NEUROPHARMACOLOGY OF THE AFFECTIVE DISORDERS

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The introduction of drugs (e.g., monoamine oxidase inhibitor antidepressants, tricyclic antidepressants, and lithium salts) which proved to be effective in the treatment of depressive and manic disorders (the affective disorders) has had a major impact not only on clinical psychiatric practice but also on biological research in psychiatry (1). The effects of these drugs on the metabolism of the biogenic amines have been studied extensively and aspects of this literature have been considered in a number of recent reviews (1–13). Despite some discrepancies, most data seem compatible with the hypothesis that drugs effective in the treatment of depressions may increase one or another of the biogenic amines at receptor sites in brain, whereas drugs that cause depressions, or are effective in the treatment of manias, may decrease the activity of monoamines at receptors.

These neuropharmacological findings stimulated investigation of the metabolism and physiology of the biogenic amines in patients with affective disorders; and clinical studies in this area have focused on the catecholamines (norepinephrine, epinephrine, and dopamine) or the indoleamines (serotonin and tryptamine). As direct biochemical assay of brain tissue in living man is not feasible, most research has involved the assay of monoamines or their metabolites in one or another body fluid under various clinical or pharmacological conditions. These studies have explored biochemical differences between depressed, manic, and control subjects utilizing cross-sectional research designs, and have also examined the biochemical changes that accompany alterations in affective state in depressed or manic patients studied longitudinally (14). Aspects of this expanding literature have been reviewed during the past several years (1, 12–25).

The importance of differentiating among the different types of depressive disorders when prescribing treatment was noted in the original report on the antidepressant actions of imipramine (26), and the differential responses of various types of depressions to one or another treatment modality has subsequently been documented by numerous other investigators (1, 27–31). Classification of the depressive disorders similarly has been emphasized in relation to the design and interpretation of biochemical studies (1). Although many presently available classifications of the depressions (based on clinical signs, symptoms,

and history)[1] are of some value in this regard, further refinements in our capacity to differentiate among the depressive disorders and to prescribe treatment more rationally may be expected only when these clinical distinctions can be augmented by biochemical or physiological criteria (32).

For a number of years, investigators have recognized the possibility that different subgroups of patients with depressive disorders might exhibit different specific alterations in the metabolism of one or another of the monoamines (decreased synthesis and output, increased inactivation, or decreased receptor sensitivity); and it was suggested that studies of biogenic amine metabolism might ultimately contribute to the development of a more meaningful biochemical classification of the affective disorders and a more rational approach to the treatment of these disorders (12, 33). The present review, which is more representative than comprehensive, will examine the current status of research on biogenic amine metabolism in patients with affective disorders, focusing on recent findings that indicate the possible emergence of biochemical criteria to predict responses to pharmacotherapy in depressive disorders.

Catecholamines, Metabolites and Related Substances in Urine and Blood

In a number of studies of manic-depressive patients, the urinary excretion of norepinephrine or dopamine (and, less consistently, epinephrine) has been found to be relatively lower during periods of depressions than during periods of

[1] A common feature of several of these classifications is the separation, on the basis of clinical syndromes, of one particular group of depressions variously designated "endogenous", "vital", "major", or "retarded" depressions. These depressions (which may constitute only 10–20% of all depressive disorders) are generally unresponsive to interpersonal forms of treatment or the administration of placebo, but are relatively responsive to vigorous treatment with one or another of the antidepressant drugs or electroconvulsive therapy. A further subtype of the depressive disorders (of some biological importance) is based on the history of a prior manic (or hypomanic) episode, and is variably designated as the manic-depressive or bipolar disorders; these depressions are generally subsumed under the broader category of endogenous depressions. The manic-depressive depressions constitute what is probably the most homogeneous clinically defined subgroup of the depressive disorders, although the possibility of heterogeneity even within this subgroup cannot be excluded. The manic-depressive (bipolar) depressions are distinguished from the unipolar depressions which are characterized by the absence of a prior episode of mania (or hypomania). This dichotomy of the depressive disorders (unless further subdivided) gives rise to a relatively homogeneous subtype, the manic depressive depressions, and the heterogeneous remainder, the unipolar depressions. Other dichotomous separations of the depressive disorders used by one or another investigator include: retarded vs nonretarded (or agitated or anxious); psychotic vs neurotic; endogenous vs nonendogenous (which embraces characterological, situational, or reactive as well as schizoaffective depressions). The problems inherent in these dichotomies, which in most instances separate a relatively homogeneous subgroup from the heterogeneous remainder, as well as other issues related to the classification of depressive disorders are discussed in more detail elsewhere (1).

manias or after recovery (34–40). In one of these studies, a regular cycle of norepinephrine excretion was observed in cyclothymic manic-depressive patients, with increases starting during transition phases preceding manias and decreases starting in transition phases preceding depressions (40). In another study, which examined the transition from depression into mania in a small number of subjects, an increase in urinary norepinephrine was observed on the day prior to the onset of mania when patients exhibited a brief transition period of normal behavior, and this increase of urinary norepinephrine continued during the manic period; although elevated dopamine levels were also observed during the manic phase, in contrast to norepinephrine, the increase in dopamine excretion did not appear to precede the onset of mania (39). Other investigators have also found an increase in dopamine excretion in manic patients (36, 41).

In a large series of manic patients, excretion of both norepinephrine and epinephrine was elevated above control values, but norepinephrine and epinephrine excretion in a heterogeneous group of depressed patients was not different from control values; these depressed patients, however, did have a lowered catecholamine response to insulin stress (42). Increased catecholamine excretion has been observed in some depressed patients (43), but mainly in those with agitated or anxious depressions (18, 36, 44). In a recent study, elevated levels of plasma epinephrine and norepinephrine were observed in a group of patients with depression and anxiety, most of whom were diagnosed as depressive or anxiety neuroses; the correlation between the concentration of plasma catecholamines and the degree of anxiety was highly significant, whereas the correlation between plasma catecholamines and the degree of depression was not significant (45). Depressed patients with delusions or hallucinations have been found to excrete higher levels of catecholamines and metabolites than patients who did not manifest these psychotic symptoms (46, 47). In one study, levels of norepinephrine in cerebrospinal fluid were reported to be higher in depressed and manic patients (as well as in schizophrenic patients) than in controls (47a); however, further studies will be needed to replicate these findings as well as to confirm the specificity of the method used to determine norepinephrine in cerebrospinal fluid.

A gradual rise in the excretion of normetanephrine, the O-methylated metabolite of norepinephrine that may reflect noradrenergic activity (48–50), was observed during the period of definitive clinical improvement in a series of patients with endogenous depressions treated with the tricyclic antidepressant imipramine (51); this has recently been confirmed by other investigators (52, 53)[2]. Patients with retarded depressions had lower levels of normetanephrine excretion before treatment (when depressed) than after discontinuation of imipramine

[2] The tricyclic antidepressant imipramine, as well as the monoamine oxidase inhibitor phenelzine, was initially observed to decrease the urinary excretion of VMA in depressed patients, suggesting that the tricyclic antidepressants as well as the monoamine oxidase inhibitors might decrease the deamination of norepinephrine (46, 54). This was subsequently demonstrated in studies in animals (55–57).

