Psychiatry Research, 3, 75-83 (1980)

Depression Vulnerability and 5-Hydroxytryptophan Prophylaxis

Herman van Praag and Sietse de Haan

Received February 5, 1980; revised version received June 6, 1980; accepted June 9, 1980.

Abstract. Previous studies have indicated that (1) The group of vital (endogenous) depressions encompasses a subgroup with a central serotonin (5-hydroxytryptamine; 5-HT) deficiency. (2) Abolition of this deficiency—with the aid of 5-hydroxytryptophan (5-HTP), a 5-HT precursor, or clomipramine, a 5-HT reuptake inhibitor— leads to abatement of depressive symptoms. It therefore seems plausible that the suspected 5-HT deficiency contributes to the development of depressive symptoms instead of resulting from them. (3) In a majority of patients, the suspected 5-HT deficiency persists even when the depressive symptoms have disappeared and the medication has been discontinued. This suggested that the disturbed central 5-HT metabolism is not a direct causal, but a predisposing factor. If so, abolition of the suspected 5-HT deficiency, e.g., with the aid of 5-HTP, would be expected to have a prophylactic effect. As predicted, 5-HTP was found in the present study to reduce the relapse rate in recurrent vital depressions with both a unipolar and a bipolar course. The prophylactic effect was most pronounced in patients with persistent disorders of central 5-HT metabolism; this observation, however, requires corroboration. 5-HTP prophylaxis is the first aimed (i.e., pathological substrate-oriented) type of chemoprophylaxis known in psychiatry.

Key Words. Depression, depression vulnerability, depression prophylaxis, central serotonin metabolism, serotonin precursors.

There are indications of a central deficiency of serotonin (5-hydroxytryptamine; 5-HT) in certain types of vital (endogenous) depression with a unipolar or bipolar course (Van Praag, 1978*a*).

Evidence of such a deficiency falls into two major categories: (1) A decreased concentration of 5-hydroxyindoles has been reported in certain raphe nuclei in suicide victims (Lloyd et al., 1974) and in depressive patients who died from natural causes (Birkmayer and Riederer, 1975). The raphe nuclei are the principal localization of cell bodies of serotonergic neurons. (2) Studies of cerebrospinal fluid (CSF) have found a decreased baseline concentration of 5-hydroxyindoleacetic acid (5-HIAA), the principal 5-HT metabolite (Åsberg et al., 1976), and a decreased 5-HIAA accumulation after probenecid administration (Van Praag et al., 1970; Sjöström and Roos, 1972; Post and Goodwin, 1978). Probenecid inhibits transportation of 5-HIAA from the central nervous system (CNS) to the blood stream. The resulting 5-HIAA accumulation is an indication of 5-HT degradation. (For a discussion of the probenecid test, see Van Praag, 1977*a*.)

Herman van Praag, M.D., Ph.D., is Professor and Head, and Sietse de Haan, Ph.D., is Statistician, Department of Psychiatry, University Hospital Utrecht, Catharijnesingel 101, P.B. 16250, 3500 CG Utrecht, The Netherlands. (Reprint requests to Professor van Praag.)

The group of vital depressions, which tends toward homogeneity of symptomatology, includes patients with and without demonstrable disorders of central 5-HT metabolism. This biological heterogeneity suggested the possibility of a biochemical typology of vital depressions (Van Praag and Korf, 1971), a concept subsequently corroborated by other observations (Maas, 1975; Åsberg et al., 1976; Goodwin et al., 1977; Van Scheyen et al., 1977).

Disorders of central 5-HT metabolism are probably primary; that is, they contribute to the development of depressive symptoms (or of certain depressive symptoms) instead of resulting from them. This conclusion stems from the observation that an increase of the amount of 5-HT available in the brain leads to abatement or disappearance of depressive symptoms. The amelioration of symptomatology can be achieved with 5-hydroxytryptophan (5-HTP) (Van Praag et al., 1972; Sano, 1972; Angst et al., 1977; Van Praag, 1978*a*; Kaneko et al., 1979; Van Hiele, 1980), a 5-HT precursor, and with clomipramine (Van Praag, 1977*b*), a tricyclic antidepressant which strongly inhibits the uptake of 5-HT (Carlsson et al., 1969). The strongest therapeutic effect is obtained with a combination of 5-HTP and clomipramine (Van Praag, 1978*b*). These 5-HT-potentiating compounds are also effective in "normo-serotonergic" vital depressions, but the effect is less pronounced (Van Praag, 1977*c*, 1978*b*).

