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Depressions and Biogenic Amines

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DEPRESSIONS AND BIOGENIC AMINES [1]

> Even in descriptive psychiatry the definition of melancholia is uncertain; it takes on various clinical forms (some of them suggesting somatic rather than psychogenic affections) that do not seem definitely to warrant reduction to a unity.
>
> Sigmund Freud, *Mourning and Melancholia*

Introduction

The studies of biogenic amine metabolism in the depressive disorders were identified in the first edition of the *American Handbook of Psychiatry* as one of the most promising and rapidly evolving areas of biochemical research in psychiatry. Examination of the present chapter, in relation to that earlier one, will serve to document the extensive development of this field during the past several years. Aspects of this expanding literature have been reviewed frequently.

Advances in pharmacology have served to stimulate this area of neurochemical research in psychiatry through 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, and through the elucidation of the effects of these drugs on biogenic amine metabolism. Various aspects of this area of neuropharmacology, as well as the basic biology of the biogenic amines, have

been considered in a number of recent reviews. Despite some discrepancies, most data seem compatible with the hypothesis that drugs which are 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.

Studies of the metabolism and physiology of the biogenic amines in patients with affective disorders (depressions and manias) have focused on the catecholamines (norepinephrine, epinephrine, and dopamine) or the indoleamines (serotonin and tryptamine). Since 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. In accordance with the rationale described in the first edition of the *Handbook,* these studies have explored the 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.

The importance of differentiating among the different types of depressive disorders when prescribing treatment has been stressed by many investigators, and the differential responses of various types of depressions to

one or another treatment modality have been documented in numerous studies. Similarly, the heterogeneity of the depressive disorders has been emphasized in relation to the design and interpretation of biochemical studies. Although many of the presently available systems for classifying the depressions on the basis of clinical signs, symptoms, and history are of some value in this regard, these classifications represent limited and temporary solutions to this very basic problem in psychiatry.

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 to 20 percent of all depressive disorders, are generally unresponsive to interpersonal forms of treatment or the administration of placebos, but they are relatively responsive to vigorous treatment with one or another of the antidepressant drugs or electroconvulsive therapy; and many neurochemical studies have focused on this group of depressions. 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 (i.e., bipolar) depressions are distinguished from the unipolar depressions, which are characterized by the absence of a prior episode of mania or hypomania. It is worth noting that 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 that have been employed in one or another study include: retarded versus non-retarded (or agitated or anxious); psychotic versus neurotic; endogenous versus non-endogenous, which embraces characterological, situational, or reactive depressions.

The problems inherent in these dichotomies, which in most instances separate a relatively homogenous subgroup from the heterogeneous remainder, as well as other issues related to more complex systems for classifying the depressive disorders on the basis of clinical signs, symptoms, and history are discussed in detail elsewhere. While the need for systems of classification that are more meaningful biologically is widely recognized, it seems likely that further refinements in our capacity to differentiate among the depressive disorders and to prescribe treatment more rationally may be expected only when clinical distinctions can be augmented by biochemical or physiological criteria.

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; 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.' The present review, which is more representative than comprehensive, will examine the current status of research on biogenic amine metabolism in patients with depressive disorders, focusing on recent findings that indicate the possible emergence of biochemical criteria to predict differential responses to various modalities of treatment.

Catecholamines and Related Substances

The alterations in catecholamine metabolism produced by drugs used in the treatment of the affective disorders have been studied extensively during the past decade. On the basis of the initial findings of these studies, it was suggested that some, if not all, depressions may be associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine at functionally important receptor sites in the brain, whereas manias may be associated with an excess of such monoamines. This formulation has come to be known as the catecholamine hypothesis of affective disorders.

The functional deficiency of norepinephrine, suggested to occur in some (but not necessarily all) depressions may be seen as a final common pathway, since many environmental and constitutional factors could conceivably contribute to its development and several different biochemical mechanisms might be operative immediately in producing it. These mechanisms could include decreased norepinephrine synthesis and output, impairment of norepinephrine binding and storage, increased enzymatic inactivation of norepinephrine by deamination or O-methylation, increased inactivation by neuronal reuptake, and decreased receptor sensitivity to norepinephrine. The operation of these different mechanisms in one or another subtype of depressive disorder could possibly account for differences in clinical phenomenology and responses to pharmacological as well as psychotherapeutic interventions.