(when in clinical remission) (51). In some, but not all patients with agitated depressions, normetanephrine as well as norepinephrine and epinephrine are higher during the depression than after improvement (44). In longitudinal studies, the excretion of normetanephrine has been observed to be relatively higher during manias or hypomanias than during depressions, with intermediate values observed in periods of remission; the magnitude of the normetanephrine elevations appears to be related to the clinical severity of the hypomanic symptoms (37, 38, 51, 58).

Although muscular activity may produce significant changes in catecholamine excretion (59), the alterations in excretion of the catecholamines or metabolites in association with changes in affective state did not appear to be a consequence of changes in motor activity in one study where this was specifically measured (37). Moreover, the increases in urinary norepinephrine appeared to precede the onset of mania in two studies (39, 40); however, one cannot exclude the possibility that these increases in norepinephrine excretion might have been secondary to subtle behavioral or postural changes. Normetanephrine and metanephrine excretion has been reported to be elevated in association with agitated and unstable behavior in depressed patients and in other subjects (60).

The urinary excretion of 3-methoxy-4-hydroxymandelic acid (VMA) has also been found relatively elevated during episodes of hypomania or mania when compared with normal or depressed phases (37, 61, 62). This increase in VMA excretion appeared to be associated with the level of physical activity in one study (62), but not in another (37). In one longitudinal study, however, significant increases in urinary VMA were not observed during episodes of hypomania (relative to levels observed during retarded depressions or clinical remissions) despite significant increases in the levels of norepinephrine, normetanephrine, and epinephrine during these hypomanic episodes (38). This could conceivably reflect a relative decrease in the rate of deamination of norepinephrine and normetanephrine in some hypomanic patients, as suggested by the recent report of a decrease in platelet monoamine oxidase activity in some manic-depressive patients, described below (63).

After infusion with radioactive norepinephrine, patients with retarded depressions classified as manic-depressives were found to have an elevated ratio of radioactive amines to deaminated metabolites in the urine when compared with normal controls or patients with agitated unipolar depressions (64, 65). Many factors could account for this finding, including an alteration in the disposition of the infused radioactive norepinephrine as well as a decrease in the deamination of norepinephrine or normetanephrine in the manic-depressive depressed group.

Because all studies have not employed a uniform system for classifying the depressions, it is difficult to summarize these findings. In general, however, norepinephrine and normetanephrine excretion appear to be relatively decreased in patients with retarded (endogenous) depressions and increased in patients with manias. Findings in patients with agitated or anxious depressions are less consis-

tent and some of these patients seem to show increased excretion of norepinephrine and normetanephrine as well as epinephrine and metanephrine.

Because of the relatively effective brain-blood barrier to norepinephrine and normetanephrine (66–69), it is probable that only a small fraction of urinary norepinephrine or normetanephrine derives from the brain. Thus, the urinary excretion of norepinephrine and normetanephrine may primarily reflect the activity of the peripheral sympathetic nervous system. It has been suggested recently that 3-methoxy-4-hydroxyphenylglycol (MHPG) may be the urinary metabolite of norepinephrine (and normetanephrine), which provides some index of the synthesis and metabolism of norepinephrine in the brain (69–72). Not all findings support this (73), and it is, moreover, generally recognized that the brain cannot be regarded as the sole source of MHPG (72); but recent studies in nonhuman primates suggest that approximately 50% of urinary MHPG may derive from norepinephrine originating in the brain (70).

A number of studies have examined the excretion of MHPG in patients with affective disorders. In one study, urinary MHPG was significantly lower in a diagnostically heterogeneous group of depressed patients than in a nondepressed control population (74). Subsequent studies indicate that all depressed patients do not excrete low levels of MHPG but that this may be characteristic of a particular subgroup of depressive disorders and a criterion for predicting the response to specific forms of pharmacotherapy as discussed below (53, 75, 76).

In a longitudinal study of a small group of manic-depressive patients, levels of urinary MHPG were lower during the depressions than after clinical remissions, but hypomanic patients had higher levels of MHPG excretion prior to clinical remission. One cannot simply relate the reduced levels of MHPG in these depressed patients to a decrease in motor activity and a reduction in peripheral sympathetic or adrenomedullary activity, because the depressed patients in this study had agitated depressions, during which some showed relatively increased levels of norepinephrine, normetanephrine, epinephrine, and metanephrine (44). Similar findings were observed in a longitudinal study of two manic-depressive patients in which urinary MHPG excretion was relatively elevated in the manic phases, decreased in the depressed phases, and intermediate during interval phases; these investigators felt that it was unlikely that the increased output of MHPG in the manic phase was simply a reflection of increased motor activity because the peaks of MHPG output occurred on different days and preceded the peaks of mania (77).

The changes in MHPG excretion and affective state occurring in the context of amphetamine abuse and withdrawal were recently studied in a small group of patients (78, 79). During self-administration of amphetamines, the patients were clinically hypomanic and urinary MHPG excretion was elevated. Following the abrupt withdrawal of amphetamines, urinary MHPG excretion decreased and patients became depressed. Subsequently there was a gradual increase in urinary MHPG excretion and a concurrent decrease in the depressive symptomatology. The changes in MHPG excretion occurred with or possibly preceded the clinical changes and were also associated with changes in REM sleep (78, 79). The changes

in VMA excretion observed in this study differed from the changes in MHPG, suggesting that the latter were not simply a reflection of an increased output of norepinephrine or epinephrine from peripheral sympathetic nerves or adrenal glands during amphetamine administration, and a decreased output following withdrawal (80).

However, urinary excretion of MHPG has been shown to increase in response to various forms of stress (81, 82) and may also vary in response to changes in motor activity or posture. Additional studies will be needed to determine the extent to which these factors may have contributed to the changes in MHPG excretion observed to occur in association with changes in affective state.

Recent findings have suggested that urinary excretion of MHPG may provide a biochemical basis for classifying depressed patients and for predicting differential clinical responses to treatment with various tricyclic antidepressants. In one study it was found that patients who excreted relatively low levels of MHPG prior to treatment with imipramine or desmethylimipramine responded better to treatment with these agents than did patients who excreted relatively higher levels of MPHG. In this study, the patients who responded best to treatment excreted more normetanephrine and MHPG during drug treatment (relative to the predrug period), whereas those patients who responded least well had a decrease in the excretion of these two metabolites (83). In another study of a small group of depressed patients, favorable reponses to treatment with amitriptyline were observed in patients with relatively high levels of urinary MHPG (as well as normetanephrine and VMA) but not in patients with lower levels of MHPG and other metabolites (75, 76).

