Brain Biogenic Amine Depletion and Mood

Joseph Mendels, MD, Alan Frazer, PhD, Philadelphia

To evaluate the hypothesis that clinical depression is associated with reduced brain biogenic amine activity, the behavioral effects, in man, of drugs that deplete the brain of biogenic amines were reviewed. The behavioral changes associated with reserpine administration were interpreted as being primarily a psychomotor retardation-sedation syndrome, due perhaps to a dopamine deficiency, and would not be an adequate model for clinical depression. In susceptible persons, particularly those with a prior history of depression, this psychomotor retardation-sedation might be sufficient to trigger a depression-like episode.

More selective amine depletion, produced either by alpha-methylparatyrosine or by parachlorophenylalanine is not associated with depression. Yet, these drugs produce a more consistent and greater reduction in amine metabolite concentrations than that reported to occur in depressed patients.

In light of this, it is suggested that the depletion of brain norepinephrine and dopamine, or serotonin, is, in itself, not sufficient to account for clinical depression.

It has been widely argued that pathological alterations in mood (either depression or mania) may be mediated through changes in the function of brain biogenic amines, primarily norepinephrine (NE) or serotonin. Several hypotheses have arisen that have generated a substantial number of experiments. Much of this material has been reviewed[1-10] and will not be repeated here. Nevertheless, there is very limited evidence from the clinical studies that is consistent with the amine hypotheses.[9,10] The failure of many of these studies to provide definitive evidence in favor of these hypotheses may of course be due to the indirect methods that the clinical investigator must frequently use. However, it is possible that such failures may reflect important problems with these theories.

An important advance for our understanding of these theories (and indeed for the more general question of the relationship between brain aminergic function and behavior) has been the discovery of compounds that produce a relatively selective depletion of brain monoamines (in contrast to the unselective depletion produced by agents such as reserpine). It is our purpose in this report to review the findings from studies of the effects of these amine-depleting drugs on mood and behavior in man and to consider the implications of these results for the amine theories of affective illness.

In addition, as the reported development of depression in response to reserpine administration generated much of the interest in brain monoamines, on the assumption that it was due to amine depletion, it seems profitable to review the nature of these depression-like episodes. We do not intend a comprehensive review of all the evidence relevant to these studies, but will concentrate on the findings from studies in which there has been a pharmacologically induced reduction of brain aminergic function in man. The biogenic amine hypotheses would predict that such a reduction would be accompanied by clinical depression, or by a depression-like syndrome. As will be shown, the evidence to date does not confirm this prediction.

We are concerned with the possibility that the biogenic amine hypotheses of affective disorders may have led to premature closure on some important issues, and may provide an oversimplistic framework for our understanding of the relationship between the psychopathology and underlying biology. While the proponents of these hypotheses do note their limits, there remains a prevalent tendency to design experiments that fall within the framework of the hypotheses and to interpret results according to how they affect the amine hypotheses. It may be that this creates a type of "tunnel thinking" that could lead to a failure to consider alternative explanations and interpretations of experimental data.

Reserpine

The gross behavioral syndrome and sedation produced by the administration of reserpine as originally described by Bein[11] in rats, has been proposed as a model for depression. The subsequent discovery that reserpine depleted the brain of serotonin[12] and catecholamines (CA)[13,14] served as an impetus for the theories linking monoamines with depression.

During the 1950s there were a number of reports of "depression" in patients being treated with reserpine for hypertension.[15-22] However, only a small and varying percentage of patients developed this syndrome. Many of the reports are retrospective, poorly documented, and difficult to evaluate, especially insofar as the criteria used to diagnose depression are concerned. While the true incidence of this syndrome cannot be determined from these reports it has been estimated that about 6% of the patients who received reserpine for long periods of time, did develop a syndrome suggestive of "endogenous depression."[23] Further, in most cases the syndrome only developed after months and was infrequent, even in patients who received relatively large doses of reserpine for many months. It seems probable from the available reports that many, if not most, of the patients who developed this syndrome had a previous history of psychiatric disturbance, often depression. Goodwin and Bunney[23] have concluded that the more the reserpine syndrome resembled the clinical presentation of "endogenous depression," the more likely it was that the patient had a past history of depression. Thus, it would seem possible that rather than cause a depression-like syndrome in man, reserpine precipitates the syndrome in a relatively small number of *susceptible* persons.

