Central Monoamine Metabolism in Depressions. II. Catecholamines and Related Compounds

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THE METABOLISM in depression of serotonin (5-hydroxytryptamine; 5-HT) has been studied at the same time as that of the catecholamines (CA), often in the same patients. The principal CAs in the brain are noradrenaline (NA) and dopamine (DA). Both are formed by the amino acid tyrosine, with 3,4-dihydroxyphenylalanine (DOPA) as intermediary metabolite (Table 1). They function as neurotransmitters and do this in relatively well-defined neuronal systems.[1] The principal NA-bearing cell bodies are localized in the locus coeruleus. Their number is relatively small, but their extensions fan out over large areas of the brain and spinal cord. The DA-ergic system can be divided into three distinct parts.

1. The nigrostriatal system, whose cell bodies are localized in the compact zone of the substantia nigra while the fibres ascend to the caudate nucleus and the putamen. This system is involved in the extrapyramidal regulation of motor activity.
2. The mesolimbic and mesocortical system, with cell bodies in the ventral tegmental area and fibers extending to certain nuclei of the limbic system (e.g., the nucleus accumbens and the olfactory bulb) and to the cerebral cortex. This system may be part of the cerebral system involved in mood and impulse regulation.
3. The tubero-infundibular system, with cell bodies in the arcuate and paraventricular nuclei and fibres extending to the medial eminence. Via the inhibiting and releasing factors in the hypothalamus, this system regulates the release of certain anterior pituitary hormones.

WHY CA RESEARCH IN DEPRESSIONS?

The question of whether the NA metabolism can be disturbed in depressions was prompted by the same observations that stimulated research into the correlation between 5-HT and depression (see Part I). On the one hand, there was the fact that both types of antidepressant potentiate central NA, but via different mechanisms. MAO inhibitors inhibit the degradation of NA, whereas tricyclic antidepressants inhibit the reuptake of NA in the neuron. Reuptake is the principal mechanism by which NA and other monoamines (MA) are inactivated after having transmitted information from one neuron to the other. As a result, the amount of transmitter available at the receptors per unit of time increases. On the other hand it was found that reserpine, a compound with depressogenic properties, empties not only the 5-HT stores but those of the

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Table 1. Simplified Diagram of CA Metabolism

Tyrosine → Dihydroxyphenylalanine (DOPA) →	Dopamine (DA) →	Noradrenaline (NA)
	↓	↓
	Homovanillic acid (HVA)	3-Methoxy-4-hydroxy-phenylglycol (MHPG)
	↓	↓
	Dihydroxy-phenylacetic acid (DOPAC)	Vanillylmandelic acid (VMA)

CAs as well. Finally it was discovered that other compounds that suppress CA activity in the brain can also provoke depression. In this context I mention methyldopa and propanolol.[2] These findings raised the suggestion of a possible relationship between central NA deficiency and the development of certain depressive symptoms.

The reuptake of DA in the neuron is hardly influenced, if at all, by tricyclic antidepressants. Possibly because of this, DA initially attracted little attention in biologic depression research. This changed as a result of observations like the following:[3,4] (1) In Parkinson's disease, which in part can be regarded as a DA deficiency disease, the rate of (vital) depressions is increased. There is no reason to assume that this results exclusively from the psychological stress caused by a disabling illness. (2) Amphetamines (compounds with a euphorizing effect) proved vigorously to potentiate central DA. (3) Direct DA agonists were developed with which it is possible to activate central DA-ergic systems with a high degree of selectivity; examples are bromocriptine and piribedil.

The DA and NA data will be separately discussed for didactic reasons; not to indicate independent operations of these systems for such a suggestion would be at odds with the facts.