While other possible interpretations cannot be excluded (as noted below), it has been suggested that the low levels of MHPG may reflect a reduced rate of synthesis of norepinephrine as well as a reduction in its net output from presynaptic neurons (i.e. a decrease in neuronal discharge or an increase in neuronal reuptake); whereas the higher levels of MHPG would be consistent with an increase in the enzymatic inactivation of norepinephrine or a deficiency in postsynaptic receptor sensitivity to norepinephrine which is partially compensated by an increase in the output of norephinephrine from presynaptic neurons (76). [Findings compatible with these interpretations have been reported (52, 84, 85).] In these studies, patients with low MHPG excretion tended to have depressions that were often classified as manic-depressive, whereas patients with higher levels of MHPG tended to have depressions that were often classified as involutional or chronic characterological (neurotic); but there were exceptions to this association between MHPG excretion and clinical phenomenology or diagnostic subtype.

Another group of investigators was unable to confirm the finding that a favorable response to treatment with imipramine was associated with a low pretreatment level of MHPG; but as the investigators noted, the patients in this study were drug free for as little as five days before the pretreatment MHPG levels were measured. Residual drug effects may have influenced the initial MHPG values (52). Further investigation is clearly required to determine whether

the level of MPHG excreted in the urine will provide a clinically useful criterion for classifying depressive disorders and predicting differential responses to pharmacotherapy.

The urinary excretion of beta-phenylethylamine, both free and conjugated, has been found by several groups of investigators to be decreased in depressed patients (86–88); and increased levels of phenylethylamine have been observed in manic as well as schizophrenic patients (89). Treatment with imipramine or monoamine oxidase inhibitor antidepressants increases levels of phenylethylamine in animal brain as well as in the urine of depressed patients; whereas reserpine has been observed to decrease levels of phenylethylamine in animal brain (88, 89). Further studies are required to confirm these interesting observations as well as to control for the possible effects of diet, concurrent drug administration, and other factors related to the clinical and psychiatric status of the patients.

The levels of tyrosine in blood plasma of depressed patients have been examined by several investigators. In one study, manic-depressive patients showed no difference in the fasting levels of plasma tyrosine when compared with normal controls, but both manic and depressed patients showed greater elevations of plasma tyrosine than did control subjects after an oral load of tyrosine (90). In another study, plasma tyrosine levels of depressed patients were observed to be significantly lower at 8 A.M. when compared with normal controls, but this difference did not persist into the evening and it was suggested that depressed patients had an altered diurnal rhythm of plasma tyrosine (91). In a third study, significantly lower levels of plasma tyrosine were observed at 11 A.M. in patients with endogenous depressions compared with neurotic depressives, schizophrenics, or healthy controls, but no significant differences were observed when tyrosine was measured at 8 A.M.; the reponse to an oral load of tyrosine was not significantly different in endogenous depressions when compared with controls (92). Further investigations are needed to explore these apparent discrepancies.

Indoleamines, Metabolites and Related Substances in Urine and Blood

The urinary excretion of 5-hydroxyindoleacetic acid (5HIAA), the deaminated metabolite of serotonin, has been studied extensively in patients with affective disorders (34, 93–98). These findings have been considered in a recent comprehensive review (20) and will not be discussed in detail here. Although there are many discrepancies, the findings reported in these various studies suggest that urinary 5HIAA levels may differ in different subtypes of depressive disorders and two studies indicate that the response to treatment with monoamine oxidase inhibitors may be more favorable in patients with relatively low levels of urinary 5HIAA than in patients with relatively higher levels (93, 96), but not all studies concur (97). In longitudinal studies of manic-depressive patients, the levels of 5HIAA have been found to be relatively higher during episodes of mania than during episodes of depression. However, these findings must be interpreted cautiously, as it is thought a considerable fraction of urinary 5HIAA may derive from indoleamines in the gastrointestinal tract (94, 99) and that dietary factors may be of considerable importance.

The urinary excretion of tryptamine was relatively reduced in depressed patients, and increased after clinical improvement in several studies (52, 94, 100). However, in another recent study, tryptamine levels were relatively elevated during depressions when compared with values obtained after recovery (98). Most urinary tryptamine probably derives from the decarboxylation of tryptophan in the kidney and relatively little may be of central origin; dietary factors may also cause alteration in tryptamine excretion (94, 100). Depressed patients were reported to have relatively decreased rates of liberation of $C^{14}O_2$ from carboxy-labelled 5-hydroxytrytophan in one study (101), but the investigators did not observe the phenomenon in a further study (17).

A shift in the pathways of metabolism of tryptophan, possibly mediated by an increase in tryptophan pyrrolase leading to increased metabolism by the kynurenine pathway and decreased synthesis of indoleamines, has been suggested as a possible mechanism to account for some of the changes in indoleamine metabolism reported to occur in depressive disorders (22, 102, 103). This has been explored by a number of investigators.

Excretion of xanthurenic acid, a product of the kynurenine pathway of tryptophan metabolism, was found to be greater in depressed than in manic patients (104). After a tryptophan load, female patients with endogenous depressions excreted more kynurenine and 3-hydroxy-kynurenine, but not the subsequent metabolite 3-hydroxyanthranilic acid, than did female control subjects in a recent study (105).

In two manic-depressive patients studied longitudinally, the conversion of intravenously administered radioactive tryptophan to kynurenine was greater during episodes of depressions than of mania or during normal periods (106); but the excretion of endogenous kynurenine was significantly lower during depression than during mania (107). In another study, the excretion of kynurenine in depressive patients was significantly lower than in normal subjects (91). However, these findings on alterations in levels in one or another of the urinary metabolites of tryptophan deriving from the kynurenine pathway are difficult to interpret in the absence of additional data on the other intermediary and final metabolites from this metabolic pathway.

In a recent study, the uptake and release of radioactive serotonin was compared in platelets obtained from depressed patients and normal subjects. No differences were observed to suggest any abnormality in the depressed patients (108).

Monoamine Metabolites in Cerebrospinal Fluid

Considerable interest in a number of laboratories has recently been focused on the measurements of one or another metabolite of the biogenic amines (e.g., MHPG, HVA and 5HIAA) in lumbar cerebrospinal fluid. Findings suggest that measurements of these biogenic amine metabolites in lumbar cerebrospinal fluid (CSF) may yield information about the cerebral metabolism of the monoamines (72, 109). However, some of the 5HIAA in lumbar CSF may come from the spinal cord (110), whereas a fraction of the HVA may derive from brain capillaries (111). Concentrations of both 5HIAA and HVA are considerably

higher in ventricular CSF than in lumbar CSF, with intermediate values found in cisternal CSF, suggesting a transport system for the removal of acid metabolites from the CSF in the region of the fourth ventricle (109). A comparable gradient may not exist for MHPG, since preliminary results have suggested that levels of MHPG in ventricular and lumbar CSF are similar (112).

Because the rate of efflux of these substances from the CSF may vary over time and among subjects, measurements of the level of a metabolite in lumbar CSF at an instant in time do not necessarily reflect the rate of production of the metabolite during a given time interval. Information of the latter sort may be obtained by blocking the efflux of metabolites from the cerebrospinal fluid, and probenecid has accordingly been used to block the efflux of the carboxylic acid metabolites of biogenic amines (i.e., 5HIAA and HVA) (113). This technique has its limitations when applied clinically—the concentration of probenecid accumulating at sites of transport may vary from subject to subject (114), and probenecid itself may conceivably alter the metabolism of the biogenic amines under investigation. Moreover, the rate of efflux of these metabolites may vary from subject to subject and the degree of blockade produced by a given concentration of probenecid may not be uniform. In two clinical studies, probenecid did not appear to block the efflux of MHPG from the CSF (112, 115).