Catecholamines, Normetanephrine and VMA 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 manias or after recovery. 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. In another study that 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, the increase in dopamine excretion, in contrast to norepinephrine, did not appear to precede the onset of mania. Other investigators have also found increased dopamine excretion in manic patients.

In a large series of manic patients, excretion of both norepinephrine and epinephrine was elevated above control values, but norepinephrine and epinephrine levels in a heterogeneous group of depressed patients were not different from control values; these depressed patients, however, did have a lowered catecholamine response to insulin stress. Increased catecholamine excretion has been observed in some depressed patients, but mainly in those with agitated or anxious depressions. 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 having 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. 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. 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; 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, was observed during the period of definitive clinical improvement in a series of patients with endogenous depressions treated with the tricyclic antidepressant imipramine; and this has recently been confirmed by other investigators.[2] Patients with retarded depressions had lower levels of normetanephrine excretion before treatment (when depressed) than after discontinuation of imipramine (when in clinical remission). In some, but not all, patients with agitated depressions, normetanephrine as well as norepinephrine and epinephrine are higher during the depression than after improvement.

In longitudinal studies, the excretion of normetanephrine has been observed to be relatively higher during manias or hypo-manias 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.

Although muscular activity may produce significant changes in catecholamine excretion, the alterations in the 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. Moreover, the increases in urinary norepinephrine appeared to precede the onset of mania in two studies; 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 have been reported to be elevated in association with agitated and unstable behavior in depressed patients and in other subjects.

The urinary excretion of 3-methoxy-4-hydroxymandelic acid (VMA), a deaminated O-methylated metabolite of norepinephrine, has also been found to be relatively elevated during episodes of hypomania or mania when compared with normal or depressed phases. The increase in VMA excretion appeared to be associated with the level of physical activity in one study, but not in another. 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 and normetanephrine as well as epinephrine during these hypomanic episodes; 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.

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. 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.

Since all studies have not employed a uniform system for classifying the depressions, it is difficult to summarize the findings reviewed above. In general, however, norepinephrine and normetanephrine excretion appear to be relatively decreased in patients with retarded (endogenous) depressions and increased in patients with manias. The findings in patients with agitated or anxious depressions are less consistent and some of these patients seem to show increased excretion of norepinephrine and normetanephrine as well as

epinephrine and metanephrine.

MHPG in Urine and Cerebrospinal Fluid

Because of the relatively effective brain-blood barrier to norepinephrine and normetanephrine, 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), a deaminated O-methylated metabolite of norepinephrine, may be the urinary metabolite of norepinephrine (and normetanephrine) that provides some index of the synthesis and metabolism of norepinephrine in the brain. All findings, however, do not support this, and it is, moreover, generally recognized that the brain cannot be regarded as the sole source of MHPG; but recent studies in nonhuman primates suggest that approximately 50 percent of urinary MHPG may derive from norepinephrine originating in the brain.

A number of studies have examined the excretion of MHPG in patients with affective disorders. In one of these studies, urinary MHPG was significantly lower in a diagnostically heterogeneous group of depressed patients than in a non-depressed control population. Subsequent studies, however, 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 responses to specific forms of pharmacotherapy —as discussed below.

In a longitudinal study of a small group of manic-depressive patients, levels of urinary MHPG were lower during depressions and higher during hypomanic episodes than after clinical remissions. The depressed patients in this study had agitated depressions, during which some showed relatively increased levels of norepinephrine and normetanephrine as well as epinephrine and metanephrine. Therefore, one cannot simply relate the reduced levels of MHPG in these depressed patients to a decrease in motor activity or a reduction in peripheral sympathetic or adrenomedullary activity. 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 since the peaks of MHPG output occurred on different days and preceded the peaks of mania.

The changes in MPIPG excretion and affective state occurring in the context of amphetamine abuse and withdrawal were recently studied in a small group of patients. 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. The changes in VMA excretion observed in this study were not similar to 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.

However, the urinary excretion of MHPG has been shown to increase in response to various forms of stress and may also vary in response to changes in motor activity or posture. Additional studies, therefore, 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 the urinary excretion of MHPG may provide a biochemical basis for classifying depressed patients and for predicting the 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 MHPG. 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. In another study of a small group of depressed patients, favorable responses to treatment with amitriptyline were observed in patients with relatively high levels of urinary MHPG but not in patients with lower levels of MHPG.