In the majority of patients, changes in CSF 5-HIAA persist even after depressive symptoms have disappeared and medication has been discontinued (Van Praag, 1977*c*). This led us to the hypothesis that the suspected central 5-HT deficiency is not a direct causal but a predisposing factor (Van Praag, 1977*c*). If this hypothesis is correct, then abolition of the 5-HT deficiency (e.g., with the aid of 5-HTP) can be expected to reduce the "vulnerability" to vital depressions. In a preliminary study, we did indeed find indications of a prophylactic effect of 5-HTP against depressions of this type (Van Praag, 1977*c*). The present study was designed to verify these preliminary findings. It focuses on two questions: (1) Does 5-HTP reduce the relapse rate in recurrent vital depressions with a unipolar or bipolar course? (2) If so, is this effect most marked in patients with signs of a persistently disturbed cerebral 5-HT metabolism?

Methods

Patients. The sample comprised 20 depressive patients (13 females and 7 males) who ranged in age from 31 to 57 years. All were suffering from recurrent vital depressions. During the 4 years before the study, all had been hospitalized at least three times in connection with depressive episodes. Fourteen patients had never experienced manic or hypomanic phases (unipolar depressions), but six had (bipolar depressions).

The syndrome of vital depressions is roughly equivalent to the syndrome referred to in the Anglo-American literature as endogenous depression. The syndrome is etiologically nonspecific; that is, it can be precipitated by various factors—endogenous, psychosocial, or somatic in nature. (For a more detailed discussion of vital depression, see Van Praag et al., 1965; Van Praag, 1978*b*.)

Unipolar depression is defined as recurrent depression (at least two episodes characterized by the vital depressive syndrome, irrespective of the presence or absence of precipitating events). A diagnosis of bipolar depression is applied to a patient who, in addition to the vital depression syndrome, has also experienced one or more episodes

of mania or hypomania. Thus, in our terminology, subtype diagnoses of unipolar and bipolar depression are based on two criteria: symptomatology and course.

Biochemical characteristics. In 13 patients, a subnormal postprobenecid 5-HIAA accumulation was observed, both during depressive phases and during asymptomatic intervals. 5-HIAA concentrations more than two standard deviations from the mean were defined as abnormal values (Van Praag et al., 1973). The mean accumulation at the most recent observation was 47 ± 12.1 ng/ml. In the other seven patients, 5-HIAA accumulation was always within normal limits. At the most recent observation, a mean accumulation of 119 ± 34.0 ng/ml was found. The concentration of catecholamine metabolites in the CSF showed no persistent abnormalities.

Treatment. Before entering the 5-HTP study, all patients had been hospitalized in connection with a vital depressive episode and successfully treated for 3-6 months with clomipramine (Anafranil). This medication was discontinued at the time of discharge, and the 5-HTP experiment was started 3-4 weeks later, when all test subjects were free of depressive symptoms. The patients were randomly divided into two groups. For a period of 1 year, group A (10 patients) received L-5-HTP (200 mg daily) in combination with the peripheral decarboxylase inhibitor carbidopa (150 mg daily). 5-HTP was supplied in coated capsules that pass through the stomach unchanged and do not dissolve until they enter the small intestine (at $pH = 8.6$). Moreover, the dosage was gradually increased in the course of a few weeks. In this way, gastrointestinal side effects were avoided in the majority of cases. During the next year, these patients received identical placebo capsules. In group B (10 patients), the 5-HTP/placebo sequence was reversed.