In the only controlled prospective study of the effect of reserpine on mood that we know of, Bernstein and Kaufman[22] reported that there was no significant depression in

Accepted for publication Nov 3, 1973.

From the Depression Research Unit, departments of psychiatry and pharmacology, the University of Pennsylvania, and the Veterans Administration Hospital, Philadelphia.

Reprint requests c/o VA Hospital, University and Woodland avenues, Philadelphia, PA 19104 (Dr. Mendels).

a group of 50 patients who received reserpine for 12 to 18 months. This study is notable in that there was a careful base line evaluation of the patients *prior* to reserpine treatment, and the patients were seen regularly throughout treatment. In most other reports the first psychiatric evaluation occurred *after* the patient had developed symptoms while receiving reserpine. Twelve of Bernstein's and Kaufman's patients developed a "pseudodepression," "a reaction of excessive tranquilization, with diminished psychomotor activity"; they were "slowed down," "tired," and "lacking push." However, none were suicidal, self-deprecatory, crying, or "blue." Associated symptoms of depression such as insomnia or anorexia were mild and infrequent. Bernstein and Kaufman suggest that a reserpine-associated "depressive reaction" may not be due to the pharmacological action of reserpine per se, but to the psychological meaning of the psychomotor retardation produced by the drug to the individual patient. They suggested that the patients who developed depressive symptoms were those who tended to use psychomotor activity as a means of reassuring themselves of their adequacy—patients who feared passivity; who were threatened by being calmed.

This interpretation of the mood alteration produced by reserpine is compatible with the results of subsequent experiments by Schachter and Singer,[24] who noted that the physiological arousal produced by an injection of epinephrine was not in itself sufficient to produce mood changes. Also, manipulation of the environment in the absence of an injection of epinephrine produced little emotional arousal. However, the physiological changes made by an injection of epinephrine predisposed a person to react to environmental manipulation with a variety of emotional responses. They suggested that an emotional state is a function of *both* a state of physiological arousal and of a cognition appropriate to this state of arousal. Goldstein et al[25] also recently reported data suggesting that "actual physiological arousal was a crucial mediator of emotion, since, regardless of a subject's artifically provided cognition of physiological arousal, he seemingly did not experience much emotion unless there was actual physiological arousal." If so, it may be that the physiological changes produced by reserpine that lead to psychomotor retardation, trigger a depression-like syndrome in susceptible persons. These patients would be those who interpreted the psychomotor retardation produced by reserpine as "depression."

It seems to us that there may not have been sufficient effort to distinguish between the mood components of depression and psychomotor retardation, and to evaluate the psychological effects of long-term psychomotor retardation on certain susceptible persons.

The view that reserpine produces primarily psychomotor retardation in man rather than depression is strengthened by the recent observations that suggest that the sedation or tranquilization seen in reserpine-treated animals results from dopamine depletion or inhibition of uptake of dopamine into storage granules.[26-28] Dopamine is located primarily in the caudate nucleus,[29,30] an area of the brain previously not considered to be involved with "emotional behavior" but known to play a critical role in locomotor activity and, perhaps in certain "stereotyped" behaviors.[31-34] It seems possible, then, that the behavioral changes in man attributed to reserpine are at least in part a consequence of the "sedative-motor" effect of dopamine depletion. Certainly, the reports of increased motor activity in depressed patients produced with 3',4' dihydroxyphenylalanine (levodopa) without alleviation of the "depression"[35] is in keeping with this. It is of course possible that dopamine may play some role in the mediation of emotions as well as motor activities, and further attention should be given to this possibility.

The comments that follow review the behavioral changes produced by alpha-methyl-para-tyrosine (AMPT) and by parachlorophenylalanine (PCPA). These agents produce a relatively selective depletion of either brain CA or of serotonin, respectively. Depletion of these amines is produced by inhibition of the enzymes that are rate-limiting in their synthesis, tyrosine hydroxylase for CA and tryptophan hydroxylase for serotonin.

This mechanism of action deserves to be emphasized insofar as it has been considered that the total biogenic amine content of a neuron is divided into at least two different "pools": (1) a large, stable pool that turns over slowly and possibly functions in some reserve capacity and (2) a smaller pool that turns over rapidly and from which amines are normally released to produce their effects.[36] Evidence has been presented that it is, at least for NE, newly synthesized or newly stored amine that is important functionally.[37-39] Perhaps then, it is this newly synthesized or newly stored amine that corresponds to the "functional" pool.