DIRECT INDICATIONS OF A DISTURBANCE IN CENTRAL CA METABOLISM IN DEPRESSIONS

Noradrenaline

Direct indications of a central NA deficiency in certain types of depression have been scanty.[5] Postmortem studies have been negative in this respect. The results of studies of cerebrospinal fluid (CSF) are not unequivocal. These studies involved determination of the concentration of NA itself as well as the concentrations of its metabolites: 3-methoxy-4-hydroxyphenyl glycol (MHPG) and vanillylmandelic acid (VMA). In the CNS, MHPG is the principal NA metabolite, while VMA is subordinate. In the periphery the reverse is true. The group of Post and Goodwin[6] repeatedly reported the existence of a subgroup of vital depressions with decreased CSF MHPG and VMA levels. Other studies reported negative findings, but it is to be noted that the Goodwin group studied by far the largest number of patients. Moreover, it is to be kept in mind that determination of MHPG in the CSF is less instructive than determination of the DA and 5-HT metabolites homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA), respectively. To begin with, the transport of MHPG differs from that of HVA and 5-HIAA in that it is not probenecid-sensitive. We must

therefore rely on baseline concentrations, which afford less information than postprobenecid levels (see Part I). Moreover, the MHPG in lumbar CSF largely originates from the spinal cord and not from the brain on which we are trying to obtain information. To a much lesser degree this applies to HVA and 5-HIAA. Finally, until recently, MHPG determination was a complicated procedure, and in view of this, the reliability of the observations reported in older studies is not incontrovertible.

Dopamine

Postmortem studies revealed no abnormalities, but CSF studies did.[5] In most studies the postprobenecid HVA accumulation was decreased, particularly in the group of vital depressions. This finding indicates decreased degradation of the mother substance DA in the CNS. According to most investigators, the baseline CSF HVA level is not decreased, and this indicates that the probenecid technique does indeed enhance the value of CSF studies, as postulated in Part I. We personally established that a decreased postprobenecid HVA accumulation is found in particular in vital depressions with marked motor retardation,[7] and this was corroborated by Banki.[8] In Parkinson's disease, too, the postprobenecid HVA accumulation is usually subnormal.[9] The values found in retarded vital depressions and in Parkinson patients are of the same order of magnitude. Both conditions involve hypokinesia, and the DA disorder is possibly related to this (Table 2).

INDIRECT INDICATIONS OF DISORDERS OF CENTRAL CA METABOLISM IN DEPRESSIONS

Noradrenaline

Renal MHPG excretion. Determination of the renal excretion of a MA metabolite makes sense only if a substantial part of it originates from the CNS. To some extent, this applies to MHPG. The estimate is that over 50% of the MHPG excreted in urine is formed in the CNS.[10] In rats, stimulation of the locus coeruleus, which largely consists of NA-bearing neurons, leads to a substantial increase in plasma MHPG concentration.[11] Moreover, motor activity exerts little influence on MHPG excretion (Hollister et al., 1978), but the degree of anxiety possibly does have a more marked effect.[12]

Table 2. CSF HVA Concentration Before and After Probenecid in Patients With Depression and Parkinson's Disease

	Number of Test Subjects	HVA Concentration (Mean ± SD in ng/ml)		
		Before Probenecid	After Probenecid	Difference
Depression (not retarded)	12	43 ± 17	136 ± 36	63 ± 37
Depression* (retarded)	8	32 ± 8	53 ± 32	20 ± 28
Parkinson's*	26	30 ± 25	60 ± 55	30 ± 49
Controls	12	42 ± 16	91 ± 26	50 ± 33

*HVA accumulation significantly decreased.[7,8]

Accepting a rather wide margin of uncertainty, it can be stated that renal MHPG is an indicator of NA degradation in the CNS. Several authors have reported diminished renal MHPG excretion during depressive phases in a subgroup of vital depressions. The VMA excretion was normal.[13,14] This could indicate a reduced cerebral NA turnover with undisturbed peripheral NA metabolism. Unfortunately, one of these studies included simultaneous determination of CSF MHPG. Depressive patients with subnormal and normal MHPG excretions were not symptomatologically distinguishable. I remind the reader that the same applied to depressive patients with and without indications of a central 5-HT metabolism. Findings of this type prompted us to formulate the postulate of the biochemical classifiability of depressions.[15]

Neuroendocrine research. A diminished CA turnover does not necessarily imply hypofunction of CA-ergic systems. For the latter to become plausible, real functional disorders have to be demonstrated. For this purpose the neuroendocrine strategy was introduced (see Part I). Via inhibiting and releasing factors from the hypothalamus, CA-ergic systems influence the release of anterior pituitary hormones. If a diminished CA turnover is indeed associated with reduced CA-ergic function, then this should become manifest in a disturbed release of these hormones.

