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# BIOLOGICAL ASPECTS OF AFFECTIVE ILLNESS

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# BIOLOGICAL ASPECTS OF AFFECTIVE ILLNESS[1]

**J. Mendels**

During the past decade, there has been a major upsurge of investigation into biological correlates of mood disturbance. The development of pharmacological agents that alleviate the symptoms of depression and mania or induce symptoms resembling clinical depression has encouraged efforts to explore and define the biological changes associated with affective illness.

At this time, there is no final resolution to the question of whether affective illness results from a psychological or biological disturbance or from alterations in one system interacting with some pre-existing vulnerability in the other. It is, however, clear that there are alterations in the central nervous system, autonomic nervous system, and endocrine system, in association with changes in mood, regardless of whether the psychopathological symptoms are primary or secondary.

In this chapter, we are concerned with the biological changes

associated with depressive illness. It must be remembered that the syndrome of depression (and perhaps mania) probably represents a heterogeneous group of conditions in terms of etiology, pathology, and symptomatology. These issues have been discussed in detail elsewhere,neec[ not repeated here. However, the fact that we are probably dealing with several distinct conditions suggests that the biological correlates will not be necessarily the same for all. A major difficulty in current investigations of the psychobiology of depression has been the frequent failure to distinguish between specific groups of depressed patients.

There are many analogies in general medicine. For example, the recognition that pernicious anemia constitutes a separate condition with a unique pathology, etiology, and treatment, separate from other forms of anemia, required the recognition of the relationship between this syndrome and vitamin B12 deficiency. Treating 100 consecutive patients with anemia (i.e., a significant reduction in hemoglobin concentration) with vitamin B12 alone would be of no significant value. Similarly, the separation of phenylketonuria from the broad syndrome of mental deficiency required the recognition of the unique features of this condition. It is possible that similar problems are

relevant to the study of clinical depression. Thus, the failure to define consistent and specific biological alterations in depression may be at least in part a function of the fact that investigators have studied mixed groups of patients. For example, there are now reports of possibly important differences between groups of depressed patients with and without a previous history of mania.

Much of the information which underlies the psychobiological hypotheses of the affective illnesses derives from pharmacological rather than from clinical studies. While this information is of importance, we remain without a real understanding of the biological changes in our patients. To a large extent, this is the result of the limitation on the type of experiments which can be conducted in patients. We do not have the techniques to study the details of brain function or the relationship between brain function and mood and behavior in man. Therefore, much of the research has been indirect, concerned with changes in peripheral systems or in electrical measurements of brain function.

It must also be remembered that the demonstration of a biological alteration in patients with a particular psychiatric syndrome

(albeit a consistent abnormality) does not necessarily mean that this is the cause of the condition. The change may be a result of another and perhaps undetectable biological change or may result from psychological events. Further, the complex interrelationships between multiple biological systems in man have yet to be clearly understood and defined, let alone explored systematically in clinical depression.

In spite of these problems, there has been progress in developing models of the psychobiology of depression, together with the investigation of these in patients. Alterations in a number of different systems have been observed or postulated. These include a genetic predisposition; alterations in biogenic amine function (norepinephrine, dopamine, serotonin), and perhaps in other neurotransmitters; changes in electrolyte metabolism (sodium, potassium, magnesium, and calcium); neuroendocrine changes including hypothalamic-pituitary activity, adrenocortical function, growth hormone release, and thyroid function; studies of electrophysiological activity, such as cortical evoked potential, electromyography, and sleep electroencephalography; and, more recently, suggestions of alterations in receptor sensitivity, cell membrane function and in adenyl cyclase-cyclic AMP activity.

For purposes of convenience, these will be reviewed separately, but it should be remembered that the interrelationships between these systems are very important. It is essential to recognize and define these interrelationships and to begin to incorporate them into a meaningful hypothesis.