If this is the case, then functional effects would be expected to be seen with agents that inhibit synthesis (or recent storage). There may be a time lag for such effects to become apparent—the time necessary for the storage compartment to be utilized. Indeed, Rech et al[40] have shown that prior administration of reserpine to rats enhances the intensity and rapidity of the behavioral effects of AMPT. Thus, studies using these agents probably do provide a good indication of the behavior effects of functional amine depletion. It should be noted that one cannot be certain, in man, just how much synthesis inhibition is occurring in the central nervous system (CNS), and if this inhibition is uniform throughout the brain. Limited studies of lumbar fluid amine metabolite, together with extensive studies in animals, suggest that major brain amine depletion does occur with these agents. Indeed, they do have behavioral effects suggesting alterations in CNS function.

Alpha-Methyl-Para-Tyrosine

Alpha-methyl-para-tyrosine selectively depletes the brain of dopamine and NE, with little effect on serotonin. The AMPT competitively inhibits tyrosine hydroxylase,[41] the rate-limiting enzyme in CA biosynthesis[42] with a resultant decrease in tissue stores of dopamine and NE.[43] It depletes both brain and peripheral CA. This must be considered in the interpretation of reports of the behavioral effects of AMPT, as changes in peripheral adrenergic function can alter behavior.[44,45]

The administration of AMPT to man has not, in the main, been associated with important alterations in mood. Sjoerdsma et al[46] and Engelman et al[47] gave up to 4,000 mg AMPT to 52 medical patients. They estimated that peripheral CA synthesis (as reflected by changes in urinary

metabolites) was reduced by 50% to 80%. While behavioral alterations varied, the most frequent was a mild sedation in 44 of the 46 patients who received more than 1,000 mg of AMPT daily. Sedation occurred within 24 hours of the onset of treatment and unless the dose was increased, disappeared in about seven days. In doses above 2,000 mg daily, sedation and feelings of fatigue tended to persist. None of the 52 patients developed a true depression. Several did become agitated or anxious (especially those with a history of psychiatric illness). Withdrawal of AMPT was associated with "anxiety or agitated depression and changes in sleep patterns" in some patients. Patients who had had an overt sedative response to AMPT developed a striking behavioral change consisting of "a pleasant feeling of alertness and ambition accompanied by insomnia for 48 to 72 hours" on withdrawal of the drug.

Two groups of investigators[48,49] have given AMPT (up to 3,000 mg daily) to schizophrenic patients. Both noted varying degrees of sedation but neither reported any clinical depression. Gershon et al[49] specifically observed for signs of depression but found none. Indeed one patient became "transiently euphoric" while receiving AMPT.

Brodie et al[50] administered AMPT to seven manic patients and to three depressed patients. The dose of AMPT used and the reductions in urinary CA metabolites produced are similar to those of the previous investigators. Five of the seven manic patients given AMPT improved clinically but only two relapsed when the drug was withdrawn, suggesting that for at least three of the patients the clinical change may not have been due to the pharmacological actions of AMPT. Further, one manic patient had a serious aggravation in his manic state with AMPT administration and improved when the drug was *withdrawn*. The three psychotically depressed patients given AMPT became increasingly worse. However, these three patients were characterized by psychomotor retardation and, in view of the sedative effects of AMPT, it is possible that the apparent aggravation in depression may simply have been the result of its sedative effect on patients who were already "slowed down."

It is clear from these clinical studies that there is relatively little evidence that AMPT has a direct effect on mood in either normal or psychiatrically disturbed persons.

Of all the studies reviewed, only that of Brodie et al[50] provides even suggestive support for the view that a reduction in catecholamines is associated with depression, and in their study only two out of seven manic patients unequivocally improved (as predicted by the hypotheses) while one deteriorated (contrary to the hypotheses). It is possible that these changes, as well as those seen in their depressed patients could have been due to AMPT excreting a sedative effect, as suggested by the observations of the other investigators who have used this compound in man.

In animals, AMPT administration is associated with certain behavioral changes. In brief it produces sedation and decreased spontaneous motor activity[43,51-53]; decreases rotorod performance, a measure of motor coordination[53-55]; suppresses conditioned-avoidance responses[53-57]; self-stimulatory behavior[58]; and fighting in mice made aggressive by housing in isolation.[59] These behavioral effects appear to be the result of CA depletion rather than a direct effect of AMPT on CNS activity or a toxic effect of the drug.[40,53-55,60] While these changes are of interest and clearly reflect brain CA's important role in behavior, they are not in any way suggestive of depression, or would be predicted by the hypotheses.

