA**	13	1	12
Persistently normal postprobenecid CSF 5-HIAA	7	5	2

*The same 20 patients as in Table 3.

**Significantly greater prophylactic effect of 5-HTP.

5-HT Disorders and Depression Rate

Another finding that supports the predisposition hypothesis is the observation that the depression rate in the group of patients with persistent disorders of the central 5-HT metabolism differs from that in the group without these disorders.[40] The depression rate was higher in the former group (Table 5), as could be expected if the persistent 5-HT deficiency indeed represents a biologic vulnerability factor, i.e., a factor that increases the risk of depression when the individual is exposed to menacing endogenous or exogenous stimuli.

Vulnerability Research in Psychiatry

I consider the study of vulnerability factors to be one of the most important developments in psychiatry in recent years. Why do some individuals respond to a somatic or psychological noxa by psychological decompensation (in this case: depression), while others do not? The relevant research is done on three different levels:[41] (1) the psychological level: which personality factors render the individual vulnerable? (2) the social level: which factors in the environment increase this risk? and (3) the biologic level: which imperfections in the cerebral mood-regulating mechanisms render an individual depression-prone?

The above discussed 5-HT disorder might well come under the last heading. Buchsbaum, Coursey, and Murphy[42] recently described a factor of a possibly comparable nature: the MAO concentration in the blood platelets. The MAO values in a sample of the normal population proved to vary widely. Test subjects with low MAO values showed a significantly higher psychiatric morbidity than those with high MAO values. In a pedigree study, Dorus et al.[43] found a significant correlation between low MAO values and the development of psychiatric disturbances in mood regulation.

It is still to be established whether (1) the low MAO values in the periphery can be extrapolated to strategic areas in the brain and (2) whether the 5-HT disorders observed correlate with the MAO disorders. In any case, however, both observations demonstrate that biologic variables must not be disregarded in psychiatric vulnerability research.

Conclusion

In view of the data now available, a predisposing role of the 5-HT disorders observed in depressions seems more plausible than a causative role. Vulnerability research is of paramount importance to psychiatry and should be three-dimensional.

Table 5. Psychiatric Admissions and 5-HIAA Response

Number of Admissions	Subnormal 5-HIAA Group	Normal 5-HIAA Group	Probability
Depression	89	61	$p < 0.002$
Mania	19	10	NS
Other psychiatric disorders	7	6	NS

REVERSED 5-HT HYPOTHESIS

The disorders of central 5-HT metabolism diagnosed in vital depressions point in the direction of a 5-HT deficit. The "classical" 5-HT hypothesis regards this as a primary phenomenon that gives rise to reduced neuronal activity in central serotonergic systems. In principle, the alleged 5-HT deficiency can also be a secondary phenomenon, based on increased sensitivity of the postsynaptic serotonergic receptors. In order to avoid hyperactivity in the system, one may reason, the 5-HT production diminishes. The "reversed 5-HT hypothesis"—hyperactivity in serotonergic systems as a factor in the pathogenesis of vital depressions—has in fact been advanced.[44] To me, however, it seems rather improbable. My principal argument against it has already been discussed. 5-HT potentiation, if it has any effect, is more likely to alleviate than to provoke depression. Moreover, there is not a single clue that diminished 5-HT availability could be an antidepressant factor. On the contrary, Shopsin et al.[45] demonstrated that successful medication with a 5-HT-potentiating tricyclic antidepressant is rapidly brought to an end by administration of parachlorophenylalanine, a compound which inhibits tryptophan hydroxylase and therefore 5-HT synthesis. Finally, I might point out that electroshocks potentiate 5-HT effects in test animals.[46] Electroshock therapy is still the procedure with the highest success rate in the treatment of vital depressions. Assuming that 5-HT potentiation occurs in human individuals also, this finding argues in favor of the "classical" and against the "reversed" 5-HT hypothesis.