## Genetics

There is considerable evidence that genetic factors play an important role in the etiology of affective illness. There is a significant difference between concordance rates for manic-depressive illness in monozygotic and dizygotic twin pairs. A review of six twin studies indicated a concordance rate for monozygotic twins of 74 percent, whereas the concordance rate for dizygotic twins was only 19 percent. A comparable concordance rate was found in a review of case reports of twelve monozygotic twins reared apart. Although these findings suggest a substantial genetic component, twin studies do have important methodological limitations.

The prevalence of affective illness in the first-degree relatives of manic-depressive patients is approximately 20 percent, while in

uniphasic patients it is estimated to be 13 percent. This contrasts with an estimated incidence in the general population of only 1 percent. It is of interest to note that while most studies have shown depression in general to be more common in females than in males (a mean of male-female ratios of 0.69 has been reported, this difference may not occur among manic-depressives. Here the incidence is the same in both sexes, whereas among uniphasic depressives it is higher among women.

Twin studies and family history studies have provided evidence of a genetic factor but have not provided unequivocal support for the specific mode of genetic transmission. The hypothesized modes of transmission include a single dominant autosomal gene with incomplete penetrance, polygenic transmission, and an X-linked dominant gene with incomplete penetrance.

The hypothesis of a single dominant autosomal gene has been supported by similar prevalences of affective illness in parents, siblings, and children of patients. A prevalence rate of less than 50 percent in the siblings and children of patients, the fact that not all patients have an affected parent, and that not all monozygotic twins

are concordant, suggest incomplete penetrance of the gene.

The hypothesis of polygenic mode of transmission is also supported by similar prevalences in parents, siblings, and children of probands, as well as by the continuum of manic and depressive characteristics, ranging from mild to severe, in the general population. A single dominant autosomal gene transmission and polygenic transmission would both have prevalence rates among relatives which decrease toward the population prevalence at different rates, as more and more remote relatives are examined. One test to discriminate between a single dominant autosomal gene and polygenic transmission in a disorder with a population incidence of approximately 1.0 percent would be the relative prevalence of the disorder in second- and first-degree relatives, respectively. The single dominant autosomal gene hypothesis suggests that the ratio should be approximately 1:2, while the polygenic hypothesis suggests approximately 1:4.

The available data are equivocal, and more data are needed on second-degree and more remote relatives. It is also of interest to note that polygenic models of transmission assume random mating with

regard to the trait or disorder in question. This assumption has been challenged by a report indicating a significantly higher prevalence of affective illness in wives (and in their family history) of male patients with affective illness than would be expected with random mating.

A dominant X-chromosome with incomplete penetrance has also been proposed as the mode of transmission. This would be consistent with a higher prevalence of affected females than males and with the report of an absence of father-son pairs in a sample of bipolar patients. However, other investigators have documented cases of similarly affected father-son pairs, and thus, if one assumes that these cases do not represent undetected transmission by the mother, an additional genetic factor (or factors) must be postulated.

The suggestion of X-linkage in manic-depressive illness led to investigation of the possibility of linkage between manic-depressive illness and X-linked marker traits. Linkage can be demonstrated when two genes, each affecting a different trait, are in close enough proximity on a chromosome that they do not assort independently. Thus, greater than chance association between two such traits would support the X-linkage hypothesis. Reports of linkage between manic-

depressive illness and both Xg blood system and deutan and protan color blindness have been made. They provide more compelling evidence of X-linked transmission than family psychiatric history data in general.

## Biogenic Amines

Following the discovery by Walter Cannon in 1915 that animals exposed to rage- or fear-inducing situations secrete increased amounts of epinephrine (adrenalin), there has been an increasing interest in the association between emotional behavior, epinephrine, and the other biogenic amines. The subsequent description of the behavioral syndrome induced by reserpine administration to rats, and the recognition that this was associated with a depletion of brain catecholamines (dopamine and norepinephrine) and serotonin, have led to an extensive series of investigations designed to explore the relationship between brain amine function and behavior. The widespread use of reserpine for the treatment of hypertension, and the development of a syndrome thought by some to be a model for clinical depression, spurred investigation of the association between depression and brain biogenic amine metabolism. These investigations