Redmond et al[61,62] suggested that AMPT produced a behavioral state analogous to human depression in monkeys. Chronic dietary administration of AMPT to *Macaca speciosa* resulted in decreased total social interactions and initiatives, postural and facial changes suggestive of withdrawal, diminished motor activity without tremor or dysfunction, together with a continued willingness to remain near other monkeys and respond appropriately to their social initiatives. While these animals did show a decrease in social initiatives, they remained within the group rather than withdrawing and continued to respond to stimuli from others. This is unlike the behavior of depressed patients who are more likely to withdraw from social contacts and to show a reduced response to initiatives. Further, the monkeys did not develop such symptoms of depression as sleep disturbance, and loss of appetite and weight and loss of libido. It seems that while these monkeys may have had some of the features associated with clinical depression (perhaps due to dopamine depletion), they did not exhibit some of the key affective and vegetative symptoms seen in clinical depression. This would suggest that it may be inappropriate to extrapolate from the model to clinical depression—at least without more extensive studies.

Parachlorophenylalanine

Parachlorophenylalanine inhibits brainstem tryptophan hydroxylase[63] reducing the conversion of tryptophan to serotonin and leading to a depletion of brain serotonin.[64] In addition to the pronounced reduction in serotonin, PCPA does cause some lowering of NE stores.[65,66] However, with doses that produce 80% to 90% depletion of serotonin, the tissue content of NE is usually not lowered more than 25%.

Clinical experience with PCPA is limited. Daily doses of up to 4 gm have been given to six healthy male volunteers, 12 patients with carcinoid syndrome, nine migrainous patients, and one addict receiving methadone.[67-70] Various measures including blood serotonin levels and urinary and cerebrospinal fluid, 5-hydroxyindoleacetic acid (5HIAA) were reduced by 60% to 80% of base line values. While there were a variety of behavioral side effects including tiredness, restlessness, a feeling of unease, anxiety, and at higher doses more severe symptoms such as confusion, agitation, and paranoid thinking, there was no great tendency for these patients to become depressed. Carpenter[69] conducted a systematic psychiatric evaluation of seven patients with carcinoid tumors who were receiving PCPA and concluded that the changes did not resemble any particular syndrome and were nonspecific in nature. Those changes that did occur were all self-limited.

While the administration of PCPA to animals results in a number of striking behavioral changes, it does not produce a reserpine-like syndrome or indeed any significant behavior resembling depression, nor does it prevent its development of the reserpine-induced syndrome.[64] Indeed it is more common to see insomnia,[71-75] hypersexual,[76-79] and hyperaggressive[80-82] behaviors, and, in general, an irrita-

bility and hyperreactivity to the environment.[83] These behavioral changes are, if anything, reminiscent of mania. It must be noted that PCPAs inhibition of tryptophan hydroxylase does not appear to occur to the same degree in all tissues, eg, it does not inhibit tryptophan hydroxylase in the pineal.[84] Thus, it is possible that the failure to produce a depression-like syndrome with PCPA is because it does not affect serotonin production in some crucial localized area of the CNS.

Comment

The literature reviewed here strongly suggests that the depletion of brain NE, dopamine, or serotonin is in itself not sufficient to account for the development of the clinical syndrome of depression. Such depletion, even if severe and accompanied by a reduction in amine turnover produces few *persistent* behavioral changes compatible with depressive symptomatology. In fact, when one considers how much amine reduction is necessary to produce behavioral deficits in animals, it seems unlikely that such severe depletion could occur in depressed patients and not be more readily detectable, unless it were sharply localized. And if it did only occur in a restricted area of brain, then this would be a convincing argument against a research strategy (designed to explore etiology) that was based on the measurement of amine metabolism in blood, or other investigations that measured amine metabolism in general. Further, it should be noted that the extent of amine depletion produced with synthesis inhibitors appears to be greater and more consistent than that seen in depressed patients.[9] However, such strategies may be of value in other areas, eg, treatment response.[85,86]