DISCUSSION

The data now available on 5-HT and depression warrant, I think, the following conclusions:

1. The group of vital depressions includes a subgroup, consisting of about 40% of the patients examined, in whom indications of a central 5-HT deficit are found. The distinction "5-HT deficient" and "5-HT-nondeficient" does not coincide with the dichotomy "unipolar" and "bipolar."
2. This 5-HT deficit is a primary phenomenon, and not a result of 5-HT receptor hypersensitivity.
3. It plays a role in the pathogenesis of these depression types.
4. It is a predisposing rather than a causative factor.

These conclusions should be qualified as "tentative." This qualification is necessary because two crucial experiments have yet to be reduplicated. The first concerns our observations that patients in the "5-HT-deficient subgroup of vital depressions" provide a preferential indication for 5-HT-potentiating compounds or, in other words, show a better response to such compounds than patients without demonstrable 5-HT disorders. The second concerns the observation of Åsberg et al.[47] that patients in the "5-HT-deficient subgroup" show a less favorable response to nortriptyline than patients without demonstrable 5-HT disorders. Nortriptyline is a tricyclic antidepressant that potentiates NA in the brain but exerts no demonstrable influence on 5-HT. If these

two observations should be confirmed, then I would be inclined to drop the restrictive qualification "tentative." It would be premature to conclude that real substitution therapy can be given with 5-HT precursors. Nevertheless the availability of these compounds is even now of practical and scientific importance. They paved the way for the concept of the biologic classifiability of depressions and, therefore, for the notion that—besides symptomatology, aetiology and course—pathogenesis might also be a valid classification principle in psychiatry. They stimulate the development of antidepressants with, on the biochemical level, a more specific effect than existing compounds. This promises further individualization of the pharmacotherapy of depressions. Also, physiologic substances are to be preferred to nonphysiologic compounds in pharmacotherapy. It is fortunate that, with the introduction of certain endorphines, a comparable development is probably on its way in the field of psychoses of the schizophrenic type.[48,49]

SUMMARY

This article reviews research into the possible significance of disorders of the central 5-HT metabolism in the pathogenesis of recurrent depressions. The available data would seem to warrant the tentative conclusion that such metabolic disorders are indeed involved in a certain subcategory of vital depressions and play a (possibly predisposing) role in the pathogenesis of these depressions.

The use of 5-HT precursors in depressions is regarded as a potential asset, although the conclusion that real substitution therapy can thus be given would be premature.

REFERENCES

1. van Praag HM: Neuroendocrine disorders in depression and their significance for the monoamine hypothesis of depression. Acta Psychiat Scand 57:389–404, 1978

2. Sangdee C, Franz DN: Enhancement of central norepinephrine and 5-hydroxytryptamine transmission by tricyclic antidepressants. Psychopharmacology 62:9–16, 1979

3. van Praag HM: Depression and schizophrenia. A contribution on their chemical pathologies. New York, Spectrum Publications, 1977

4. Whitlock FA: Depression and suicide, in: Burrows GD (ed): Handbook of studies on depression. Amsterdam, London, New York, Excerpta Medica, 1977, pp 379–403

5. Goodwin FK, Wehr T, Post RM: Clinical approaches to the evaluation of brain amine function in mental illness: Some conceptual issues, in Lovenberg W, Youdim M (eds): Essays in Neurochemistry and Neuropharmacology. London, John Wiley and Sons, 1978

6. van Praag HM: Significance of biochemical parameters in the diagnosis, treatment and prevention of depressive disorders. Biol Psychiatry 12:101–131, 1977

7. Lloyd KJ, Farley IJ, Deck JHN, et al: Serotonin and 5-hydroxyindoleacetic acid in discrete areas of the brainstem of suicide victims and control patients. Adv Biochem Psychopharmacol 11:387–397, 1974

8. Birkmayer W, Riederer P: Biochemical post-mortem findings in depressed patients. J Neurol Trans 37:95–109, 1975

9. Åsberg M, Thoren P, Traskman L, et al: "Serotonin depression": a biochemical subgroup within the affective disorders? Science 191:478–480, 1976