In vital depressive patients (as previously stated, not in all patients but only in a certain subcategory), the following endocrine disorders have so far been diagnosed:

1. Cortisol hypersecretion:[16,17] The 24-hour profile of plasma cortisol normally shows 7–9 peaks, and production diminishes to zero between about 10:00 p.m. and 2:00 a.m. In a subgroup of vital depressions the number of cortisol peaks is increased, the peaks are higher than normal, and considerable cortisol secretion is also observed during what is normally the "silent period." When the adrenals are intact, cortisol secretion virtually parallels that of ACTH. These findings, therefore, are suggestive of ACTH hypersecretion. Via the corticotropin-releasing factor (CRF), Na-ergic cells in the hypothalamus inhibit ACTH secretion.[18] One (not *the*) explanation of the cortisol overproduction observed is therefore hypoactivity of hypothalamic Na-ergic systems. The hypothesis is supported by the fact that, in depressive patients with cortisol hypersecretion, it is difficult to suppress cortisol production with the aid of dexamethasone,[19] a synthetic corticosteroid that as a rule vigorously inhibits ACTH secretion. When this inhibitory effect is diminished, disinhibition of the CRF/ACTH system seems likely.
2. Growth hormone (GH) is an anterior pituitary hormone whose release is stimulated by, among other things, NA-ergic systems in the hypothalamus, with the GH-releasing factor as intermediary. In particular, the GH release provoked by insulin-induced hypoglycaemia is believed to be NA-ergically mediated. In postmenopausal depressive women, the GH response after insulin proved to be decreased.[20] Hypoactivity of NA-ergic cells in the hypothalamus is one of the possible explanations.
3. Luteinizing hormone (LH) is another hormone that is probably partly NA-ergically controlled, with the LH-releasing factor as intermediary.

The plasma LH level, too, is decreased in some vital depressions,[21] and this phenomenon is likewise consistent with NA-ergic hypoactivity in the hypothalamus.

The abovementioned hormonal phenomena are not likely to be based on primary hypophyseal insufficiency. Although the production of GH and LH is decreased, that of ACTH/cortisol is increased. A hypothalamic disorder is therefore more likely. Its nature is still obscure, and several explanations are conceivable, however, Na-ergic hypoactivity could be a common denominator. In my opinion, therefore, these endocrine observations can be interpreted for the time being as supporting the MA hypothesis.

Hormonal disorders do not occur in all vital depressive patients any more than do NA disorders. They characterize a certain subcategory that is not identifiable in psychopathologic terms. Hormonal and neurotransmitter status have not been simultaneously studied as yet in depressive patients. Should it be found that the hormonal disorders occur in particular in vital depressive patients with signs of a central NA deficit, then the hypothesis that NA-ergic systems are disturbed in depressions would be firmly supported.

Dopamine

DA metabolites in the urine. So far as we know, DA occurs in the periphery in only modest amounts. It is therefore conceivable that a by no means unimportant proportion of the DA metabolites in the urine, i.e., HVA and dehydroxyphenylacetic acid (DOPAC), is of central origin. Surprisingly, this possibility has not been investigated, to my knowledge; and the same applies to the urinary excretion of DA metabolites in depressive patients.

Neuroendocrine research. The anterior pituitary hormone prolactin[22] is known in particular as a detector of central DA disorders (in the tuberoinfundibular DA system). Its release is vigorously inhibited by DA-ergic cells. The hypothalamic prolactin-inhibiting factor (PIF) is the intermediary. Activation of this DA system reduces prolactin release, while suppression of this system causes increased prolactin release.

A single determination of plasma prolactin in depressive patients revealed no evidence of DA disorders. Singular determinations, however, can be deceptive, for prolactin release is not constant; the release at night exceeds that during the day. Measurement of the 24-hour profile is much more instructive. This has so far been done only once, in a study which revealed that prolactin secretion can be increased in the evening hours in vital depressions (Table 3).[23] This phenom-

Table 3. Mean Serum Prolactin Concentration in Depressive Patients and Normal Controls[23]

Time*	Prolactin Concentration (ng/ml)		Significance p Value (Student's t test)
	Depressive (N = 7)	Controls (N = 5)	
8–10 a.m.	26.6 ± 9.7	21.4 ± 5.7	< 0.025
4–6 p.m.	29.3 ± 14.0	22.2 ± 7.0	< 0.05
6–8 p.m.	49.3 ± 47.5	23.0 ± 5.1	< 0.005
10–10 p.m.	33.5 ± 19.5	25.7 ± 7.3	NS

*Blood was collected every 30 min over a 24-hr period.

enon might be suggestive of hypoactivity of DA-ergic systems. Unfortunately, CSF HVA was not measured in this study.