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 norepinephrine from presynaptic neurons. Findings compatible with these interpretations have been reported. 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

classified as chronic characterological (i.e., neurotic); but there were a number of 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; however, 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 and residual drug effects may have influenced the initial MHPG values. Further investigation will clearly be required to determine whether the level of MHPG excreted in the urine will provide a clinically useful criterion for classifying depressive disorders and predicting responses to pharmacotherapy.

Free and conjugated MHPG have been demonstrated in human cerebrospinal fluid, and several studies have recently examined the levels of MHPG in the lumbar cerebrospinal fluid (CSF) 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. 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. However, 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. 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 these various groups before treatment, nor did any significant changes occur after treatment; however, the investigators noted that there was a wide scatter in the concentrations of MHPG in the lumbar CSF of these patients (and this study differs from others in that a spectrophotofluorometric, rather than gas chromatographic, method was used to determine MHPG).

While further studies of MHPG in the CSF of patients with affective disorders are clearly indicated, the available data suggest that levels of MHPG in the CSF may be decreased in some (but not all) depressed patients and increased in some patients with manias. However, some patients with affective disorders may have normal levels of MHPG in lumbar cerebrospinal fluid. As described above, 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, since the findings of a recent study demonstrated a statistically nonsignificant trend toward increases in CSF MHPG—as well as increases in homovanillic acid (HVA) and

5-hydroxy-indoleacetic acid (5HIAA)—after increased psychomotor activity was induced by simulating mania. 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 percent) of the urinary MHPG as recent findings suggest.

HVA in Cerebrospinal Fluid

Homovanillic acid (HVA), a deaminated O-methylated metabolite of dopamine, can be determined in lumbar cerebrospinal fluid and may provide information about the cerebral metabolism of dopamine, although some of the HVA in CSF may derive from brain capillaries. Interpretation of such findings is further complicated by the fact that the concentration of HVA in lumbar CSF is considerably lower than in ventricular CSF, suggesting that there may be a transport system for the removal of HVA in the region of the fourth ventricle.

Baseline levels of HVA in the CSF have been found to be lower in depressed patients than in control subjects in a number of recent studies.® In one study, decreased baseline HVA levels were observed in patients with retarded depressions but not in patients with non-retarded depressions, but

the decrease in CSF HVA did not appear to be related to motor activity in all studies.' In another study, patients with recurrent depressions (unipolar depressions) had lower HVA levels than patients with manic-depressive depressions (bipolar depressions) 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.

In one study the reduced levels of HVA observed in depressed patients did not increase after electroconvulsive therapy, although considerable clinical improvement was observed. 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. 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.

Baseline levels of HVA in hypomanic and manic patients have been observed to be equal to or lower than control values in several studies.® 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 often could not be maintained prior to the lumbar puncture.

Because the rate of efflux of one or another metabolite from the CSF may vary over time and among subjects, measurements of the levels of these metabolites in lumbar CSF at an instant in time do not necessarily reflect the rates of production of the metabolites during a given time interval. Information of the latter sort may be obtained by blocking the efflux of acid metabolites from the cerebrospinal fluid with probenecid, a drug that inhibits the transport of the carboxylic acid metabolites of biogenic amines (e.g., HVA as well as 5-hydroxyindoleacetic acid (5HIAA), a deaminated metabolite of serotonin); but in two clinical studies, probenecid did not appear to block the efflux of MHPG (a glycol) from the CSF. Probenecid has been used more extensively in studies of 5HIAA, and the problems inherent in this technique are discussed in conjunction with these studies (see below).

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. 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 non-retarded depressions was slightly greater than control values. The levels of HVA following probenecid administration (i.e., 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.

Tyrosine in Blood

The levels of tyrosine, an amino acid precursor of the catecholamines, 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. 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. 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 response to an oral load of tyrosine was not significantly different in endogenous depressions when compared with controls. Further investigations will be required to explore these apparent discrepancies.