Rating. Patients were seen at least once every 4 weeks, at which times their mental state was rated using the Hamilton Depression Scale. In addition, a 4-point global rating was made, in which scores ranged from 0 (absence of depressive symptoms) to 3 (pronounced presence of depressive symptoms). The global rating was keyed to three behavioral modalities: mood, motor activity, and ability to experience emotions. In principle, therefore, it was possible for a test subject to receive a score of 0 but nevertheless not to be entirely free from symptoms (e.g., slept badly or mentioned somatic complaints). We chose this rating method for two reasons. To begin with, we were primarily interested in whether 5-HTP prevents disturbances in the above-mentioned behavioral modalities. Secondly, with conventional depression scales (e.g., Hamilton's) it is possible to obtain an elevated depression score even though these modalities are undisturbed. We wanted to avoid this. At every visit to the outpatient clinic, we tested the patient's blood pressure, blood picture, liver and kidney functions, and asked questions aimed at detecting possible side effects. The patients were aware of the fact that a new (potential) prophylactic method was being tested.

Relapses. A score of 2 or higher on the global rating scale and/or a score of 21 or higher on the Hamilton Depression Scale was defined as a relapse. In that case the patient was treated with clomipramine (150-225 mg daily), while 5-HTP or placebo was continued. The patient remained on clomipramine until 4 weeks after the disappearance of the depressive symptoms. Treatment was carried out in an outpatient setting, unless the risk of suicide necessitated hospitalization.

Results

During the placebo period, nine patients in *group A* developed relapses: one patient had three relapses, three patients two, and five patients one; during the 5-HTP period, three patients developed one relapse each. This is a mean relapse rate of 1.4 per patient during the placebo period, and a rate of 0.3 during the 5-HTP period (Table 1). The difference in relapse rate is statistically significant ($p < 0.005$, sign test; $p < 0.05$, McNemar test).

In *group B*, eight patients developed relapses during the placebo period: two patients had two relapses and six patients had one; during the 5-HTP period, three patients developed relapses: one patient had two relapses and two patients had one. This is a mean relapse rate of 1.0 per patient during the placebo period, and a rate of 0.4 during the 5-HTP period (Table 1). The difference in relapse rate is statistically significant ($p < 0.05$, McNemar test; $p < 0.05$, sign test).

Table 1. Number of patients who relapsed, and number of relapses, during placebo and 5-HTP periods

	Number of patients who relapsed		Number of relapses	
	Placebo period	5-HTP period	Placebo period	5-HTP period
Group A[1] ($n = 10$)	9	3	14	3
Group B[2] ($n = 10$)	8	3	10	4

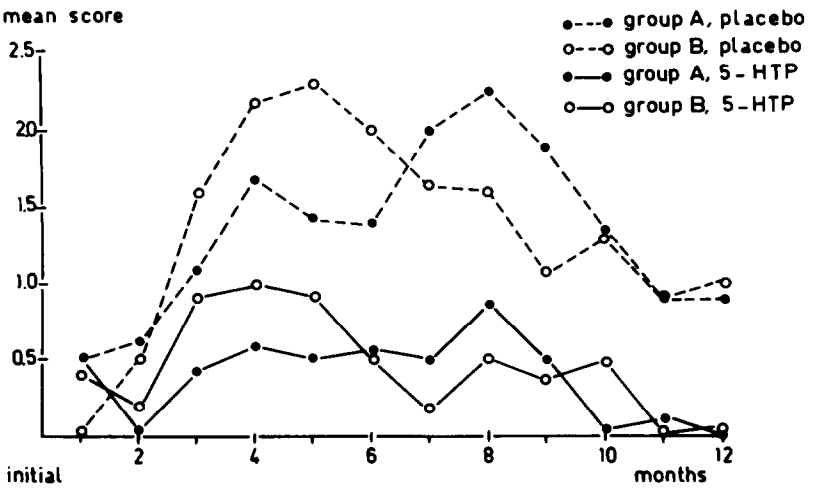
1. One year of 5-HTP medication, followed by 1 year of placebo medication.
2. One year of placebo medication, followed by 1 year of 5-HTP medication.
Note: The difference in relapse rate is statistically significant both in group A ($p < 0.005$, sign test; $p < 0.05$, McNemar test) and in group B ($p < 0.005$, sign test; $p < 0.05$, McNemar test).