Conclusion

Both research into renal MHPG excretion and neuroendocrine research have yielded indirect indications of the existence of NA disorders in some vital depressive patients. The weight of this conclusion would increase substantially if it were found that both types of disorder could occur in the same patients.

The peripheral DA metabolism in depressions is still largely unexplored territory. The only study so far made of the 24-hour plasma prolactin profile supports the hypothesis that DA-ergic hypoactivity can occur in vital depressions.

ARE THE CA DISORDERS IN DEPRESSIONS OF CAUSATIVE SIGNIFICANCE?

Strategy

As in the case of 5-HT disorders, the crucial question is that of the relationship between the suspected CA disorders in the brain and the depressions involved: do the metabolic disorders play a causative role, are they secondary to the behavior disorders, or is there no relationship whatever? The strategy used is likewise the same administration of CA-potentiating compounds followed by analysis of the effects on behavior. Alleviation of certain depressive symptoms would indicate a causal relation between metabolic disorders and behavior. Absence of alleviation indicates that a secondary relation or coincidence is more likely.

CA Precursors

Tyrosine. The effect of the amino acid tyrosine, the mother substance of CA, has not been studied in depressions. This is probably due to the fact that the enzyme tyrosine hydroxylase, which converts tyrosine to DOPA, is normally saturated with substrate. Additional tyrosine administration therefore does not lead to increased CA production.

This argument does not apply in the case of a diminished tyrosine supply, e.g., due to diminished conversion of phenylalanine to tyrosine. This is why I consider a study of the effect of tyrosine in depressions to be justifiable. My opinion is supported by the observations of Beckman and coworkers,[24] who demonstrated in an open study that phenylalanine can be therapeutically effective in vital depressions. In this context I note that the effect of phenylalanine can also be explained in a different way, for this amino acid is not only hydroxylated to tyrosine but also decarboxylated to phenylethylamine, a compound with central stimulant properties.[25]

l-DOPA. This is a precursor of NA as well as of DA, but exogenous l-DOPA is largely converted to DA. It has a therapeutic effect in depressions in that it stimulates motor activity and enhances the level of initiative. This effect is most apparent in patients with retarded vital depressions and a subnormal postprobenecid CSF HVA response. The mood as such is hardly influenced.[26,27] These observations suggest a causal relationship between motor retardation and diminished DA turnover (Table 4).

Table 4. DA Metabolism and Therapeutic Response to l-DOPA in Depressive Patients[27]

	Number of Test Subjects	Postprobenecid HVA Concentration (Group Mean/Range in ng/ml)	Motor Retardation*	
			Before Treatment	After Treatment
DA-deficient patients	5	74/65–90	6.8/4–8	2.7/0–3
Patients without DA disorders	5	121/107–143	2.1/0–3	2.4/0–3

Studies With Other CA-Potentiating Compounds

Patients with NA disorders. Do patients with disorders of central NA metabolism show a predilection for a certain type (i.e., a NA-potentiating) of antidepressant? Several independently working groups have reported that the vital depressive patients with decreased renal MHPG excretion respond more favorably to imipramine than corresponding patients without this disorder.[6]

In animal experiments, imipramine has a more marked inhibitory effect on NA reuptake than on 5-HT reuptake. However, the selectivity in favor of NA is too slight to warrant the conclusion that vital depressive patients with peripheral indications of a central NA deficiency respond preferentially to NA-potentiating compounds. There are now NA reuptake inhibitors (nortriptyline, maprotiline) which are virtually 100% selective, but these have not yet been used in studies of the type mentioned above.