Dopa Administration

Dihydroxyphenylalanine (Dopa), an amino-acid precursor of the catecholamines, can cross the blood-brain barrier, and under some conditions may elevate levels of dopamine or norepinephrine in the brain. Consequently, Dopa has been administered to patients with affective disorders, both to explore its clinical effects as well as to investigate the possible relationship of alterations in biogenic amine metabolism to changes in affective state. However, since the initial clinical trials of Dopa more than a decade ago, it has become apparent that in addition to increasing catecholamine levels, Dopa produces many other biochemical and neuropharmacological effects; consequently, the interpretation of the findings of such studies may not be as straightforward as was initially assumed. One cannot be certain that the administration of Dopa will necessarily lead to an increased concentration of catecholamines at specific neuronal sites; nor can one be certain that any clinical effects observed are direct physiological effects of catecholamines

derived from Dopa rather than the pharmacological effects of Dopa acting directly or indirectly upon other mono-aminergic systems (i.e., by releasing monoamines, by displacing monoamines through the production of false transmitters, or by interfering with the metabolism of monoamines). Moreover, Dopa may affect many other diverse biochemical systems. The literature on the use of Dopa and other monoamine precursors in the treatment of depressions has been discussed recently in a detailed and extensive review.

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, 1-isomer were used. In other early studies, improvement in depressed patients was observed after intravenous administration of L-Dopa, and elevation of mood was reported in a group of patients treated with a monoamine oxidase inhibitor and Dopa. (This combination of drugs can produce severe hypertension and cardiac arrhythmias.) 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. 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; depressed mood often persisted during these episodes of hypomania and it has been suggested, on the basis of this observation, 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 since some investigators do not consider the symptom of depressed mood to be necessary for the diagnosis of endogenous depressions (which are 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. 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 us to better coordinate clinical concepts with underlying biological substrates.

When L-Dopa has been used in the treatment of Parkinson's disease, improvement in depression and hypomanic-like states have 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. As noted above, the effects of Dopa on biogenic amine metabolism (i.e., indoleamines as well as catecholamines) are complex,® and it is not possible at the present time to definitively relate any of the clinical effects of Dopa to specific changes in catecholamine metabolism.

Alpha-methylparatyrosine

It was initially suggested that clinical studies with alpha-methylparatyrosine (a drug that inhibits catecholamine biosynthesis by blocking the conversion of tyrosine to Dopa) might provide crucial data to evaluate the catecholamine hypothesis of affective disorders. 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.- In the course of these early clinical trials of alpha-methylparatyrosine, I had the opportunity to evaluate some of the patients treated with this drug. During the initial phase of treatment, 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—that could be descriptively classified as a mild endogenous depression,

following the criteria that I have described elsewhere. 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. However, depressions were not observed in two studies of alpha-methylparatyrosine in schizophrenic patients.-

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 treated with this drug. During treatment with alpha-methylparatyrosine, the levels of VMA, MHPG, and dopamine in urine decreased by more than 50 percent and cerebrospinal fluid levels of homovanillic acid decreased by more than 40 percent; 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 that it was not as effective as lithium carbonate.

In another recent study of subjects who abused amphetamine, the euphoric effects of large doses of intravenously administered d, 1-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 the result of compensatory receptor super-sensitivity). On the basis of these results and

the findings from studies of the effects of drugs thought to block dopaminergic or noradrenergic receptors selectively, the investigators suggested that dopamine may be of importance for the euphoric effects of amphetamine. However, as noted above, 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; and these findings suggest that norepinephrine may also be of some importance in amphetamine-induced alterations in affective state.

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, as well as 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 the behavioral syndrome in one animal using L-Dopa was unsuccessful. In a further study, these investigators reported that parachlorophenylalanine, 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. After administration of parachlorophenylalanine to patients with carcinoid syndrome, nonspecific alterations in behavior including psychotic confusional states as well as nonpsychotic behavioral changes, sometimes with depressive components, have been observed in some patients.'

Beta-phenylethylamine

The urinary excretion of beta-phenylethylamine (both free and conjugated) has been found to be decreased in depressed patients by several groups of investigators; and increased levels of phenylethylamine have been observed in manic as well as schizophrenic patients. 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. Further studies will be 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.