Taking groups A and B together, we find an even more marked difference in relapse rate between placebo and 5-HTP periods: $p < 0.001$ (McNemar test) and $p < 0.001$ (sign test).

Of the 17 patients who developed relapses during the placebo period, seven were hospitalized for 4-8 weeks (average 43 days). Of the six patients who developed relapses during the 5-HTP period, three were hospitalized for an average of 52 days.

Not only is the number of relapses during the placebo periods larger than that during the 5-HTP periods, the depressive morbidity during the placebo periods also exceeds that during the 5-HTP periods (Fig. 1). If we calculate the mean depression score per person over the placebo year and over the 5-HTP year and compare these mean values, we find the mean depression score over the placebo year significantly exceeds that over the 5-HTP year, both in group A ($p = 0.001$, sign test) and in group B ($p = 0.001$, sign test).

Fig. 1. Mean depression score during 5-HTP and placebo medication on a 4-point global depression scale in groups A and B



Note: Group A received 5-HTP for 1 year followed by a 1-year placebo period; group B followed the reverse sequence. The mean depression score over the placebo year significantly exceeds that over the 5-HTP year both in group A ($p = 0.001$, sign test) and in group B ($p = 0.001$, sign test).

No manic or hypomanic phases developed during the placebo periods, but during the 5-HTP periods three patients developed one such phase each. These phases were treated with 9-24 mg haloperidol daily for 3-6 weeks, without hospitalization. 5-HTP was continued during haloperidol administration. No adverse interactional effects were observed during the combined treatment.

Thirteen patients belonged to the group with persistent low postprobenecid CSF 5-HIAA accumulation. In the other seven patients, this value had always been normal, both during the depressive phases and during the symptom-free/medication-free intervals. Of the six patients who relapsed during the 5-HTP period, five were of the "normo-serotonergic" type, while one was of the "5-HT-deficient" type (Table 2). The relapse rate in the "5-HT-deficient" subgroup is significantly lower than that in the "normo-serotonergic" subgroup ($p < 0.02$, Fisher's exact probability test, two-tailed). It seems that treatment with 5-HTP is especially protective for the former type. Unipolar or bipolar subtype diagnoses did not correlate with relapse or nonrelapse during the 5-HTP period.

During the 5-HTP periods, nausea and vomiting occurred in six patients, always during the first 2 months. Three patients developed similar complaints during the placebo periods, likewise in the initial period. No other significant side effects were observed. There is reason to assume, therefore, that the raters remained blind to the medication.

Table 2. Patients who relapsed during 5-HTP periods: Comparison between patients with normal and those with subnormal postprobenecid CSF 5-HIAA concentrations

Patient groups	Number of patients	Relapse during 5-HTP	No relapse during 5-HTP
Persistent normal postprobenecid CSF 5-HIAA	7	5	2
Persistent subnormal postprobenecid CSF 5-HIAA	13	1	12

Note: The relapse rate in the "5-HT deficient" subgroup is significantly lower than that in the "normo-serotonergic subgroup ($p < 0.02$, Fisher's exact probability test, two-tailed). "Persistent" means: during depressive episodes *and* in symptom-free intervals.

Discussion

Treatment with L-5-HTP, plus a peripheral decarboxylase inhibitor, exerts a prophylactic influence on patients who suffer from recurrent vital depressions. It reduces the relapse rate and the depressive morbidity in general. Because there are at present no reasons to attribute this prophylactic effect to the decarboxylase inhibitor, it is presumably due to 5-HTP, a 5-HT precursor, which is converted to 5-HT in both central serotonergic (Korf et al., 1974) and catecholaminergic cells (Butcher et al., 1972; Ng et al., 1972). 5-HTP decarboxylase, the enzyme which converts 5-HTP to 5-HT, and dopa decarboxylase, which transforms dopa to dopamine, are identical enzymes (Yuwiler et al., 1959).