In a study of a small number of patients, we were unable to demonstrate a relation between CSF MHPG values and the therapeutic efficacy of nortriptyline (Van Praag 1977). An observation of importance in this context is that reported by Simon et al.,[28] who found that salbutamol, a compound that stimulates β-adrenergic receptors (in the brain also), could be an antidepressant. However, their study was open, and the therapeutic results were not related to variables of NA metabolism.

Patients with DA disorders. The "DA-deficient subgroup" of vital depressions (low HVA response to probenecid) was further investigated with the aid of two different DA-potentiating compounds: piribedil, a compound that activates the postsynaptic DA receptors, and nomifensine, a DA and NA reuptake inhibitor. Both compounds were found to be most effective in the group of the low HVA responders.[29,30] This suggests that the DA disorders are of significance in the pathogenesis of the depression.

Conclusion

The data available are still insufficient to assess the probability that NA disorders in the brain are of significance in the pathogenesis of certain types of vital depression. All observations reported so far indicate, however, that DA disorders correlate causally with certain—possibly motor—components of the depression.

The CSF HVA response to probenecid shows normalization as the depression abates (Van Praag 1977). The same applies to renal MHPG excretion.[31] There is therefore no reason to believe that these metabolic disorders, like those in the 5-HT system (see Part I), could be a predisposing factor.

DISCUSSION

Disorders of central DA metabolism can occur in patients with vital depressions. They are suggestive of a DA deficiency and have been found in particular in patients with manifest motor retardation and loss of initiative; they probably contribute to the pathogenesis of these symptoms. Since the DA disorders disappear as the motor symptoms disappear, there is no reason to believe that, like the 5-HT disorders (see Part I), they may be a predisposing factor.

The majority of patients with Parkinson's disease show similar disorders of DA metabolism. They also suffer from diminished motor activity and loss of initiative. It is therefore conceivable that a DA deficiency underlies these symptoms in both syndromes. This would imply that central DA disorders are nonspecific, i.e., not bound to a particular syndrome (retarded vital depression) or a particular disease entity (Parkinson's disease) but to a given functional condition characterized by hypokinesia and inertia. This led us to the hypothesis that neurobiological variables can be more meaningfully correlated with disturbances in certain well-defined psychological functions than with complex concepts such as psychiatric and neurologic syndromes and nosologic entities.[32]

In principle, the DA findings in depressions and Parkinson's disease give momentum to the development of a more functional psychopathology. I define functional psychopathology as the description of psychiatric conditions in terms of disturbed psychological functions. I envisage such a functional psychopathology not as an alternative to but rather as an important complement of the traditional, more syndromal and/or nosological oriented psychopathology.

Disorders of central NA metabolism also occur in vital depressions, but data are not yet sufficient to establish with a fair degree of probability whether they are of causative significance.

Central NA disorders are not unequivocally related to the motor components of depression, nor are the central 5-HT disorders. NA disorders and 5-HT disorders do not necessarily occur in the same patient. In fact it seems more likely that, within the group of vital depressive patients with central MA disorders, it is either the 5-HT system or the NA system that is predominantly disturbed.[33,34] However, it is too early to decide whether it is really justifiable to distinguish between a 5-HT-deficient and a NA-deficient subgroup within the group of vital depressions. It should be borne in mind in this context that a significant percentage of vital depressive patients show no demonstrable disorders of MA metabolism. It therefore seems likely that (1) the group of vital depressions is heterogeneous in biochemical terms, i.e., in terms of pathogenesis, and (2) non-MA-ergic mechanism may also be involved in the pathogenesis of vital depressive symptoms. Nothing is known as yet about the cause of the MA disorders suspected in vital depressions.

For the time being, the disorders of central CA metabolism observed in vital depressions are best viewed by reference to the "classical" MA hypothesis, in which MA-ergic hypoactivity is the central postulate. The alternative possibility—primary hypersensitivity of CA receptors with secondary diminution of CA synthesis—is less plausible, because procedures that increase CA availability in the brain usually are more likely to have an antidepressant than a

depressant effect. As pointed out in Part I, I take the same view of the 5-HT disorders.