A number of studies have suggested that MHPG or its sulfate conjugate may be the principal metabolite of norepinephrine and normetanephrine in the brain of several different animal species (69, 70, 71, 116, 117), and free and conjugated MHPG have been demonstrated in human cerebrospinal fluid (72, 112, 117a). Several studies have recently examined the levels of MHPG in the lumbar cerebrospinal fluid of patients with affective disorders. In a small number of depressed patients (not classified with respect to diagnostic subtypes), MHPG levels were significantly lower than in control subjects (112). Further studies from that laboratory have confirmed this decrease in CSF MHPG levels in a larger series of depressed patients; CSF MHPG levels were not different from control values in a small group of manic patients (118). In another recent study, MHPG levels in CSF were not different from control values in a small heterogeneous group of depressed patients, but some manic patients showed markedly elevated levels of MHPG with a decrease to normal values during successful treatment with lithium carbonate (119). In another small series of patients with recurrent (unipolar) depressions, manic-depressive depressions, and manias, there were no differences in the mean levels of MHPG between the various groups before treatment, nor did any significant changes occur after treatment, but the investigators noted that there was a wide scatter in the concentrations of MHPG in the lumbar CSF of these patients; this study differs from others in that a spectrophotofluorometric, rather than gas chromatographic, method was used to determine MHPG (120).

While further studies of MHPG in the CSF of patients with affective disorders are clearly indicated, available data suggest that levels of MHPG in the CSF may be decreased in some depressed patients and increased in some patients

with manias. However, some patients with affective disorders appear to have normal levels of MHPG in lumbar cerebrospinal fluid. Similar findings have emerged from studies of urinary MHPG (as well as normetanephrine and norepinephrine) in patients with affective disorders. Differences in motor activity could conceivably contribute to these differences in levels of CSF MHPG, as the findings of a recent study demonstrated a statistically non-significant trend toward increases in CSF MHPG (as well as significant increases in HVA and 5HIAA) after increased psychomotor activity was induced by simulating mania (121). The differences in CSF levels of MHPG could also reflect differences in the rate of efflux of MHPG from the CSF rather than differences in its rate of production; simultaneous measurement of CSF MHPG and urinary MHPG might help to clarify this if the brain contributes as large a fraction (approximately 50%) of the urinary MHPG as recent findings suggest (70).

Baseline levels of homovanillic acid (HVA) in the CSF have been found in a number of recent studies, to be lower in depressed patients than in control subjects (119, 121–127). In one study decreased baseline HVA levels were observed in patients with retarded depressions but not in patients with non-retarded depressions (128), but the decrease in CSF HVA did not appear to be related to motor activity in all studies (119, 121, 124). In another study patients with recurrent depressions (unipolar depressions) had lower HVA levels than patients with manic-depressive depressions (bipolar depressions) (120), but other investigators who found decreased levels of HVA in depressed patients (compared to controls) observed no differences in HVA levels between unipolar depressions and bipolar depressions (126).

In one study the reduced levels of HVA observed in depressed patients did not increase after electroconvulsive therapy, although considerable clinical improvement was observed (125). Another study indicated that the initial reduction of HVA in CSF in three depressed patients was followed by a relative increase after treatment; but one of these patients was noted to have shown little change in clinical condition and to have received large doses of L-dopa for five weeks (126). Other investigators observed no correlations between the changes in various clinical ratings and CSF HVA values in a small group of depressed patients studied before and during treatment with amitriptyline; in this study HVA levels tended to decrease during treatment (123).

Baseline levels of HVA in hypomanic and manic patients have been observed to be equal to or lower than control values in several studies (119, 121–123, 126). In one of these studies, patients with severe mania, exhibiting a high degree of motor activity, had elevated levels of HVA, whereas levels of HVA in hypomanic patients were slightly lower than control values. The increased levels of HVA in patients with severe mania were attributed to increased motor activity and the fact that total bed rest could not often be maintained prior to the lumbar puncture (121).

Several studies have recently examined the accumulation of HVA in lumbar

CSF following administration of probenecid in patients with affective disorders. (The difference between the level of HVA determined after probenecid administration and the baseline level of HVA is referred to as the accumulation of HVA.) The accumulation of HVA following probenecid was decreased in a small group of depressed patients when compared with controls; the accumulation of HVA in manic patients was not different from control values (122). In another study, the accumulation of HVA was significantly lower than control values in patients with retarded depressions, whereas the accumulation of HVA in patients with nonretarded depressions was slightly greater than control values (128). The levels of HVA following probenecid adminstration (not accumulation, since baseline levels were not subtracted) were higher in a diagnostically heterogeneous group of depressed patients than in a control population in one study (129).

Since the initial report that 5-hydroxyindole compounds were decreased in the cerebrospinal fluid of depressed patients (130), numerous investigators have found that CSF levels of 5-hydroxyindoleacetic acid are lower in depressed patients than in controls. In most studies statistically significant decreases (126, 131–135a) or nonsignificant decreases (123, 124) in CSF 5HIAA levels have been observed in depressed patients. However, in several studies depressed patients were found to have essentially normal levels of 5HIAA in the cerebrospinal fluid (119, 122, 125, 136). Levels of 5HIAA in the CSF have been observed to be higher in subjects over the age of 55 than in middle-aged subjects (137); and in one study, depressed patients over 60 years of age had significantly higher 5HIAA levels than did depressed patients under 60 years (138). In several other studies no age correlation was observed (124, 125, 136).

The variability observed in the many studies of CSF 5HIAA in depressions might be accounted for by a number of factors, including the nature of the control group to which depressed patients were compared, and differences in age or sex of the various groups; differences in the conditions under which the samples of cerebrospinal fluid were obtained; or in techniques used for chemical determination (including the possibility that some of these methods may be relatively nonspecific). Possible differences in the diagnostic subgroups of depressive disorders as well as in the clinical phenomenology of the patients examined in various studies may also be of importance.

In two recent studies, patients with unipolar (recurrent) depressions had lower levels of 5HIAA in the CSF than did patients with bipolar (manic-depressive) depressions (120, 126). In one of these studies, normal levels of 5HIAA were observed in the patients with manic-depressive depressions (120). Depressed patients classified as psychotic (on the basis of the presence of delusions) had lower CSF levels of 5HIAA than did nonpsychotic depressed patients in one study (126). In another recent preliminary study of a small group of patients with endogenous depressions, patients with relatively low pretreatment levels of CSF 5HIAA did not improve clinically during treatment with nortriptyline, whereas patients with higher levels of 5HIAA responded favorably to treatment with this drug (138).