As noted earlier, there is little consistent evidence from clinical studies favoring the simplistic notion of a depletion in aminergic function in depression.[9,10] However, in view of the wealth of pharmacological data on amines and mood, it would be inappropriate to argue that some dysfunction in aminergic activity does not play some role in this syndrome. Rather, it seems necessary to conclude that some other systems must be involved as well. These may either be more important than the changes in amine function (assuming such changes exist) and in themselves be responsible for the development of the syndrome, or may act synergistically with the amine changes to produce the abnormal clinical state.[87-90]

Two additional considerations are of importance. (1) There is extensive evidence that the syndrome of clinical depression includes several distinct conditions. It is therefore possible, that the failure to demonstrate consistent differences in amine metabolism in groups of depressed patients *may be* the result of not separating these patients into meaningful subgroups. (2) In interpreting the findings from the studies utilizing amine-depleting agents, it must be remembered that they probably have complex interactions with multiple brain biochemical systems, either directly, or as a consequence of their primary actions. It is reasonable to assume that much more remains to be learned of these interactions, which may produce a modification of the drugs' primary action.

The fact remains, however, that administration of drugs to humans in amounts sufficient to produce greater depletion of amines than has consistently been reported to occur in depressed patients does not in itself produce depression.

This study was supported in part by Research Funds from the Veterans Administration.

Dr. Bernard James Carroll commented and made suggestions for this study.

References

1. Prange AJ Jr: The pharmacology and biochemistry of depression. *Dis Nerv Syst* 25:217-221, 1964.
2. Bunney WE Jr, Davis JM: Norepinephrine in depressive reactions: A review. *Arch Gen Psychiatry* 13:483-494, 1965.
3. Schildkraut JJ: The catecholamine hypothesis of affective disorders: A review of supporting evidence. *Am J Psychiatry* 122:509-522, 1965.
4. Coppen A: The biochemistry of affective disorders. *Br J Psychiatry* 113:1237-1264, 1967.
5. Davis JM: Theories of biological etiology of affective disorders, in Pfeiffer CC, Smythies JR (eds): *International Review of Neurobiology*. New York, Academic Press, 1970, vol 12, pp 145-175.
6. Lapin IP, Oxenkrug GF: Intensification of the central serotoninergic processes as a possible determinant of the thymoleptic effect. *Lancet* 1:132-136, 1969.
7. Mendels J, Stinnett J: Biogenic amine metabolism, depression and mania, in Mendels J (ed): *Biological Psychiatry*. New York, Interscience-John Wiley & Sons Inc, 1973, pp 99-131.
8. Mendels J: Biological aspects of affective illness, Arieti S, et al (eds): *The American Handbook of Psychiatry*. New York, Basic Books Inc Publishers, chap 1, 1974.
9. Robins E, Hartman BK: Some chemical theories of mental disorders, in Albers RW, et al (eds): *Basic Neurochemistry*. Boston, Little Brown & Co, 1972, pp 607-644.
10. Carroll BJ: Monoamine precursors in the treatment of depression. *Clin Pharmacol Therap* 12:743-761, 1971.
11. Bein HJ: Zur pharmakologie des reserpin, eines neven alkaloids aus *Rauwolfia serpentia* benth. *Experientia* 9:107-110, 1953.
12. Pletscher A, Shore PA, Brodie BB: Serotonin as a mediator of reserpine action in brain. *J Pharmacol Exp Therap* 116:84-89, 1956.
13. Holzbauer M, Vogt M: Depression by reserpine of the noradrenaline concentration in the hypothalamus of the cat. *J Neurochem* 1:1-7, 1956.
14. Carlsson A, et al: Effect of reserpine on the metabolism of catecholamines, in Garattini S, Ghetti V (eds): *Psychotropic Drugs*. Amsterdam, Elsevier Publishing Co, 1957, pp 363-372.
15. Dustan HP, et al: Clinical experience with reserpine (Serpasil): A controlled study. *Ann NY Acad Sci* 59:136-140, 1954.
16. Freis ED: Mental depression in hypertensive patients treated for long periods with large doses of reserpine. *New Engl J Med* 251:1006-1008, 1954.
17. Achor RWP, Hanson NO, Gifford RW: Hypertension treated with Rauwolfia serpentina (whole root) and with reserpine. *JAMA* 159:841-845, 1955.
18. Muller JC, et al: Depression and anxiety occurring during Rauwolfia therapy. *JAMA* 159:836-839, 1955.
19. Smirk FH, McQueen EG: Comparison of rescinnamine and reserpine as hypotensive agents. *Lancet* 269:115-116, 1955.
20. Lemieux G, Davigon A, Genest J: Depressive states during Rauwolfia therapy for arterial hypertension: A report of 30 cases. *Can Med Assoc J* 74:522-526, 1956.
21. Jensen K: Depressions in patients treated with reserpine for arterial hypertension. *Acta Psychiatr Neurol Scand* 34:195-204, 1959.
22. Bernstein S, Kaufman MR: A psychological analysis of apparent depression following Rauwolfia therapy. *J Mt Sinai Hospital* 27:525-530, 1960.
23. Goodwin FK, Bunney WE Jr: Depressions following reserpine: A re-evaluation. *Semin Psychiatry* 3:435-448, 1971.
24. Schachter S, Singer JE: Cognitive, social and physiological determinants of emotional state. *Psychol Rev* 69:379-399, 1962.
25. Goldstein D, Fink D, Mettee DR: Cognition of arousal and actual arousal as determinants of emotion. *J Pers Soc Psychol* 21:41-51, 1972.
26. Carlsson A, Lindqvist M: Metatyrosine as a tool for selective protection of catecholamine stores against reserpine. *Eur J Pharmacol* 2:192-197, 1967.
27. Anden N-E: Effects of amphetamine and some other drugs on central catecholamine mechanisms, in Costa E, Garattini S (eds): *Amphetamines and Related Compounds*. New York, Raven Press, 1970, pp 447-462.
28. Ahlenius S, Engel J: Behavioural and biochemical effects of L-DOPA after inhibition of dopamine β-hydroxylase in reserpine pretreated rats. *NS Arch Pharmakol* 270:349-360, 1971.
29. Carlsson A: The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol Rev* 11:490-493, 1959.
30. Adam HM: The topology of brain amines: A review, in Hooper G (ed): *Metabolism of Amines in the Brain*. London, Mac-