An additional advantage of the classical theory is that it affords a still speculative but verifiable explanation of the empirical fact that vital depression and hypomania are relatively often observed in the same individual. As a result of transmitter deficiency, the postsynpatic CA and 5-HT receptors can become hypersensitive. If the transmitter production increased at a given moment, for whatever reason, then the system enters a state of hyperactivity. This MA-ergic hyperactivity could produce the manic syndrome.

One empirical fact is not readily reconcilable with the MA hypothesis. Inhibition of MA reuptake and inhibition of their degradation in response to tricyclic antidepressants and MAO inhibitors, respectively, occur much more rapidly than any therapeutic effect they may produce, which usually does not become apparent until after 10–20 days. However, the long latency is not necessarily inconsistent with the classical MA hypothesis. It is to be remembered that a latent phase develops, not only with traditional antidepressants but also with MA precursors such as 5-HTP. It is therefore conceivable that the capacity of synthesizing 5-HT and NA is so decreased that, after inhibition of reuptake or degradation or precursor medication, it takes some time before a sufficient amount of neurotransmitter has accumulated at the postsynaptic receptors.

SUMMARY

CA research in depressions is reviewed. The present situation can be outlined as follows:

Vital depressive patients may show central CA disorders that point in the direction of CA deficiency. In principle, this deficiency can be a primary phenomenon or a secondary development: the result of hypersensitivity of postsynaptic CA receptors. The former possibility is considered more plausible than the latter.

The DA disorder seems to be related to motor retardation and loss of initiative and probably plays a role in their pathogenesis. There is no reason to assume that this disorder is a predisposing factor.

The NA disorder is not related to motor symptoms. Its causative significance is still uncertain.

An important byproduct of CA research in depressions is the momentum it gives to attempts to "translate" behavior disorders in terms of disturbed psychological functions. Such a functional psychopathology could be an important supplement to the traditional, more syndromal, and nosological classification of psychiatric conditions.

REFERENCES

1. Cooper JR, Bloom FE, Roth RH: The Biochemical Basis of Neuropharmacology. New York, Oxford University Press, 1978

2. Bant WP: Antihypertensive drugs and depression: a reappraisal. Psychol Med 8:275–283, 1978

3. van Praag HM: The possible significance of cerebral dopamine for neurology and psychiatry. Psychiatr Neurol Neurochir 70:361–379, 1967

4. van Praag HM: Dopamine and the development of disorders of human behaviour, in

Horn AS, Korf J, Westerink B (eds): The Neurobiology of Dopamine. London, Academic Press, 1979

5. van Praag HM: Amine hypotheses of affective disorders. Handbook of Psychopharmacology 13:187–297, 1978

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

7. van Praag HM, Korf J: Retarded depression and the dopamine metabolism. Psychopharmacologia 19:199–203, 1971

8. Banki CM: Correlation between cerebrospinal fluid amine metabolites and psychomotor activity in affective disorders. J Neurochem 29:255–257, 1977

9. Olsson R, Roos BE: Concentration of 5-hydroxyindole acetic acid and homovanillic acid in the cerebrospinal fluid after treatment with probenecid in patients with Parkinson's disease. Nature 219:502–503, 1968

10. Ebert MH, Kopin IJ: Differential labelling of origins of urinary catecholamine metabolites by dopamine-C14, Trans Assoc Am Physicianse 28:256–264, 1975

11. Crawley JN, Maas JW, Roth RH: Increase in plasma 3-methoxy-4-hydroxyphenethylene glycol following stimulation of the nucleus locus coeruleus. Psychopharm Bull 15:27–29, 1979

12. Sweeney DR, Maas JW, Henninger GR: State, anxiety, physical activity and urinary 3-methoxy-4-hydroxytryphenethylene glycol excretion. Arch Gen Psychiatry 35:1418–1423, 1978

13. Schildkraut JJ, Orsulak PJ, Schatzberg AF, et al: Toward a biochemical classification of depressive disorders. 1. Differences in urinary excretion of MHPG and other catecholamine metabolites in clinically defined subtypes of depressions. Arch Gen Psychiatry 35:1427–1433, 1978

14. Schildkraut JJ, Orsulak PJ, LaBrie RA, et al: Toward a biochemical classification of depressive disorders. II. Application of multivariate discriminant function analysis to data on urinary catecholamines and metabolites. Arch Gen Psychiatry 35:1436–1439, 1978