In most studies the decrease in CSF 5HIAA levels in depressed patients persisted after recovery (120, 126, 135), although a slow rise to normal values upon recovery from depression was noted in one study of a small number of patients (132). During treatment with amitriptyline, imipramine, or nortriptyline, a further decrease in CSF 5HIAA has been observed in depressed patients (123, 124, 138). No changes in CSF 5HIAA levels were observed in depressed patients after ECT in one study in which pretreatment levels of 5HIAA were not decreased (125).

In some studies, low baseline levels of CSF 5HIAA have been observed in hypomanic or manic patients both before treatment and after recovery (120, 123, 132, 135); but the decreases in pretreatment levels were not statistically significant in all of these. Other investigators have observed normal or increased CSF 5HIAA levels in manic patients (122, 131, 136). CSF 5HIAA levels in lumbar cerebrospinal fluid have been shown to increase after exercise or periods of "simulated mania" with increased psychomotor activity (121, 139). A concentration gradient of 5HIAA appears to exist within the cerebrospinal fluid system (with lowest levels observed in the lumbar CSF), which could conceivably result from an increased mixing of CSF from various levels during periods of increased physical activity (131). In the light of these observations, the relatively low levels of CSF 5HIAA in manic or hypomanic patients, observed by a number of investigators, are of particular interest. However, in relation to these findings in patients with affective disorders, it should be pointed out that decreased levels of 5HIAA have been observed in other psychiatric conditions including schizophrenic disorders (123, 131).

The accumulation of 5HIAA in the CSF following administration of probenecid (i.e., the difference between levels of CSF 5HIAA after probenecid and before probenecid) was found to be decreased in a number of recent studies of depressed patients (122, 133, 135a, 136). Differences were statistically significant in most but not all of these studies. The possibility has been suggested that decreased 5HIAA accumulation may be characteristic of only a subgroup of patients with endogenous (vital) depressions, who are not otherwise distinguishable on the basis of psychopathological features or differences in motor activity (133, 135a). In one of these studies, the reduced accumulation of 5HIAA in the CSF following probenecid correlated significantly with reduced baseline levels of 5HIAA, but a similar correlation was not observed in the other study. In another study, the levels (not the accumulation) of 5HIAA in CSF after probenecid administration were not different from control values in a group of patients with unipolar depressions; during treatment with amitriptyline, 5HIAA levels after probenecid administration markedly decreased (129).

The accumulation of 5HIAA in CSF was compared before and after improvement in a small group of depressed patients; variable results were observed, with 5HIAA accumulation increasing in some patients after improvement but not in all (140).

In one study, a significantly lowered 5HIAA accumulation was observed in

manic patients (122), and CSF 5HIAA accumulation tended to be lower in manic patients in another study (136).

The problems in interpreting data on the accumulations of acid monoamine metabolites in lumbar CSF following probenecid have been discussed elsewhere (141, 142), and will not be considered in detail here. Issues of relevance include: possible variations in the effects of probenecid from subject to subject (including differences in CSF probenecid levels); possible individual variations in transit time for 5HIAA (or HVA) to pass from brain to lumbar CSF; possible inter-individual variations in the rate of transport of acid metabolites out of CSF; variations in the extent to which the transport of these metabolites is inhibited by the maximum dose of probenecid that may be administered to human subjects; possible variations in the volume of the cerebrospinal fluid; and possible effects of probenecid on monoamine metabolism apart from the inhibition of transport of acid metabolites. Because 5HIAA may not be the sole metabolite of cerebral serotonin (just as HVA is not the sole metabolite of dopamine), the possible contribution of the corresponding alcohol derivatives or other metabolites must also be considered when interpreting these findings.

In a pilot study of the effects of 5-hydroxytryptophan in patients with vital (endogenous) depressions, 3 of 5 patients improved with 5-hydroxytryptophan, whereas none of 5 subjects improved with placebo; the 3 patients who improved during treatment with 5-hydroxytryptophan showed low pretreatment accumulations of 5HIAA in CSF after probenecid, whereas the 2 patients who did not improve had higher pretreatment accumulations of 5HIAA (143). However, another group of investigators failed to demonstrate a therapeutic response to 5-hydroxytryptophan in 6 of 7 depressed patients, although in this study 5-hydroxytryptophan administration was shown to produce increases in plasma 5-hydroxytryptophan, cerebrospinal fluid 5HIAA and urinary 5HIAA; and the one patient who showed a moderate response to treatment with 5-hydroxytryptophan did not exhibit an exacerbation after withdrawal of the drug (127). The results of this study need not necessarily contradict the preceding findings, as the accumulation of 5HIAA in the CSF after probenecid administration was not studied and baseline 5HIAA levels (although reduced) were not significantly lower in these depressed patients than in control subjects.

Other investigators have examined the changes in CSF 5HIAA following tryptophan administration in depressed patients. In one study (144), L-tryptophan (in conjunction with vitamin B6) did not ameliorate either the depressive symptoms or the insomnia in a group of depressed patients. These depressed patients, however, showed less of an increase in CSF 5HIAA after tryptophan administration than did a group of schizophrenic patients. On the basis of these and similar findings, it has been suggested that some depressed patients may not adequately form serotonin from tryptophan (144, 145). Another group of investigators, however, has observed that L-tryptophan produced an increase in platelet serotonin, urinary and CSF 5HIAA, as well as accumulation of 5HIAA in the CSF after probenecid without an accompanying improvement in the depression in most of the patients (146, 147).

These findings will be considered below in further detail in conjunction with other studies of the effects of monoamine precursors on clinical state in patients with affective disorders.

In a recent study, levels of tryptophan in the cerebrospinal fluid of depressed and manic patients were found to be significantly reduced in comparison with control subjects; in a small number of patients following recovery from depression, normal CSF tryptophan levels were observed (148).

Monoamines and Metabolites in Brain after Suicide

Several studies have examined the levels of monoamines and 5HIAA in the brains of depressed patients after suicide. In one study, levels of serotonin in the hindbrain were lower in depressed patients after suicide than in a control group of subjects who had died from accidents or acute illnesses (149). This difference in serotonin levels was not replicated in a more recent study by some of the same investigators, but 5HIAA was reported to be lower in depressed patients after suicide than in control subjects after death from natural causes. Statistically significant differences in the levels of norepinephrine were not observed (150).

In another study (151), serotonin levels were lower in the brain stem of patients after suicide than in control subjects; the major effect in this study was observed in patients with reactive depressions who had suicided rather than in patients with endogeneous depressions. Moreover, in this study a positive correlation was found between age and serotonin concentration and the authors note that decrease observed in patients after suicide was offset to some extent by the difference in age between the suicide and control groups. There were no significant differences in concentrations of 5HIAA in brain stem, norepinephrine in hypothalamus, or dopamine in caudate nucleus between suicides and controls in this study (151).

Interpretation of these data is exceedingly difficult because of the many uncontrolled variables that may have influenced the results of these studies. These include: the ingestion of psychoactive drugs before suicide; differences in age between the suicide and control groups; and the fact that many of the low 5HIAA values, observed in patients after suicide in the study where this difference was significant, seemed to be associated with barbiturate ingestion. Another variable recently commented upon is the length of time during which frozen specimens were stored between the necropsy and assay (152).