It is conceivable that 5-HT comes to function as a false transmitter in catecholaminergic cells, thus reducing the activity in these systems. Could this effect underlie the depression-preventing (and antidepressant) effect of 5-HTP? The classical monoamine (MA) hypotheses on the pathogenesis of depressions postulate that hypoactivity of serotonergic and/or noradrenergic systems in the brain contributes to the development of (certain) depressive symptoms (Van Praag, 1962; Schildkraut, 1965; Bunney and Davis, 1965; Lapin and Oxenkrug, 1969). The signs of a reduced MA turnover in certain depressive patients are regarded as primary phenomena. But there is also an alternative MA hypothesis, which holds that the primary defect lies in hypersensitivity of serotonergic and/or noradrenergic postsynaptic receptors. In this hypothesis the signs of a reduced MA metabolism are interpreted as secondary to the primary receptor defect (Post and Goodwin, 1978; Sulser et al., 1978). I have elsewhere argued that this alternative hypothesis is not very plausible on clinical grounds (Van Praag, 1977*a*). We therefore consider it unlikely that suppression of catecholaminergic activity could underlie the prophylactic effect of 5-HTP; instead we assume that this effect is based on an increased amount of available 5-HT in the brain. This interpretation is supported by a number of additional observations.

- 5-HTP has proved to be an effective antidepressant in patients with vital (endogenous, primary) depressions (Van Praag et al., 1972; Sano, 1972; Angst et al., 1977; Kaneko et al., 1979; Van Praag, 1980; Van Hiele, 1980) and particularly in those with a disturbed 5-HT metabolism (Van Praag et al., 1972; Van Praag, 1978*b*). We have

demonstrated that patients of the latter type, too, are able to convert 5-HTP to 5-HT, and in fact do so (Van Praag, 1977*c*). A 5-HTP effect, per se, is therefore not likely to be involved.

• The antidepressant effect of 5-HTP is enhanced by clomipramine, a tricyclic antidepressant which strongly inhibits 5-HT reuptake and therefore additionally increases the availability of 5-HT at the postsynaptic receptors (Van Praag et al., 1974; Van Praag, 1978*c*). This is not to say, of course, that clomipramine selectively potentiates 5-HT. Its main degradation product is a rather strong uptake inhibitor of noradrenaline.

• In normal test subjects, 5-HTP (administered by intravenous drip) has a euphoric effect (Trimble et al., 1975; Pühringe et al., 1976).

• In patients treated with 5-HTP for myoclonus, too, evidence of euphoria has been reported; and maniacal disinhibition has been described as well (Van Woert et al., 1977).

Since low 5-HIAA accumulation after probenecid persists even during clinical recovery in many "5-HT-deficient" depressive patients, we have assumed that this 5-HT deficiency is a predisposing rather than a causal factor. The fact that (1) 5-HTP prevents a substantial percentage of relapses in unipolar and bipolar depressions and (2) 5-HTP prophylaxis seemed to be most effective in patients with signs of a persistent 5-HT deficiency supports this hypothesis. The unipolar-bipolar distinction did not predict success of 5-HTP prophylaxis.

We recently reported additional evidence that would support the view that 5-HT deficiency is a factor predisposing to depression: In patients with signs of persistently disturbed 5-HT metabolism, the depression rate was higher than that in "normoserotonergic" patients. In family members of the former patients, too, the depression rate was increased (Van Praag and De Haan, 1979).

In the present study, three patients developed a maniacal disinhibition during the 5-HTP period; all were suffering from bipolar depressions. Two of them had a hypomanic mood swing during clomipramine treatment before entering the 5-HTP study. The manic switches occurred in the second half of the 5-HTP period, seemingly unrelated to the withdrawal of clomipramine. Therefore possible receptor supersensitivity is not a likely explanation. The mania could have been provoked by 5-HTP, or could have been independent of 5-HTP: simply a phase in the natural course of illness. Our data are inconclusive in this respect. Generally speaking, few data are available on the relation between central 5-HT metabolism and mania; and the available data are controversial (Van Praag, 1978*a*).

In summary, the data presented support the hypothesis that (1) central serotonergic systems are involved in mood regulation; (2) these systems are permanently disturbed in a certain category of depressive patients; (3) this leads to depression "vulnerability": an increased tendency to respond to endogenous and exogenous stimuli with a pathological depression of mood; (4) increased "vulnerability" to depressions can be reduced with the aid of 5-HTP.