and the observations that most antidepressant drugs have pharmacological actions that presumably increase the amount of the amine available at receptor sites led to the formulation of the biogenic amine hypothesis of affective disorders. This states that clinical depression is associated with a functional deficiency of norepinephrine or serotonin at significant receptor sites in the brain, whereas mania is associated with an excess of the amine. These hypotheses are based mainly on indirect pharmacological observations with limited evidence from clinical studies. Much of this material has been reviewed elsewhere, and will only be summarized here. Likewise, the reader is referred to several reviews for a detailed discussion of the metabolism and pharmacology of the biogenic amines. Recently, several investigators have questioned the view that the syndrome induced by reserpine is a model for depression.' It may rather be the result of sedation and psychomotor retardation in certain susceptible individuals, particularly those with a history of previous depressive episodes. Furthermore, recent evidence indicates that the gross behavioral syndrome produced by reserpine is likely to result from dopamine depletion, as a consequence of reserpine's inhibition of the uptake of dopamine into storage granules and its

storage within such granules, rather than from reserpine's effect on norepinephrine or serotonin, as was originally emphasized in the development of the biogenic amine theories.

**Catecholamines: Antidepressant Drugs**

A major impetus for the catecholamine hypothesis derived from the study of the pharmacological action of the antidepressant and antimanic drugs. While these drugs are probably of value, they are not uniformly effective.

The monoamine oxidase inhibitors (MAOI), such as tranylcypromine, nialimide, increase the intraneuronal concentration of norepinephrine, dopamine, and serotonin, by inhibiting the action of the enzyme monoamine-oxidase, which is responsible for the oxidative deamination of those compounds. They may also decrease the re-uptake of amines into the neurons from which they were released. This re-uptake process is normally the main mechanism for terminating catecholamine activity.

While the MAOIs do increase tissue concentration of amines in man, there is as yet no conclusive evidence that they produce

increased functional activity at central aminergic receptor sites. Indeed, patients receiving MAOI do not have symptoms indicative of an increase in sympathetic nervous system activity. In fact, the hypotensive effect of MAOIs may result from *decreased* sympathetic activity, as a consequence of feedback inhibition of tyrosine hydroxylase or false transmitter formation.

The tricyclic antidepressants, such as amitryptyline and imipramine, potentiate the actions of endogenously released norepinephrine by blocking its re-uptake into the nerve terminal. Iprindol is an antidepressant drug, chemically related to the tricyclic compounds and yet it does not block norepinephrine or serotonin uptake as do the other tricyclic drugs, raising the question of whether the blockage of amine re-uptake is the critically important variable in determining the clinical efficacy of the drugs.

**Catecholamines: Urinary Metabolites**

There are a number of reports dealing with the concentration of amines and their metabolites in the urine of depressed and manic patients. This strategy must be interpreted with caution in that it

probably provides little, if any, information about central nervous system amine metabolism. Almost all of the urinary compounds are derived from peripheral metabolism and we do not know whether or not there is an association between changes in peripheral and in brain amine metabolism.

Robins and Hartmann have summarized the findings from nine studies which included both depressed and manic patients and in which norepinephrine, epinephrine, dopamine, metanephrine, normetanephrine, and 3-methoxy-4-hydroxymandellic acid (VMA) were measured.

The studies involved 281 determinations of these compounds. They concluded that twenty-one observations from the depressed patients were consistent with the catecholamine hypothesis of depression, whereas seventy-one were inconsistent. The manic patients provided twenty-two determinations that were consistent, and six that were inconsistent with the hypothesis. The remaining 16x determinations were equivocal. Thus, studies of urinary metabolites of catecholamines in depressed patients have not contributed to confirmation of the hypothesis. Observations in manic patients are

more consistent with the hypothesis, but may be the result of increased activity in these patients.