millan & Co Ltd, 1968, pp 1-9.
31. Foull RLM, Carman JB: Ascending projections of the substantia nigra in the rat. *J Comp Neurol* 132:73-91, 1968.
32. Randrup A, Munkabad I: Biochemical, anatomical and physiological investigation on stereotyped behavior induced by amphetamines, in Costa E, Garattini S (eds): *International Symposium on Amphetamines and Related Compounds*. New York, Raven Press, 1970, pp 695-713.
33. Van Rossum JM: Mode of action of psychomotor stimulant drugs. *Int Rev Neurobiol* 12:307-383, 1970.
34. Ungerstedt U: Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behavior. *Acta Physiol Scand [Suppl]* 367:49-68, 1971.
35. Goodwin FK: Behavioral effects of L-DOPA in man. *Sem Psychiatry* 3:477-492, 1971.
36. Weiner N: Regulation of norepinephrine biosynthesis. *Ann Rev Pharmacol* 10:273-290, 1970.
37. Kopin IJ, et al: Selective release of newly synthesized norepinephrine from the cat spleen during sympathetic nerve stimulation. *J Pharmacol Exp Ther* 161:271-278, 1968.
38. Stjarne L, Wennmalm A: Preferential secretion of newly formed noradrenaline in the perfused rabbit heart. *Acta Physiol Scand* 80:428-429, 1970.
39. Shore PA: Transport and storage of biogenic amines. *Ann Rev Pharmacol* 12:209-226, 1972.
40. Rech RH, Carr LA, Moore KE: Behavioral effects of alpha-methyltyrosine after prior depletion of brain catecholamines. *J Pharmacol Exp Ther* 160:326-335, 1968.
41. Nagatsu T, Levitt M, Udenfriend S: Tyrosine hydroxylase, the initial step in norepinephrine biosynthesis. *J Biol Chem* 239:2910-2917, 1964.
42. Levitt M, et al: Elucidation of the rate-limiting step in norepinephrine biosynthesis in the perfused guinea-pig heart. *J Pharmacol Exp Ther* 148:1-8, 1965.
43. Spector S, Sjoerdsma A, Udenfriend S: Blockade of endogenous norepinephrine synthesis by α-methyl tyrosine, an inhibitor of tyrosine hydroxylase. *J Pharmacol Exp Ther* 147:86-95, 1965.
44. Bonn JA, Turner P, Hicks DC: Beta-adrenergic-receptor blockade with practolol in treatment of anxiety. *Lancet* 1:814-815, 1972.
45. Wenzel BB: Immuno sympathectomy and behaviour, in Steiner G, Schonbaum E (eds): *Immuno Sympathectomy*. New York, Elsevier Publishing Co, 1972, pp 199-219.
46. Sjoerdsma A, Engelman K, Spector S: Inhibition of catecholamine synthesis in man with alpha methyl tyrosine, an inhibitor of tyrosine hydroxylase. *Lancet* 2:1092-1094, 1965.
47. Engelman K, et al: Biochemical and pharmacologic effects of alpha-methyltyrosine in man. *J Clin Invest* 47:577-594, 1968.
48. Charlampous KD, Brown S: A clinical trial of alpha-methylparatyrosine in mentally ill patients. *Psychopharmacologia* 11:422-429, 1967.
49. Gershon S, et al: Alpha-methyl-p-tyrosine (AMT) in schizophrenia. *Psychopharmacologia* 11:189-194, 1967.
50. Brodie HKH, et al: Catecholamines and mania: The effect of alpha-methyl-para-tyrosine on manic behavior and catecholamine metabolism. *Clin Pharmacol Ther* 12:219-224, 1971.
51. Hanson LCF: The description of conditioned avoidance response following depletion of brain catecholamines. *Psychopharmacologia* 8:100-110, 1965.