Monoamine Oxidase and Catechol O-Methyl Transferase Activity

In one study performed a number of years ago, the conversion of orally administered radioactive serotonin to radioactive 5HIAA recovered in the urine was examined in a group of depressed patients (clinical subtypes unspecified) and normal control subjects; no differences between these groups were observed and the investigators concluded that monoamine oxidase (and aldehyde dehydro-

genase) functioned normally in the depressed patients (153). In a more recent study (154), plasma monoamine oxidase activity was significantly higher in a group of premenopausal depressed women (who did not require hospitalization) than in a group of control subjects. The depressed patients in this study did not include "schizophrenic, psychotic, manic, reactive, and involutional depressives". Orally administered conjugated estrogen (Premarin®) produced a significant decrease in plasma monoamine oxidase activity in the depressed patients and all of the depressed patients who received estrogen therapy reported an improvement in their mood. As the investigators noted, however, this study lacked the double-blind procedures adequate for a proper evaluation of the antidepressant effects of conjugated estrogens (154).

Another group of investigators recently reported that platelet monoamine oxidase activity was significantly higher in a large heterogeneous group of depressed patients than in a group of normal subjects matched for age (84). In further studies, these investigators observed that there was a progressive increase in monoamine oxidase activities in human hindbrain, platelets, and plasma, with advancing age starting at 35 in platelets and brain, and at 55 in plasma, with maximal levels observed after age 70. Women were found to have higher mean platelet monoamine oxidase activities than men at all age levels and higher mean plasma monoamine oxidase activities after 40; the mean hindbrain monoamine oxidase activity in women was slightly but not significantly greater than in men. Levels of norepinephrine in the hindbrain obtained at necropsy from patients who had died from a variety of causes decreased significantly with advancing age, and the levels of norepinephrine in hindbrain correlated negatively with hindbrain monoamine oxidase activity. Neither serotonin nor 5HIAA levels in hindbrain correlated significantly with age, but levels of 5HIAA were positively correlated with hindbrain monoamine oxidase activity. It is tempting to speculate that these findings may help to explain the generally greater frequency of depressive illnesses in women than in men, and the increasing incidence of depressive illnesses during middle age in both sexes (155, 156).

In another recent study (63), platelet monoamine oxidase activities were found to be significantly lower in bipolar than in unipolar depressed patients or normal controls of similar age and sex distribution. The levels of platelet monoamine oxidase activity in the unipolar depressed patients were slightly higher than those of controls but this difference was not statistically significant. There was a high negative correlation between platelet monoamine oxidase activity and tryptamine excretion with bipolar patients excreting significantly more tryptamine than unipolar patients. Preliminary results also indicate that the false transmitter octopamine (which accumulates in platelets after treatment with monoamine oxidase inhibitors) is present in platelets of individuals with endogenously reduced monoamine oxidase activity, particularly patients with bipolar depressions; and it has been suggested that endogenous false transmitters may play a role in the pathophysiology of some types of depressive disorders (157). In a small number of bipolar patients studied longitudinally

through both depressive and manic episodes, there was no consistent direction of change in platelet monoamine oxidase activities during either manic or depressed periods (63). Findings from one recent study indicate that at least some depressed patients have abnormal serum monoamine oxidase isoenzyme patterns. These preliminary data also suggest that serum monoamine oxidase isoenzyme patterns may differ in different subtypes of depressive disorders (157a).

It is difficult to compare the findings of these various studies, since different substrates were used in the assays of monamine oxidase activities. Further investigation is needed to determine whether platelet (or plasma) monoamine oxidase activities provide an index of the monoamine oxidase activities in other tissues, particularly the brain which may have different isoenzymes (157b). However, in the aggregate, the findings of these studies do raise the possibility that the determination of monoamine oxidase activities or isoenzyme patterns may be of value in differentiating various subtypes of depressive disorders and possibly also in predicting differential responses to pharmacotherapy. In this regard it should be noted that in addition to the monoamine oxidase inhibitor antidepressants, many other drugs that alter affective state also appear to alter the deamination of monoamines (1).

Tricyclic antidepressants (imipramine, desmethylimipramine, amitriptyline, nortriptyline, and protriptyline) produce a decrease in the deamination of norepinephrine in animal brain which cannot be explained simply on the basis of an inhibition of neuronal uptake of norepinephrine (57); and the findings from clinical studies of norepinephrine metabolism in patients treated with imipramine or amitriptyline are compatible with such a decrease in the deamination of norepinephrine (46, 54, 158). Stimulant and euphoriant drugs, such as amphetamine and cocaine, have similarly been observed to decrease the deamination of norepinephrine in animal brain; and it has previously been suggested that a decrease in deamination of norepinephrine or other monoamines may contribute to the clinical effects of many stimulants, euphoriants, and the tricyclic antidepressants as well as the monamine oxidase inhibitors (1). In contrast, lithium salts appear to increase the release and intraneuronal deamination of norepinephrine by monoamine oxidase in animal brain, and this has been suggested as a possible mechanism to account for the clinical effectiveness of lithium in the treatment of manias (56, 159). This could conceivably also account for the reported antidepressant effects of lithium when used in combination with monoamine oxidase inhibitors (160, 161), and would lead to the prediction that lithium may exert antidepressant effects in those depressed patients with endogenously reduced monoamine oxidase activity (7, 162).

The activity of catechol O-methyl transferase (COMT) in red blood cells of women with unipolar depressions was significantly lower than controls in a recent series of investigations (163, 164), whereas women with bipolar illnesses demonstrated COMT activities intermediate between unipolar women and the controls. Red blood cell COMT activity in schizophrenic women was not different from control values. Within the group of women with affective disorders,

red blood cell COMT activity was independent of the phase of the illness (depression or mania) and did not change with recovery. In contrast to the differences observed in women with affective disorders, no differences in red blood cell COMT activity were found among comparable diagnostic groups of male patients (163, 164). Another group of investigators hypothesized some years ago that malfunction of the catechol O-methyl transferase enzyme might cause some depressions by leading to the formation of noradnamine, a condensation derivative of norepinephrine (165). However, direct evidence to support this speculative hypothesis is lacking.

Monoamine Precursors

The amino-acid precursors of the catecholamines, dihydroxyphenylalanine (dopa), and the indoleamines, tryptophan and 5-hydroxytryptophan (5HTP), can cross the blood brain barrier and under some conditions elevate levels of one or another of the monoamines in the brain. Consequently, these monoamine precursors have been administered to patients with affective disorders both to explore their clinical effects and to investigate the possible relationship of alterations in biogenic amine metabolism to changes in affective state. However, since the initial clinical trials of monoamine precursors more than a decade ago, it has become apparent that in addition to increasing monoamine levels these substances produce many other biochemical and neuropharmacological effects; consequently, the interpretation of the findings of such studies may not be as straightforward as was initially assumed (166, 167). One cannot even be certain that the administration of an amino acid precursor of a biogenic amine will necessarily lead to an increased concentration of that monoamine at specific neuronal sites where it is normally found; nor can one be certain that any clinical effects observed are direct physiological effects of a specific monoamine derived from the precursor rather than the pharmacological effects of the precursor acting directly or indirectly upon other monoaminergic systems (i.e., by releasing monoamines, by displacing monoamines through the production of false transmitters, or by interfering with the metabolism of monoamines). Moreover, these monoamine precursors may effect many other diverse biochemical systems. The literature on the use of monoamine precursors in the treatment of depressions has been discussed recently in a detailed and extensive review (168).