10. Bridges PK, Barlett JR, Sepping P, et al: Precursors and metabolites of 5-hydroxytryptamine and dopamine in the ventricular cerebrospinal fluid of psychiatric patients. Psychol Med 6:399–405, 1976

11. van Praag HM, Korf J: Endogenous depressions with and without disturbances in the

5-hydroxytryptamine metabolism: A biochemical classification? Psychopharmacologia 19: 148–152, 1971

12. van Praag HM, Korf J, Schut T: Cerebral monamines and depression. An investigation with the probenecid technique. Arch Gen Psychiatry 28:827–831, 1973

13. Post RM, Goodwin FK: Approaches to brain amines in psychiatric patients: A reevaluation of cerebrospinal fluid studies. Handbook of Psychopharmacology 13:147–185, 1978

14. van Praag HM: The position of biological psychiatry among the psychiatric disciplines. Compr Psychiatry 12:1–7, 1971

15. Fernstrom JD, Wurtman RJ: Brain serotonin content: Physiological dependence on plasma tryptophan levels. Science 173:149–152, 1971

16. Knott PJ, Curson G: Free tryptophan in plasma and brain tryptophan metabolism. Nature 239:452–454, 1972

17. Stein G, Milton F, Bebbington P, et al: Relationship between mood disturbances and free and total plasma tryptophan in postpartum women. Br Med J 2:457, 1976

18. Handley SL, Dunn TL, Baker JM, et al: Mood changes in puerperium and plasma tryptophan and corisol concentrations. Br Med J 2:18–22, 1977

19. Møller SE, Kirk L, Femming KH: Plasma amino acids as an index for subgroups in manic depressive psychosis, correlation to effect of tryptophan. Psychopharmacology 49:205–213, 1976

20. Coppen A, Wood K: Tryptophan and depressive illness. Psychol Med 8:49–57, 1978

21. Pare CMB, Sandler M: A clinical and biochemical study of a trial of iproniazid in the treatment of depression. J Neurol Neurosurg Psychiatr 22:247–251, 1959

22. van Praag HM: A critical investigation of the importance of monoamine oxidase inhibition as a therapeutic principle in the treatment of depression. Utrecht, Thesis, 1962

23. Cooper AJ: Tryptophan antidepressant "physiological sedative": Fact or fancy? Psychopharmacology 61:97–102, 1979

24. Herrington RN, Bruce A, Johnstone EC, et al: Comparative trial of L-tryptophan and amitriptyline in depressive illness. Psychol Med 6:673–678, 1976

25. Wålinder J, Skott A, Carlsson A, et al: Potentiation of the antidepressant action of clomipramine by tryptophan. Arch Gen Psychiatry 33:1384–1389, 1976

26. van Praag HM: Central monoamines and the pathogenesis of depression, in van Praag HM, Lader M, Rafaelsen O, et al (eds): Handbook of Biological Psychiatry. New York, Marcel Dekker, 1979

27. Sano T: L-5-hydroxytryptophan (l-5-HTP) bei endogenes Depression. Münch Med Wschr 144:1713–1716, 1972

28. Angst J, Woggon B, Schoepf J: The treatment of depression with l-5-hydroxytryptophan versus imipramine. Arch Psychiat Nervenkrankh 224:175–186, 1977

29. Barlet P, Pailard P: Etude clinique du 5-hydroxytryptophane dans les états depressifs du troisieme age. Cahiers Med Lyonnais 50:1895–1901, 1974

30. van Hiele LJ, Ten Wolde HUW, Gjaltema-Bosch P: l-5-Hydroxytryptophan in depression. The first substitution therapy in psychiatry? Neuropsychobiol (in press)

31. Nakajima T, Kudo Y, Kaneko Z: Clinical evaluation of 5-hydroxy-l-tryptophan as an antidepressant drug. Folia Psychiatr Neurol Jap 32:223–230, 1978