Catechol O-Methyl Transferase Activity

The activity of catechol O-methyl transferase (COMT) in red blood cells

of women with unipolar primary depressions was significantly lower than controls in a recent series of investigations,' 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 primary 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 primary affective disorders, no differences in red blood cell COMT activity were found among comparable diagnostic groups of male patients. It may be of interest to note in regard to these findings that 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 derivation of norepinephrine; however, direct evidence to support this speculative hypothesis is lacking.

Indoleamines and Related Substances

Various aspects of indoleamine metabolism have been explored in patients with depressive disorders. These studies have provided further understanding of the biochemical pathophysiology underlying these clinical states.

5HIAA in Urine and Cerebrospinal Fluid

The urinary excretion of 5-hydroxyindole-acetic acid (5HIAA), a deaminated metabolite of serotonin, has been studied extensively in patients with affective disorders.® These findings have been considered in a recent comprehensive review and will not be discussed in detail in this paper. 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, but not all studies concur. 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 since it is thought that a considerable fraction of urinary 5HIAA may derive from indoleamines in the gastrointestinal tract and that dietary factors may be of considerable importance.

Various findings suggest that measurements of 5HIAA in lumbar cerebrospinal fluid (CSF) may yield information about the cerebral metabolism of serotonin, although some of the 5HIAA in lumbar CSF may come from the spinal cord. Concentrations of 5HIAA (like HVA) are

considerably higher in ventricular CSF than in lumbar CSF, with intermediate values found in cisternal CSF, suggesting that there may be a transport system for the removal of 5HIAA from the CSF located in the region of the fourth ventricle.

Since the initial report that 5-hydroxyindole compounds were decreased in the cerebrospinal fluid of depressed patients, numerous investigators have confirmed the observation that CSF levels of 5-hydroxyindoleacetic acid are lower in depressed patients than in controls. In most studies statistically significant decreases, or nonsignificant decreases, 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. Levels of 5HIAA in the CSF have been observed to be higher in subjects over the age of fifty-five than in middle-aged subjects; and in one study, depressed patients over sixty years of age had significantly higher 5HIAA levels than did depressed patients under sixty years. However, in several other studies no age correlation was observed.

The variability observed in the many studies of CSF 5HIAA in depressions might be accounted for by a number of factors: the nature of the control group to which depressed patients were compared; differences in age or sex of the various groups; differences in the conditions under which the

samples of cerebrospinal fluid were obtained; and differences 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. In one of these studies, normal levels of 5HIAA were observed in the patients with manic-depressive depressions. Depressed patients classified as psychotic (on the basis of the presence of delusion) had lower CSF levels of 5HIAA than did nonpsychotic depressed patients in one study. 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.

In most studies the decrease in CSF 5HIAA levels in depressed patients persisted after recovery, although a slow rise to normal values upon recovery from depression was noted in one study of a small number of patients. During treatment with amitriptyline, imipramine, or nortriptyline, a further decrease in CSF 5HIAA has been observed in depressed patients. No changes in CSF

5HIAA levels were observed in depressed patients after electroconvulsive therapy (ECT) in one study in which pretreatment levels of 5HIAA were not decreased.

In some studies, low baseline levels of CSF 5HIAA have been observed in hypomanic or manic patients both before treatment and after recovery; but the decreases in pretreatment levels were not statistically significant in all of the studies. Other investigators, however, have observed normal or increased CSF 5HIAA levels in manic patients. CSF 5HIAA levels in lumbar cerebrospinal fluid have been shown to increase after exercise or periods of "simulated mania" with increased psychomotor activity; since a concentration gradient of 5HIAA appears to exist within the cerebrospinal fluid system (with lowest levels observed in the lumbar CSF) this could conceivably result from an increased mixing of CSF from various levels during periods of increased physical activity. 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.

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; the 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. (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.

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.

In one study, significantly lowered 5HIAA accumulation was observed in manic patients, and CSF-5HIAA accumulation tended to be lower in manic patients in another study.