52. Moore KE: Effects of alpha-methyl-tyrosine on brain catecholamines and conditioned behavior in guinea pigs. *Life Sci* 5:55-65, 1966.
53. Rech RH, Borys HK, Moore KE: Alterations in behavior and brain catecholamine levels in rats treated with alpha-methyl-tyrosine. *J Pharmacol Exp Ther* 153:412-419, 1966.
54. Moore KE, Rech RH: Antagonism by monoamine oxidase inhibitors of alpha-methyltyrosine-induced catecholamine depletion and behavioral depression. *J Pharmacol Exp Ther* 156:70-75, 1967.
55. Pirch JH, Rech RH: Effect of isolation on alpha-methyltyrosine-induced behavioral depression. *Life Sci* 7:173-182, 1968.
56. Corrodi H, Hanson LCF: Central effects of an inhibitor of tyrosine hydroxylation. *Psychopharmacologia* 10:116-125, 1966.
57. Schoenfield RI, Dieden LS: Effect of α-methyltyrosine on operant behavior and brain catecholamine levels. *J Pharmacol Exp Ther* 167:319-327, 1969.
58. Poschel BPH, Ninteman FW: Hypothalamic self-stimulation: Its suppression by blockade of norepinephrine biosynthesis and reinstatement by methamphetamine. *Life Sci* 5:11-16, 1966.
59. Welch AS, Welch BL: Failure of natural stimuli to accelerate brain catecholamine depletion after biosynthesis inhibition with alpha-methyltyrosine. *Brain Res* 9:402-405, 1968.
60. Dominic JA, Moore KE: Acute effects of alpha-methyl-tyrosine on brain catecholamine levels and on spontaneous and amphetamine-stimulated motor activity in mice. *Arch Int Pharmacodyn Ther* 178:166-176, 1969.
61. Redmond DE Jr, et al: Social behavior of monkeys selectively depleted of monoamines. *Science* 174:428-431, 1971.
62. Redmond DE, et al: Changes in primate social behavior after treatment with alpha-methyl-para-tyrosine. *Psychosom Med* 33:97-113, 1971.
63. Jequier E, Lovenberg W, Sjoerdsma A: Tryptophan hydroxylase inhibition: The mechanism by which *p*-chlorophenylalanine depletes rat brain serotonin. *Mol Pharmacol* 3:274-278, 1967.
64. Koe BK, Weissman A: P-chlorophenylalanine: A specific depletion of brain serotonin. *J Pharmacol Exp Ther* 154:499-516, 1966.
65. Welch AS, Welch BL: Effect of *p*-chlorophenylalanine on brain noradrenaline in mice, letter to the editor. *J Pharm Pharmacol* 19:632-633, 1967.
66. Welch AS, Welch BL: Effect of stress and para-chlorophenylalanine upon brain serotonin, 5-hydroxyindoleacetic acid and catecholamines in grouped and isolated mice. *Biochem Pharmacol* 17:699-708, 1968.
67. Cremata VY Jr, Koe BK: Clinical-pharmacological evaluation of *p*-chlorophenylalanine: A new serotonin-depleting agent. *Clin Pharmacol Therapy* 7:768-776, 1966.
68. Engelman K, Lovenberg W, Sjoerdsma A: Inhibition of serotonin synthesis by *p*-chlorophenylalanine in carcinoid syndrome. *N Engl J Med* 277:1103-1108, 1967.
69. Carpenter WT: Serotonin now: Clinical implications of inhibiting its synthesis with para-chlorophenylalanine. *Ann Intern Med* 73:607-629, 1970.
70. Sicuteri F, Anselmi B, Fanciullacci M: A therapeutic trial in migraine with parachlorophenylalanine, a specific serotonin depletor. *Headache* 10:124-125, 1970.
71. Torda C: Effect of brain serotonin depletion on sleep in rats. *Brain Res* 6:375-377, 1967.