A more recent strategy has involved the measurement of the urinary concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG). Some observers have suggested that it may be the major metabolite of brain norepinephrine and that the percentage of urinary MHPG coming from the brain may be higher than the percentage of the other metabolites.' While this conclusion has been questioned, several investigators have measured urinary MHPG in groups of psychiatric patients and found it to be reduced in some depressed patients. However, this finding has not been confirmed. It is possible that abnormalities in urinary MHPG (and perhaps in other amine metabolites) in depressed and manic patients may simply be the result of the differences in the level of physical activity in these patients. There is a preliminary suggestion that depressed patients with low urinary MHPG concentrations are more likely to respond favorably to imipramine than are patients with normal MHPG concentration, while a few patients with normal urinary MHPG concentration seemed to have a superior response to amitriptyline. Much more investigation is needed to clarify the exact relationship between urinary MHPG and

brain norepinephrine and changes in this compound in depression.

## Catecholamines: Brain and CSF Studies

Bourne et al. found no difference in hypothalamic and hindbrain norepinephrine concentrations or in caudate dopamine concentration after death by suicide as compared with non-suicide death.

Cerebrospinal fluid (CSF) concentration of homovanillic acid (HVA), the primary metabolite of dopamine and of MHPG, has been measured in depressed and manic patients. There are inconsistent reports of a reduction in HVA concentration while depressed, with increases to normal values after clinical improvement. There is also an increase in CSF HVA concentration after the oral administration of L-DOPA to depressed patients. However, there is no accompanying clinical improvement, suggesting the possibility that the CSF HVA level may not be directly associated with the clinical state of the patient but may reflect changes in motor activity. Others have not found an association between CSF HVA concentration and psychomotor activity. Further, lumbar fluid HVA may not originate from brain dopamine solely, but may derive from spinal cord capillaries.

There are several studies of CSF MHPG concentration in depressed and manic patients. In the main, CSF MHPG has been found to be normal in depressives. One study has reported low values, but some of the control subjects had values as low or lower than some depressives, indicating that there is no clear-cut relationship between mood and CSF MHPG concentration. An elevation in CSF MHPG was noted in a few manic patients. However, some manics had normal values and a group of schizophrenics also had a raised concentration. In view of these findings and the demonstration that MHPG concentration in urine may be in part a reflection of physical activity, it is possible that the reports of low values in a few depressed patients and elevated values in a few manics are the result of the fact that these patients had psychomotor retardation (or hyperactivity) rather than due to the depressed (or manic) mood per se. One study has not found this to apply to CSF MHPG concentration in spite of changes in CSF HVA and HIAA concentrations. There is still uncertainty over the precision of the method used to assay CSF MHPG, which may account for some of the confusion.

**Catecholamines: Enzyme Studies**

An alternative strategy for investigation involves the measurement of some of the enzymes involved in catecholamine metabolism. Catechol-o-methyltransferase (COMT) is the main enzyme involved in the extra-neuronal deactivation of norepinephrine. Most of the norepinephrine which is released into the synapse is deactivated by re-uptake into the neuron; the remainder is acted on by COMT. Erythrocyte COMT activity has been measured in several groups of psychiatric patients, recognizing that it is unknown whether it is an index of brain COMT activity or not. A large reduction in COMT activity in women with unipolar depression and some reduction in women with bipolar depression has been found. It is possible that estrogens interact with other hormones to influence COMT activity. COMT activity did not change when these patients improved clinically or when four of them became manic.

This persistence in the reduction of COMT activity suggests that it may reflect an underlying genetic abnormality. It has been proposed that COMT activity is an index of adrenergic receptor activity, and the reduction in activity in these patients is compatible with the hypothesis that there is a reduction in adrenergic receptor function in some depressed patients (*infravide*). However, it could equally well be

argued that the reduced COMT activity would allow more circulating norepinephrine to reach the receptors. Alternatively, it is possible that norepinephrine metabolism is only abnormal in the manic phase of manic depressive illness and not in the depressed phase. Roberts and Broadly had originally speculated that there might be an abnormality in COMT activity in some depressives, resulting in the formation of an abnormal norepinephrine metabolite, noradnamine.

*Monoamine Oxidase (MAO) activity* in platelets has been found to be significantly reduced in bipolar depressed patients as compared with control subjects and unipolar depressives. Others have reported normal and elevated- MAO activity in mixed groups of depressed patients. MAO activity is higher in women and in the elderly, which may be relevant to the higher incidence of depression in these groups. However, it has been shown that several different forms of MAO exist in the brain,' and it is unclear what the relevance of these findings might be for brain activity.