5-HTP prophylaxis, if replicated, is the first aimed (i.e., biochemical substrate-oriented) chemoprophylaxis known in psychiatry.

References

Angst, J., Woggon, B., and Schoepf, J. The treatment of depression with L-5-hydroxytryptophan versus imipramine: Results of two open and one double blind study. *Archiv für Psychiatrie und Nervenkrankheiten,* **224,** 175 (1977).

Åsberg, M., Thoren, P., Traskman, L., Bertilsson, L., and Ringberger, V. "Serotonin depression:" A biochemical subgroup within the affective disorders? *Science,* **191,** 478 (1976).

Birkmayer, W., and Riederer, P. Biochemical post-mortem findings in depressed patients. *Journal of Neural Transmission,* **37,** 95 (1975).

Bunney, W.E., Jr., and Davis, J.M. Norepinephrine in depressive reactions: A review. *Archives of General Psychiatry,* **13,** 483 (1965).

Butcher, L.L., Engel, J., and Fuxe, K. Behavioral, biochemical and histochemical analyses of the central effects of monoamine precursors after peripheral decarboxylase inhibition. *Brain Research,* **41,** 387 (1972).

Carlsson, A., Corrodi, H., Fuxe, K., and Hökfelt, T. Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-α-ethyl-meta-tyramine. *European Journal of Pharmacology,* **5,** 357 (1969).

Goodwin, F.K., Rubovits, R., Jimerson, D.C., and Post, R.M. Serotonin and norepinephrine "subgroup" in depression: Metabolite findings and clinical-pharmacological correlations. *Scientific Proceedings of the American Psychiatric Association,* **130,** 108 (1977).

Hiele, L.J. van. L-5-Hydroxy-L-tryptophan in depression. The first substitution therapy in psychiatry? *Neuropsychobiology,* **6,** 230 (1980).

Kaneko, M., Kumashiro, H., Takahashi, Y., and Hoshino, Y. L-5-HTP treatment and serum 5-HT levels after L-5-HTP loading in depressed patients. *Neuropsychobiology,* **5,** 232 (1979).

Korf, J., Venema, K., and Postema, F. Decarboxylation of exogenous L-5-hydroxytryptophan after destruction of the cerebral raphe system. *Journal of Neurochemistry,* **23,** 249 (1974).

Lapin, I.P., and Oxenkrug, G.F. Intensification of the central serotonergic process as a possible determinant of the thymoleptic effect. *Lancet,* **I,** 132 (1969).

Lloyd, K.J., Farley, I.J., Deck, J.H.N., and Hornykiewicz, O. Serotonin and 5-hydroxyindoleacetic acid in discrete areas of the brainstem of suicide victims and control patients. *Advances in Biochemical Psychopharmacology,* **11,** 387 (1974).

Maas, J.W. Biogenic amines and depression: Biochemical and pharmacological separation of two types of depression. *Archives of General Psychiatry,* **32,** 1357 (1975).

Ng, L.K.Y., Chase, T.N., Colburn, R.W., and Kopin, I.J. Release of (^{3}H) dopamine by L-5-hydroxytryptophan. *Brain Research,* **45,** 499 (1972).

Post, R.M., and Goodwin, F.K. Approaches to brain amines in psychiatric patients: A reevaluation of cerebrospinal fluid studies. In: Iversen, L.L., Iversen, S.D., and Snyder, S.H., eds. *Handbook of Psychopharmacology.* Vol. 13. Plenum Press, New York and London (1978).

Praag, H.M. van. A critical investigation of the significance of monoamine oxidase inhibition as a therapeutic principle in the treatment of depression. Thesis, Utrecht (1962).

Praag, H.M. van. *Depression and Schizophrenia. A Contribution on Their Chemical Pathologies.* Spectrum Publications, New York (1977*a*).

Praag, H.M. van. New evidence of serotonin-deficient depression. *Neuropsychobiology,* **3,** 56 (1977*b*).

Praag, H.M. van. Amine hypotheses of affective disorders. In: Iversen, L.L., Iversen, S.D., and Snyder, S.H., eds. *Handbook of Psychopharmacology.* Vol. 13. Plenum Press, New York and London (1978*a*).