72. Koella WP, Feldstein A, Czicman JS: The effect of parachlorophenylalanine on the sleep of cats. *Electroencephalogr Clin Neurophysiol* 25:481-490, 1968.
73. Mouret J, Bobillier P, Jouvet M: Insomnia following parachlorophenylalanine in the rat. *Eur J Pharmacol* 5:17-22, 1968.
74. Pirch JH: Effect of reserpine and *p*-chlorophenylalanine on the electrocorticogram of unrestrained rats during short and long recording sessions. *Int J Neuropharmacol* 8:535-548, 1969.
75. Weitzman E, et al: Sleep patterns of the monkey and brain serotonin concentration: Effect of *p*-chlorophenylalanine. *Science* 160:1361-1363, 1968.
76. Sheard MH: The effect of *p*-chlorophenylalanine on behavior in rats: Relation to brain serotonin and 5-hydroxyindoleacetic acid. *Brain Res* 15:524-528, 1969.
77. Tagliamonte A, et al: Compulsive sexual activity induced by *p*-chlorophenylalanine in normal and pinealectomized male rats. *Science* 166:433-435, 1969.
78. Hoyland VJ, Shillito EE, Vogt M: The effect of parachlorophenylalanine on the behavior of cats. *Br J Pharmacol* 40:659-668, 1970.
79. Salis PJ, Dewsbury D: *p*-Chlorophenylalanine facilitates copulatory behavior in male rats. *Nature* 232:400-401, 1971.
80. Ferguson J, et al: Hypersexuality and behavioral changes in cats caused by administration of *p*-chlorophenylalanine. *Science* 168:499-501, 1970.
81. Karli P, Vergnes M, Didiergeorges F: Rat-mouse interspecific aggressive behavior and its manipulation by brain ablation and brain stimulation, in Garattini S, Sigg EB (eds): *Aggressive Behavior*. New York, John Wiley & Sons Inc, 1969, pp 47-55.
82. Di Chiara G, Camba R, Spano PF: Evidence for inhibition by brain serotonin of mouse killing behavior in rats. *Nature* 233:272-273, 1971.
83. Weissman A: Behavioral pharmacology of *p*-chlorophenylalanine (PCPA), in Barchas J, Usdin E (eds): *Serotonin and Behavior*. New York, Academic Press Inc, 1973, pp 235-248.
84. Deguchi T, Barcha J: Comparative studies on the effect of parachlorophenylalanine on hydroxylation of tryptophan in pineal and brain of the rat, in Barchas J, Usdin E (eds): *Serotonin and Behavior*. New York, Academic Press Inc, 1973, pp 33-47.
85. Maas JW, Fawcett JA, Dekirmenjian H: Catecholamine metabolism, depressive illness, and drug response. *Arch Gen Psychiatry* 26:252-262, 1972.
86. Schildkraut JJ, et al: Catecholamine metabolism in affective disorders: IV. Preliminary studies of norepinephrine in depressed patients treated with amitriptyline. *J Psychiatr Res* 9:173-185, 1972.
87. Ashcroft GW, et al: Modified amine hypothesis for the etiology of affective illness. *Lancet* 2:573-577, 1972.
88. Janowsky DS, et al: A cholinergic-adrenergic hypothesis of mania and depression. *Lancet* 2:632-635, 1972.
89. Mendels J, Frazer A: Intracellular lithium concentration and clinical response: Towards a membrane theory of depression. *J Psychiatr Res* 10:9-18, 1973.
90. Kety S: Brain amines and affective disorders, in Ho BT, Mc Isaac WM (eds): *Brain Chemistry in Mental Disease*. New York, Plenum Press, 1972, pp 237-244.