Very preliminary studies of plasma *dopamine beta hydroxylase* (*DBH*) *activity* indicate no difference between patients with affective illness and control subjects. An elevation in *histamine-n-*

*methyltransferase activity* has been noted in depressed women.

## Indoleamines

There have been extensive investigations into serotonin metabolism in parallel with the studies of changes in catecholamines. por example, the antidepressant drugs have pharmacological effects on serotonin metabolism which are similar to their effects on norepinephrine.

Studies of the CSF concentration of 5-hydroxyindoles or 5-hydroxy-indoleacetic acid (5HIAA), the principal metabolite of serotonin, of depressed patients have more often than not found its concentration to be reduced. Not all investigators have confirmed this. Further, the rate of accumulation of 5HIAA in lumbar fluid after the administration of probenecid[2] (which blocks the egress of 5HIAA from CSF) is less in depressed patients than control subjects. This has been interpreted as reflecting a reduction in central serotonin turnover in depressed patients. Two related findings are of interest. A number of patients have been found to have a continued reduction in CSF 5HIAA concentrations after clinical recovery, and a similar reduction in

5HIAA has been found in some manic patients. Not all investigators have confirmed these observations, and there are also reports that some schizophrenic patients may also have low CSF 5HIAA concentration. There is disagreement as to whether the concentration of metabolites in lumbar fluid is a measure of brain serotonin activity or whether it derives primarily from the spinal cord.

While a number of investigators have reported CSF 5HIAA concentration to be low in depressives, there is disagreement which may in part be due to age, diagnosis (e.g., may be lower in unipolar than bipolar depressives), psychosis, or physical activity.

It has been hypothesized that the postulated reduction in brain serotonin in depression may be the result of an increase in hepatic tryptophan pyrrolase activity. There is an increase in plasma corticosteroids in some depressed patients, which could stimulate pyrrolase activity, resulting in an increased conversion of tryptophan to kynurenine and a reduction in the amount of tryptophan available for conversion into serotonin. However, the amount of corticosteroids required to

achieve this effect in animal studies is much higher than the increase found in depressed patients and it is questionable whether this mechanism is applicable.

An alternative strategy has been to study the metabolism of tryptophan, the precursor of serotonin, in depressed patients. Tryptophan is normally converted into kynurenine and its metabolites, and into tryptamine and serotonin. In the tryptophan load test an oral dose of tryptophan is followed by the measurement of kynurenine metabolites together with tryptamine. Several investigators have reported findings which they have interpreted as supporting the pyrrolase hypothesis. Cazzullo et al. reported an increase in basal urinary xanthurenic acid excretion. This did not increase abnormally after oral tryptophan administration. While these findings have been advanced as evidence for the enhanced metabolism of tryptophan along the kynurenine pathway in depression, they do not really support this conclusion. The dose of tryptophan used in this study was very high, and the patients received large amounts of pyridoxine prior to and during the study which render the findings difficult to interpret.

Curzon and Bridges reported that female patients with endogenous depression excreted increased amounts of kynurenine and 3-hydroxykynurenine but not of their subsequent metabolite, 3-hydroxy-anthranillic acid, after an oral dose of 30 mg./kg. of tryptophan, as compared with nine psychiatric patients without endogenous depression. The increase in kynurenine and hydroxykynurenine was presumed to be caused by an increase in hepatic tryptophan pyrrolase activity. However, some control subjects had a similar response, some depressed patients did not have this response, and several of the patients had an even greater excretion of these metabolites after recovery, as compared to when they were ill. In neither of these two studies were there controls for dietary, drug, or hormonal factors which may have influenced tryptophan metabolism. In a more carefully controlled study, Frazer et al. were unable to replicate these findings in a group of male depressed patients. There was no significant difference between tryptophan metabolism in these patients and a group of psychiatric control subjects. There are reports of a reduction in urinary tryptamine in depressed patients, while others have found normal values.