The problems in interpreting data on the accumulation of acid monoamine metabolites in lumbar CSF following probenecid have been discussed elsewhere, 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 or differences in the degree of blockade produced by a given concentration of probenecid; 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. Since 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, a precursor of serotonin, in patients with vital (endogenous) depressions, three of five patients improved with 5-hydroxytryptophan, whereas none of five subjects improved with placebo; the three patients who improved during treatment with 5-hydroxytryptophan showed low pretreatment accumulations of 5HIAA

in CSF after probenecid, whereas the two patients who did not improve had higher pretreatment accumulations of 5HIAA. However, another group of investigators failed to demonstrate a therapeutic response to 5-hydroxytryptophan in six of seven depressed patients, although in this study 5-hydroxytryptophan administration was shown to produce increases in plasma 5-hydroxytryptophan, cerebrosplinal fluid 5HIAA and urinary 5HIAA; and the one patient who showed a moderate response to treatment with hydroxytryptophan did not exhibit an exacerbation after withdrawal of the drug. However, the results of this study need not necessarily contradict the preceding findings, since 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 administration of tryptophan (an amino acid precursor of serotonin) in depressed patients. In one study, 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 the synthesis of serotonin from tryptophan may be impaired in some depressed patients.' Another group of investigators,

however, has observed that L-tryptophan produced an increase in platelet serotonin, urinary and CSF 5HIAA, as well as the accumulation of 5HIAA in the CSF after probenecid without an accompanying improvement in the depression in most of the patients. 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.

Serotonin and 5HIAA in Brain after Suicide

Several studies have examined the levels of serotonin and 5HIAA in the brains of depressed patients after suicide. In one of these studies, 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. This difference in serotonin levels, however, 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.

In another study, 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 committed suicide rather than in patients with endogenous depressions. Moreover, in this study a positive correlation was found between age and serotonin concentration and the authors note that the 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 the concentrations of 5HIAA in the brain stem, norepinephrine in hypothalamus or dopamine in caudate nucleus between suicides and controls in this study.

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 that has recently been commented upon is the length of time during which frozen specimens were stored between the necropsy and assay.

Other Metabolites of Tryptophan in Urine

The urinary excretion of tryptamine was relatively reduced during depressions and increased after clinical improvement in several studies.

However, in another recent study, tryptamine levels were relatively elevated during depressions when compared with values obtained after recovery. 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 alterations in tryptamine excretion. Depressed patients were reported to have relatively decreased rates of liberation of C02 from carboxy-labeled 5-hydroxytrytophan in one study, but the group originally reporting this finding did not observe the phenomenon in a further study of depressed patients.

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 that have been reported to occur in depressive disorders, and 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. After a tryptophan load, female patients with endogenous depressions excreted more kynurenine and 3-hydroxy-kynurenine, but not the subsequent metabolite hydroxyanthranilic acid, than did female control subjects in one recent study.

In two manic-depressive patients studied longitudinally, the conversion of intravenously administered radioactive tryptophan to kynurenine was greater during episodes of depressions than during episodes of mania or during normal periods; but the excretion of endogenous kynurenine was significantly lower during depression than during mania. In another study, the excretion of kynurenine in depressive patients was significantly lower than in normal subjects. 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.

Tryptophan and 5-Hydroxytryptophan Administration

A number of years ago, tryptophan, an amino acid precursor of the indoleamines, 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. In depressed patients, the therapeutic effects of monoamine oxidase inhibitors have been reported to be potentiated by tryptophan, but not in all studies. Some investigators have indicated that tryptophan administered alone (i.e., without the addition of a monoamine oxidase inhibitor) is effective in the treatment of depressions; but all studies have not confirmed this.

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

The antidepressant activity of monoamine oxidase inhibitors may also be potentiated by 5-hydroxytryptophan in some patients but this effect has not been observed by all investigators. One study reported a single case of a patient, refractory to both electroconvulsive treatments and amitriptyline, who responded to intravenous administration of 5-hydroxytryptophan administered 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. 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 that those with higher accumulations of 5HIAA in the CSF do not. 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. 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.

In the light of the complex biochemical pharmacology of tryptophan and 5-hydroxytryptophan, 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. Moreover, 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 tryptophan or 5-hydroxytryptophan.

Methysergide and Related Substances

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. Subsequent studies by a number of investigators failed to confirm these findings; but some investigators 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. Cinanserin, another anti-serotonin agent, has also been reported to be effective in the treatment of manias. The clinical efficacy of methysergide (and cinanserin) in the treatment of manias, if substantiated, would suggest a disturbance of indoleamine metabolism in manic states; and one of the investigators reporting therapeutic effects with this drug has proposed that methysergide may exert its clinical effects in manias by antagonizing tryptamine receptors in brain. However, 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.