Early studies of the effects of dopa in the treatment of depressions indicated that this substance was ineffective when relatively low doses of the D, L-isomer were used (93, 169). In other early studies, improvement in depressed patients was observed after intravenous administration of L-dopa (170, 171), and elevation of mood was reported in a group of patients treated with a monoamine oxidase inhibitor and dopa (172). This combination of drugs can produce severe hypertension and cardiac arrhythmias (172a). More recent studies of relatively high doses of L-dopa administered alone, or lower doses of L-dopa administered in combination with a peripheral decarboxylase inhibitor, suggest that this drug

may cause at least transient improvement in some depressed patients, particularly those with retarded depressions (173–175).

Transient hypomanic or manic episodes (characterized by increased motor and verbal activity with pressured speech, increased social involvement and intrusiveness, increased expression of anger, provocativeness, sleeplessness, euphoria, and feelings of grandiosity) occurred with regularity upon administration of L-dopa in patients with manic-depressive depressions, but not in patients with other types of depressions (176). Depressed mood often persisted during these episodes of hypomania and it has been suggested, on the basis of this observation (176), that depression and hypomania may not represent opposite poles, with respect to a catecholamine deficit (in depression) and an excess (in mania). However, this interpretation may be questioned, as some investigators do not consider the symptom of depressed mood necessary for the diagnosis of endogenous depressions (characterized by psychic retardation decreased interest and ambition, loss of initiative, impaired sense of vitality, inability to attain satisfactions or pleasures normally obtained from work or recreational activities); nor would they regard the persistence of depressed mood to be inconsistent with the remission of the core symptoms of endogenous depressions (1). Further studies will be required to resolve this critical problem related to the clinical definition and diagnosis of the depressive disorders; and it is possible that these findings with L-dopa together with other pharmacological observations may help to coordinate better the clinical concepts with underlying biological substrates (166).

When L-dopa has been used in the treatment of Parkinsonism, improvement in depression and hypomanic-like states has been observed, but the precipitation of depressions has also been reported as a frequently occurring side effect of treatment with L-dopa. These and other behavioral effects of L-dopa have been reviewed recently (177). As noted above, the effects of dopa on biogenic amine metabolism (indoleamines as well as catecholamines) are complex (178–182a), and it is not possible at present to relate any of the clinical effects of dopa definitively to specific changes in monoamine metabolism.

A number of years ago, tryptophan, the indoleamine precursor, was found to be the only one of several amino acids that produced mood elevation in patients with chronic schizophrenia, when these amino acids were administered in conjunction with a monoamine oxidase inhibitor (183). In depressed patients, the therapeutic effects of monoamine oxidase inhibitors have been reported to be potentiated by tryptophan (184–186), but not in all studies (187). Some investigators have indicated that tryptophan administered alone, without the addition of a monoamine oxidase inhibitor, is effective in the treatment of depressions (135, 188–190); but not all studies have confirmed this (147, 191, 192).

These conflicting results may in part be explained by the finding that tryptophan does not increase levels of 5-hydroxyindoles in the CSF of all depressed patients (144), but in one study, which failed to demonstrate a clinical antidepressant effect of L-tryptophan, increased levels of 5HIAA were observed in cerebrospinal fluid during L-tryptophan treatment (147). It has also been

suggested that these differences might be accounted for by the finding that not all depressed patients show a decrease in serotonin turnover in brain (as measured by 5HIAA accumulation in CSF after probenecid) (193). However, it must be remembered that tryptophan exerts many other biochemical effects besides increasing indoleamines, and the complex biochemical pharmacology of tryptophan has been reviewed elsewhere (168).

The antidepressant activity of monoamine oxidase inhibitors may also be potentiated by 5-hydroxytryptophan in some patients (194, 195) but this effect has not been observed by all investigators (21, 93). One study reported a single case of a patient refractory to both electroconvulsive treatments and amitriptyline who responded to intravenous administration of 5-hydroxytryptophan in conjunction with barbiturates, diazepam, and a small dose of opium; this was accompanied by an increase in levels of 5HIAA in the cerebrospinal fluid (196). Preliminary findings from another recent study suggest that patients with endogenous depressions who have decreased accumulation of 5HIAA in the cerebrospinal fluid following probenecid administration respond clinically to treatment with 5-hydroxytryptophan, but those with higher accumulations of 5HIAA in the CSF do not (143). In another recent study, 5-hydroxytryptophan was not effective in the treatment of a small number of depressed patients although it did produce a significant increase in levels of 5HIAA in the CSF; but the probenecid-induced accumulation of 5HIAA in CSF was not measured (127). One cannot necessarily assume that alterations in mood which may be produced by 5-hydroxytryptophan result simply from an increase in indoleamines at specific receptors in brain; for example, 5-hydroxytryptophan may also release and displace catecholamines centrally (197, 198).

In the light of the complex biochemical pharmacology of the monoamine precursors, it would seem unwarranted to attempt to draw theoretical inferences concerning the possible roles of one or another of the monoamines in affective disorders on the basis of these data. Interpretations of the clinical results are complicated by the fact that different clinical diagnostic criteria may have been employed in the selection of patients in these various studies, and, as noted above, even depressed patients who appear similar clinically, may be different in terms of underlying biochemical pathophysiology. Further investigations will be required to determine whether specific clinical or biochemical subgroups of depressed patients may be responsive to treatment with one or another of these monoamine precursors.

Monoamine Synthesis Inhibitors and Receptor Blockers

It was initially suggested that clinical studies with alpha-methylparatyrosine (the inhibitor of catecholamine biosynthesis) might provide crucial data to evaluate the catecholamine hypothesis of affective disorders, which proposes that some if not all depressions are associated with an absolute or relative deficiency of catecholamines (particularly norepinephrine) at functionally important adrenergic receptor sites in the brain, whereas manias may be associated with an excess

of these monoamines (12). Subsequent clinical studies have indicated that this drug regularly produces sedation when first administered and that some hypertensive patients may become depressed during treatment with alpha-methylparatyrosine, while transient hypomanic-like reactions frequently occur upon withdrawal of the drug (199, 200)[3]. However, depressions were not observed in two studies of alpha-methylparatyrosine in schizophrenic patients (201, 202).

It has recently been reported that alpha-methylparatyrosine decreased mania in some manic patients, whereas it increased depression in a small number of depressed patients. During treatment with alpha-methylparatyrosine, the levels of VMA, MHPG, and dopamine in urine decreased by more than 50% and cerebrospinal fluid levels of homovanillic acid decreased by more than 40%; thus catecholamine biosynthesis appeared to have been markedly but not completely inhibited. The authors concluded that under these conditions alpha-methylparatyrosine was therapeutically effective in some manic patients but not as effective as lithium carbonate (203).