Careful consideration of all of the available data leads to the

conclusion that there is no significant evidence to support the hypothesis of an enhanced metabolism of tryptophan along the kynurenine pathway (at least in male depressed patients), and no evidence of enhanced tryptophan pyrrolase activity in these patients.

CSF tryptophan concentration has been reported to be low in depressed patients (and also in three manic patients). Total plasma tryptophan concentration was normal, but it is probable that free tryptophan (as opposed to the protein-bound fraction) would be a more critical measure. It is known that increasing plasma tryptophan concentration will result in an increase in brain tryptophan concentration and may alter the rate of serotonin synthesis. A low CSF tryptophan *may* reflect a reduced brain tryptophan concentration producing a reduction in brain serotonin. There are also reports of a reduction in hindbrain serotonin concentration of people who died from suicide, as compared with control subjects, as well as a relatively low concentration of 5HIAA. These findings are difficult to interpret because of the large number of factors which may have influenced the results, including ingestion of drugs, age differences, and post-mortem effects.

## Amine Depletion Studies

As discussed above, considerable attention has been directed to the behavioral syndrome found in animals and some people after reserpine administration.

The development of this syndrome is in part related to dose, but more significantly, to a previous history of depression. There is doubt whether this syndrome is an appropriate model for clinical depression. It is possible that sedation and/or psychomotor retardation may be more important complications, with depression occasionally developing as a secondary complication in vulnerable individuals. When treatment with reserpine is associated with prospective evaluation of the patient's clinical state, no significant depression occurs.

One major disadvantage of the use of reserpine is that it not only affects biogenic amine metabolism but also involves other systems, such as acetylcholine, making interpretation of results more difficult. A more selective approach to depletion of individual brain amines has been attempted under both experimental and clinical conditions, with results that do not support the hypothesis that a general depletion of

brain amines in itself necessarily leads to a clinical depression.

Several strategies have been adopted. The intraventricular injection of 6-hydroxydopamine (6OHDA) results in a significant and permanent decrease in brain norepinephrine and depending on dose, of dopamine, with probably little significant effect on serotonin. There is also a long-lasting interference with tyrosine hydroxylase activity, resulting in a reduction in the synthesis of new catecholamines. In spite of these profound and persistent effects, there are few significant persistent behavioral changes. While there is an increased irritability and an enhancement of aggressive behavior, there are no changes suggestive of clinical depression, when brain norepinephrine is reduced by 60-70 percent. It is probable that some form of "super-sensitivity" of the postsynaptic cell may develop, countering the effects of its reduction in concentration and turnover.

Likewise, the administration of alpha-methyl-paratyrosine (AMPT), which inhibits tyrosine hydroxylase, the rate limiting enzyme in catecholamine synthesis, with a decrease in the production and tissue stores of dopamine and norepinephrine, is not associated in animal or man with behavioral changes suggestive of clinical

depression. There is some sedation and decreased spontaneous motor activity.

The chronic administration of AMPT to *Maccaca speciosa* is reported to produce behavioral changes analogous to human depression. These included a decrease in total social interactions and initiatives, postural and facial changes suggestive of withdrawal, diminished motor activity, together with a continued willingness to remain close to other monkeys in the colony and to respond appropriately to their social initiatives. It is difficult to determine whether this is an appropriate model for clinical depression. These animals apparently were willing to remain within the group and had normal social responses, which is often not the case in depressed individuals who are withdrawn and "nonreactive" in spite of social initiatives. Further, these animals did not have the loss of appetite, weight, and libido, and the insomnia often seen in depressives. The administration of relatively large doses of AMPT to medical and to schizophrenic' patients was not associated with the development of clinical depression, in spite of a significant reduction in catecholamines. One possible exception to these findings is the report of an aggravation of clinical state in three depressed patients given

AMPT. However, these patients had significant psychomotor retardation prior to the administration of AMPT, and in view of AMPT's sedative effects, it is possible that the apparent aggravation in depression may have been the result of further sedation of patients who were already "slowed down."