Praag, H.M. van. Significance of biochemical parameters in the diagnosis, treatment and prevention of depressive disorders. *Biological Psychiatry,* **12,** 101 (1977*c*).

Praag, H.M. van. *Psychotropic Drugs: A Guide for the Practitioner.* Brunner/Mazel, New York (1978*b*).

Praag, H.M. van. Central monoamine metabolism in depressions: I. Serotonin and related compounds. *Comprehensive Psychiatry,* **21,** 30 (1980).

Praag, H.M. van, Burg, W. van den, Bos, E.R.H., and Dols L.C.W. 5-Hydroxytryptophan in combination with clomipramine in "therapy-resistant" depression. *Psychopharmacologia*, **38**, 267 (1974).

Praag, H.M. van, and Haan, S. de. Central serotonin metabolism and frequency of depression *Psychiatry Research*, **1**, 219 (1979).

Praag, H.M. van, and Korf, J. Endogenous depression with and without disturbances in the 5-hydroxytryptamine metabolism: A biochemical classification? *Psychopharmacologia*, **19**, 148 (1971).

Praag, H.M. van, Korf, J., Dols, L.C.W., and Schut, T. A pilot study of the predictive value of the probenecid test in application of 5-hydroxytryptophan as antidepressant. *Psychopharmacologia*, **25**, 14 (1972).

Praag, H.M. van, Korf, J., and Puite, J. 5-Hydroxyindoleacetic acid levels in the cerebrospinal fluid of depressive patients treated with probenecid. *Nature*, **225**, 1259 (1970).

Praag, H.M. van, Korf, J., and Schut, T. Cerebral monoamines and depression: An investigation with the probenecid technique. *Archives of General Psychiatry*, **28**, 827 (1973).

Praag, H.M. van, Uleman, A.M., and Spitz, J.C. The vital syndrome interview. A structured standard interview for the recognition and registration of the vital depressive symptom complex. *Psychiatria, Neurologica und Neurochirurgica*, **68**, 329 (1965).

Pühringe, W., Wirz-Justice, A., Graw, P., Lacoste, V., and Gastpar, M. Intravenous L-5-hydroxytryptophan in normal subjects: An interdisciplinary precursor loading study: Part I. Implications of reproducible mood elevation. *Pharmakopsychiatrie*, **9**, 260 (1976).

Sano, T. α-5-Hydroxytrytophan (α-5-HTP)—Therapie bei endogener Depression. *Münchener Medicinische Wochenschrift*, **144**, 1713 (1972).

Scheyen, J.D. van, Praag, H.M. van, and Korf, J. A controlled study comparing nomifensine and clomipramine in unipolar depression, using the probenecid technique. *British Journal of Clinical Pharmacology*, **4**, 179S (1977).

Schildkraut, J.J. The catecholamine hypothesis of affective disorders: A review of supporting evidence. *American Journal of Psychiatry*, **122**, 509 (1965).

Sjöström, R., and Roos, B.E. 5-Hydroxyindolacetic acid and homovanillic acid in cerebrospinal fluid in manic-depressive psychosis. *European Journal of Clinical Pharmacology*, **4**, 170 (1972).

Sulser, F., Vetulani, J., and Mobley, Ph.L. Mode of action of antidepressant drugs. *Biochemical Pharmacology*, **27**, 257 (1978).

Trimble, M., Chadwick, D., Reynolds, E.H., and Marsden, C.D. L-5-Hydroxytryptophan and mood. *Lancet*, **I**, 583 (1975).

Van Woert, M.H., Rosenbaum, D., Howieson, J., and Bowers, M.B., Jr. Long-term therapy of myoclonus and other neurologic disorders with L-5-hydroxytryptophan and carbidopa. *New England Journal of Medicine*, **296**, 70 (1977).

Yuwiler, A., Geller, E., and Eiduson, S. Studies on 5-hydroxytryptophan decarboxylase: I. *In vitro* inhibition and substrate interaction. *Archives of Biochemistry*, **80**, 162 (1959).