In another recent study of subjects who abused amphetamine, the euphoric effects of large doses of intravenously administered d,l-amphetamine were reduced or abolished by alpha-methylparatyrosine. After one week of daily administration of alpha-methylparatyrosine, there was a reduction of this anti-amphetamine effect, possibly due to compensatory receptor supersensitivity. On the basis of these results and the findings from studies of the effects of drugs thought to block dopaminergic or noradrenergic receptors selectivity, the investigators suggested that dopamine may be important for the euphoric effects of amphetamine (204). However, other investigators have found a relative increase in the urinary excretion of MHPG during amphetamine-induced hypomanias and a relative decrease in urinary MHPG during the depressions associated with amphetamine withdrawal, suggesting that norepinephrine may also be of some importance in amphetamine-induced alterations in affective state (78).

In nonhuman primates (Macaca speciosa), alpha-methylparatyrosine has been reported to produce changes in social behavior characterized by retarded motor activity, withdrawn posture, bowed head, reduced initiated social interactions, and facial expressions suggesting a lack of concern with the environment. The investigators regarded this behavioral state as similar, in some ways, to depressive states seen in man. The urinary excretion of MHPG and VMA was decreased during administration of alpha-methylparatyrosine and an attempt to reverse

[3] During the early clinical trials of alpha-methylparatyrosine by Engelman and his associates, I had the opportunity to evaluate some of the patients treated with this drug. During the initial phase of administration, some patients experienced a syndrome—characterized, in varying degrees, by psychic retardation, fatigue or loss of energy, decreased ambition or initiative, and an impaired sense of vitality—which could be descriptively classified as a mild endogenous depression, following the criteria described elsewhere (1). Upon withdrawal of alpha-methylparatyrosine, one could observe mild transient hypomanic-like states characterized by pressure of speech and an apparent decreased need for sleep.

the behavioral syndrome in one animal using L-dopa was unsuccessful (205). In a further study, these investigators reported that p-chlorophenylalanine, the inhibitor of serotonin synthesis, did not produce a similar pattern of behavioral changes in Macaca speciosa in spite of a marked inhibition of serotonin synthesis as evidenced by a decrease in urinary 5HIAA excretion and the occurrence of weight loss, hair loss, ataxia, and debilitation in some of the animals (206). However, after administration of p-chlorophenylalanine to patients with carcinoid syndrome, psychotic confusional states, sometimes with a depressive component, have been observed in some patients (207).

Methysergide, a serotonin and tryptamine antagonist, was initially reported to be effective in the treatment of manias by three groups of investigators employing various routes of administration including intrathecal (208–211). Subsequent studies by a number of investigators failed to confirm these findings (212–216), but others have confirmed the therapeutic effects of methysergide in the treatment of a small number of manic patients, and the precipitation of depressions has been noted (217, 218). Cinanserin, another antiserotonin agent, has also been reported to be effective in the treatment of manias (219). The clinical efficacy of methysergide and cinanserin in the treatment of manias if substantiated, would suggest a disturbance of indoleamine metabolism in manic states; one of the investigators reporting therapeutic effects with this drug has proposed that methysergide may exert its clinical effects in manias by antagonising tryptamine receptors in brain (220, 221). In the light of the several negative reports it would seem that methysergide is clearly not effective in the treatment of all manic disorders, and further studies will be required to determine whether methysergide when administered in adequate doses (or by specific routes of administration) may be effective in a particular subgroup of patients with manic disorders (222, 223).

Conclusion

It has long been recognized that hypotheses relating the affective disorders to alteration in biogenic amine metabolism were, at best, reductionistic oversimplifications of very complex biological states, which undoubtedly involved many other biochemical, physiological, and psychological factors (12, 13). The body of research summarized in this review, however, attests to the heuristic value of these reductionistic hypotheses, initially formulated on the basis of the neuropharmacological effects of drugs used in the treatment of the affective disorders.

While it would be premature to attempt to integrate these diverse findings at present, it does appear that certain changes in biogenic amine metabolism (alterations in normetanephrine and MHPG excretion) may occur in association with changes in affective state, whereas other abnormalities in monoamine metabolism (as reflected by decreased 5HIAA in the CSF) may represent enduring constitutional factors in some patients with affective disorders (224). Whether or not these or the other alterations in biogenic amine metabolism, reviewed here, ultimately prove to be of etiological importance, such findings

will increase our understanding of the pathophysiological changes that occur in patients with affective disorders (14).

It is important to note that mere measurements of the levels of monoamines and their metabolites in various tissues (including brain) or body fluids (including the probenecid-induced accumulation of acid monoamine metabolites in CSF), do not enable one to distinguish among the varied phsyiological processes that may underlie alterations in these levels. For example, low levels of one or another monoamine or its metabolites might occur both with a primary deficiency in synthesis leading to a decrease of the monoamine at receptors or with a feedback-induced decrease in synthesis secondary to an excess of the monoamine at receptors. Similarly high levels of metabolites could occur both with an excess of the monoamine at receptors resulting from a primary increase in monoamine synthesis, or with a functional deficiency of monoamines at receptors (as a result of increased enzymatic inactivation of the monoamine or a decreased receptor sensitivity to the monoamine) with a consequent feedback-induced increase in monoamine synthesis. However, our increasing understanding of the neurochemical effects of the drugs used in the treatment of affective disorders, including the effects of chronic administration, as this is generally required for therapeutic effects (225, 226), may help us clarify these underlying pathophysiological processes (32, 166).

While it has been strategic in individual studies to focus on one or another of the monoamines, the physiological interactions of monoaminergic neuronal systems (noradrenergic, dopaminergic, and serotonergic) are generally recognized, and it appears that biochemical as well as physiological processes involving one monoamine may be modulated by another. Moreover, the balance between cholinergic as well as catecholaminergic and indolaminergic activity has been considered in relation to the effects of antidepressant drugs and reserpine (9, 31, 227), and recent clinical findings suggest that physostigmine can transiently decrease manic symptoms as well as precipitate depressions (228).

The heterogeneity of the depressive disorders has been noted frequently in this review, and a major goal for research in this area will be to define the biochemical and other biological criteria that will enable us to classify patients with affective disorders more meaningfully, and to prescribe treatments more rationally, than is currently possible on the basis of clinical criteria alone. It seems reasonable to suggest that a number of variables related to biogenic amine metabolism may well be included among such biochemical criteria—urinary and CSF MHPG, CSF 5HIAA and HVA, platelet and plasma monoamine oxidase activity. This line of research may be expected to have a major clinical impact during the coming decade, and biochemical as well as physiological and provocative pharmacological tests may become as routine in the diagnostic workup of depressed patients as they are now in the evaluation of patients with endocrine or other medical disorders. The differences among antidepressant drugs, with respect to biochemical as well as clinical effects (31, 57), deserve increasing attention, since a greater understanding of the differences among antidepressant drugs will further increase our capacity to determine the specific

antidepressant drug to be used in the various clinically or biochemically defined subtypes of depressive disorders.

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