Monoamine Oxidase 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 dehydrogenase) functioned normally in the depressed patients. In a more recent study, 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 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; however, as the investigators noted, this study lacked the double-blind procedures adequate for a proper evaluation of the antidepressant effects of conjugated estrogens.

Another group of investigators has 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. In further studies, this group of investigators observed that there was a progressive increase in monoamine oxidase activities in the human

hindbrain, platelets, and plasma with advancing age, starting at the age of thirty-five in platelets and brain and at the age of fifty-five in plasma, with maximal levels observed after the age of seventy. 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 the age of forty; 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 the hindbrain correlated negatively with hindbrain monoamine oxidase activity. Neither serotonin nor 5HIAA levels in the 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.

In another recent study, platelet monoamine oxidase activities were found to be significantly lower in bipolar depressed patients 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. 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.

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.

It is difficult to compare the findings of these various studies, since different substrates were used in the assays of monoamine oxidase activities. Moreover, further investigation will be required 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. 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.

Tricyclic antidepressants (i.e., 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; 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. 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 monoamine oxidase inhibitors. In contrast, lithium salts appear to increase the release and intra-neuronal 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. Moreover, this could conceivably also account for the reported antidepressant effects of lithium when used in combination with monoamine oxidase inhibitors, and would lead to the prediction that lithium may exert antidepressant effects in those depressed patients with endogenously reduced monoamine oxidase activity.

Conclusion

It has long been recognized that hypotheses relating the affective disorders to alterations in biogenic amine metabolism were, at best, reductionistic oversimplifications of very complex biological states that undoubtedly involved many other biochemical, physiological, and psychological factors. 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 the present time, it does appear that certain changes in biogenic amine metabolism (e.g., alterations in normetanephrine and MHPG excretion) may occur in association with changes in affective state, whereas other abnormalities in monoamine metabolism (e.g., as reflected by decreased

5HIAA in the CSF) may represent enduring constitutional factors in some patients with affective disorders. Whether or not these or the other alterations in biogenic amine metabolism, reviewed here, ultimately prove to be of etiological importance, such findings will, nonetheless, increase our understanding of the pathophysiological changes that occur in patients with depressive disorders.

In this connection, it is important to note that mere measurements of the levels of monoamines and their metabolites, in various tissues (including the brain) or body fluids (including the probenecid-induced accumulation of acid monoamine metabolites in CSF), do not enable one to distinguish among the varied physiological 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 the monoamine 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 since this is generally required for therapeutic effects, may help us to clarify these underlying pathophysiological processes in patients with depressions and manias.

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, and recent clinical findings suggest that physostigmine, an acetylcholinesterase inhibitor, can transiently decrease manic symptoms as well as precipitate depressions.

The heterogeneity of the depressive disorders has been noted frequently in this chapter, and it appears that a major goal for future research will be to define the biochemical as well as 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. From the recent preliminary findings reviewed above, it seems not unreasonable to suggest that a number of variables

related to biogenic amine metabolism (e.g., urinary and CSF MHPG; CSF 5HIAA, and HVA; platelet and plasma monoamine oxidase activity) may well be included among such biochemical criteria. In this context, additional attention should be directed toward possible differences in the biochemical as well as clinical effects of various antidepressant drugs, since a greater understanding of these differences will further increase our capacity to determine the specific antidepressant drug to be used in various clinically or biochemically defined subtypes of depressive disorders.

Many investigators expect this line of research to have a major clinical impact during the coming decade, and it is predicted that biochemical as well as physiological and provocative pharmacological tests will 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. Following the advances that have occurred in other areas of medical nosology, it seems quite conceivable that this approach will ultimately contribute to the development of a psychiatric nosology, based not only upon the clinical phenomenology of the depressive disorders but also upon a knowledge of the biological mechanisms underlying these phenomena.

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Notes

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2 The tricyclic antidepressant imipramine as well as the monoamine oxidase inhibitor phenelzine was observed to decrease the urinary excretion of 3-methoxy-4-hydroxymandelic acid (VMA) in depressed patients, suggesting that the tricyclic antidepressants as well as the monoamine oxidase inhibitors might decrease the deamination of norepinephrine;' and this was subsequently demonstrated in studies in animals.