15. van Praag HM, Korf J: Endogenous depressions with and without disturbances in the 5-hydroxytryptamine metabolism: A biochemical classification? Psychopharmacologia 19: 148–152, 1971

16. Sachar EJ, Hellman L, Roffwarg H, et al: Disrupted 24-hour patterns of cortisol secretion in psychotic depression. Arch Gen Psychiatry 28:19–24, 1973

17. Prange AJ, Lipton MA, Nemeroff ChB, et al: The role of hormones in depression. Life Sci 20:1305–1318, 1977

18. van Loon GR: Brain catecholamines and ACTH secretion, in Martini L, Ganong FW (eds): Frontiers in Neuroendocrinology. New York, Oxford University Press, 1973

19. Carroll BJ, Curtis GC, Mendels J: Neuroendocrine regulation in depression. I. Limbic system–adrenocortical dysfunction. II. Discrimination of depressed from nondepressed patients. Arch Gen Psychiatry 33:1039–1044, 33:1051–1058, 1976

20. Brown GM, Seggie JA, Chambers JW, et al: Psychoendocrinology and growth hormone: A review. Psychoneuroendocrinology 3:131–153, 1978

21. Altman N, Sachar EJ, Gruen PH, et al: Reduced plasma LH concentration in postmenopausal depressed women. Psychosom Med 37:274–276, 1976

22. Boyd AE, Reichlen S: Neural control of prolactin secretion in man. Psychoneuroendocrinology 3:113–130, 1978

23. Halbreich U, Grunhous L, Ben-David M: 24 Hours' rhythm of prolactin in depressive patients. Arch Gen Psychiatry (in press)

24. Beckman H, Strauss MA, Ludolph E: DL-Phenylalanine in depressed patients: An open study, J Neural Transmission 41:123–134, 1977

25. Anselman JM, Edwards DJ, Lin M: Phenylethylamine: evidence for a direct postsynaptic dopamine-receptor stimulating action. Brain Res 127:317–322, 1977

26. Goodwin FK, Murphy DC, Brodie HKH, et al: L-Dopa, catecholamines and behavior: A clinical and biochemical study in depressed patients. Biol Psychiat 2:341–366, 1970

27. van Praag HM, Korf J: Central monoamine deficiency in depression: Causative or secondary phenomenon? Pharmakopsychiat 8:321–326, 1975

28. Simon P, Lecrubier R, Jouvent R, et al: Experimental and clinical evidence of the antidepressant effect of a beta-adrenergic stimulant. Psychol Med 8:335–338, 1978

29. Post RM, Gerner RH, Carman JS, et al: Effect of a dopamine agonist piribedil in depressed patients. Arch Gen Psychiatry 35:609–615, 1978

30. van Scheyen JD, van Praag HM, Korf J: A Controlled study comparing nomifensine and clomipramine in unipolar depression, using the

probenecid technique. Br J Clin Pharmacol 4:179S–184S, 1977

31. Pickar D, Sweeney DR, Maas JW, et al: Primary affective disorder, clinical state change, and MHPG excretion. Arch Gen Psychiatry 35:1378–1383, 1978

32. van Praag HM, Korf J, Lakke JPWF, et al: Dopamine metabolism in depressions, psychoses and Parkinson's disease: The problem of the specificity of biological variables in behaviour disorders. Psychol Med 5:138–146, 1975

33. Maas JW: Biogenic amines and depression: Biochemical and pharmacological separation of two types of depression. Arch Gen Psychiatry 32:1357–1361, 1975

34. Garver DL, Davis JM: Biogenic amine hypotheses of affective disorders. Life Sci 24:383–394, 1979

35. Lakke JPWF, Korf J, van Praag HM, et al: Predictive value of the probenecid test for the effect of L-dopa therapy in Parkinson's disease. Nature New Biology 236:208–209, 1972

36. Ganong WF: Evidence for a central noradrenergic system that inhibits ACTH secretion, in: Brain–endocrine interaction: Median eminence structure and function. Basel, Karger, 1972

37. Hollister L, Davis KL, Overall JE, et al: Excretion of MHPG in normal subjects. Arch Gen Psychiatry 35:1410–1415, 1978