32. van Praag HM: Psychotropic drugs. A guide for the practitioner. New York, Brunner/Mazel, 1978

33. López-Iboz JJ, Gutierrez JJA, Iglesias MLMM: 5-Hydroxytryptophan (5-HTP) and a MAO I (nialamide) in the treatment of depression. A double-blind controlled study. Intern Pharmacopsychiatr 11:8–15, 1976

34. Takahaski S, Takahaski R, Masamura I, et al: Measurement of 5-hydroxyindole compounds during 5-HTP treatment in depressed patients. Folia Psychiatr Neurol Jap 30:463–473, 1976

35. Brodie HKH, Sack R, Siever L: Clinical studies of l-5-hydroxytryptophan in depression, in Barchas J, Usdin E (eds): Serotonin and Behavior. New York, London, Academic Press, 1973, pp 549–559

36. Trimble M, Chadwick D, Reynolds E, et al: l-5-hydroxytryptophan and mood. Lancet 1:583, 1975

37. Pühringe W, Wirz-Justice A, Graw P, et al: Intravenous l-5-hydroxytryptophan in normal subjects: an interdisciplinary precursor loading study. I. implication of reproducable mood elevation. Pharmakopsychiatr 9:260–268, 1976

38. van Woert MH, Rosenbaum D, Howieson J, et al: Long term therapy of myoclonus and other neurological disorders with l-5-hydroxytryptophan and carbidopa. N Engl J Med 296:70–75, 1977

39. Åberg A, Holmberg G: Preliminary clini-

cal test of zimelidine (H102/09) a new 5-HT reuptake inhibitor. Acta Psychiatr Scand 59:45–58, 1979

40. van Praag HM, De Haan S: Central serotonin deficiency. A factor which increases depression vulnerability? Acta Psychiatr Scand Suppl (in press)

41. van Praag HM: Psycho-psychiatry. Can psychosocial factors cause psychiatric disorders? Compr Psychiatry 20:215–225, 1979

42. Buchsbaum MS, Coursey RD, Murphy DL: The biochemical high-risk paradigm: Behavioral and familial correlates of low platelet monoamine oxidase activity. Science 194:339–342, 1976

43. Dorus E, Pandey GN, Shaughnessy R, et al: Low platelet monoamine oxidase activity, high red blood cell lithium ratio and affective disorders: a multivariate assessment of genetic vulnerability to affective disorders. Biol Psychiatry

44. Aprison MH, Tahahashi R, Tachiki K: Hypersensitive serotonergic receptors involved in clinical depression. A theory, in Haber B, Aprison MH (eds): Neuropharmacology and Behavior. New York, Plenum Press, 1978

45. Shopsin B, Gershon S, Goldstein M, et al: Use of synthesis inhibitors in defining a role for biogenic amines during imipramine treatment in depressed patients. Psychopharmacol Commun 1:239–249, 1975

46. Costain DW, Green AR, Grahame Smith DG: Enhanced 5-hydroxytryptamine-mediated behavioural responses in rats following repeated electroconvulsive shock: relevance to the mechanism of the antidepressant effect of electroconvulsive treatment. Psychopharmacology 61:167–170, 1979

47. Åsberg M, Bertilsson L, Tuck D, et al: Indolamine metabolites in the cerebrospinal fluid of depressed patients before and during treatment with nortriptyline. Clin Pharm Therap 14:277–286, 1972

48. de Wied D, van Ree JM: Endorphins and their significance for psychopathology. Ned T Geneesk 123:327–334, 1979

49. Verhoeven WMA, van Praag HM, van Ree JM, et al: Improvement of schizophrenic patients treated with (des-tyr)-γ-endorphin (DTγE). Arch Gen Psychiatry 36:294–298, 1979

50. van Praag HM, Korf J, Dols LCW, et al: A pilot study of the predictive value of the probenecid test in the application of 5-hydroxytryptophan as an antidepressant. Psychopharmacologia 25:14–21, 1972