The administration of para-chlorophenylalanine (PCPA) which, by inhibiting tryptophan hydroxylase, produces a depletion of serotonin, as well as a moderate reduction in norepinephrine, is also not associated with behavioral changes suggestive of clinical depression. This casts doubt on the suggestion that depression results from a simple reduction in brain serotonin. The effects of PCPA administration vary considerably with species, dose, and duration of administration, but there are frequent reports of increases in sexuality, aggressiveness, and insomnia, which, if anything, are compatible with manic behavior.

These approaches to depleting brain biogenic amines have not provided evidence to confirm the hypothesis that clinical depression is associated with a reduction in these amines. However, they do not necessarily disprove the hypothesis. For example, it has been

suggested that there is a “functional” intraneuronal pool from which norepinephrine is utilized at a rapid rate, and a “storage” pool which serves as a reserve depot. Thus, depletion of brain norepinephrine may have its major effect on the “storage” pool, but leave the “functional” pool sufficiently intact (with newly synthesized norepinephrine) to prevent development of a depression. A similar mechanism may apply to serotonin.

**Alteration in Receptor Sensitivity**

A functional deficiency of biogenic amine activity could arise in the presence of normal or even increased amounts of the amine if there was an abnormality of the receptor site on which the amine exerts its action. For example, depressives have been reported to have a reduced blood pressure response to norepinephrine infusion, which could be the result of a decreased receptor sensitivity. Prange et al. have suggested that their finding that small amounts of tri-iodothyronine will enhance the antidepressant effect of imipramine in depressed females may be due to the ability of thyroid hormone to increase the sensitivity of adrenergic receptors. As discussed above, the finding of a reduction in erythrocyte COMT activity may also be

compatible with this view. A reported increase in plasma norepinephrine levels in depressed patients may reflect an effort to compensate for a decreased receptor sensitivity. However, the increase in plasma norepinephrine may have been more closely related to the anxiety component of the syndrome than to the depression per se.

## Adenyl Cyclase-Cyclic AMP

Adenosine 3', 5'-monophosphate (cyclic AMP), the product of enzymatic degradation of adenosine triphosphate by adenyl cyclase, has a critical role in regulating the effects of many hormones and neurotransmitters. Adenyl cyclase's ubiquitous location in most cell membranes makes it readily accessible to stimulation by the many hormones that act upon it. The hormones initiate an increase in adenyl cyclase activity and are often referred to as the "first messenger," while cyclic AMP is known as the "second messenger." The "first messenger" carries the information to the cell, where the "second messenger" transfers the information to the cell's internal mechanisms. Thus, adenyl cyclase plays an integral part in hormonal (including catecholamine) activity.

Consequently, it is reasonable to consider the possibility that there may be some abnormality in cyclic AMP function in affective illness. There are reports of a decrease in urinary cyclic AMP excretion in depression with an elevation in mania.' Further, a marked elevation in the urinary excretion of cyclic AMP was observed on the day of an acute change from a depressed state into a manic state in six manic-depressed patients.

The relationship of these changes in urinary cyclic AMP concentration to the disease process is unclear in that a high percentage of urinary cyclic AMP is derived from the kidney, and its concentration may be influenced by physical activity and endocrine changes.' Thus, reports of levels of cyclic AMP in the urine of depressed and manic patients must be interpreted with caution.

A study of CSF cyclic AMP levels in twelve depressed, six manic, and fifteen neurological subjects showed that the depressives had higher basal levels than the other two groups. Physical activity did not seem to affect these values. However, the study of the rate of accumulation of cyclic AMP after probenecid administration led to the tentative conclusion that this was relatively low in the depressives and

relatively high in two manics, suggesting a possible deficit in cyclic AMP function in the depressed patients.

## Acetylcholine

It has been suggested that acetylcholine may serve as a synaptic transmitter in the brain, but there is little conclusive evidence as to its real role. Relatively little attention has been paid to a possible disturbance of cholinergic function in depression. However, drugs which, *inter alia,* increase brain acetylcholine activity will produce central nervous system depression (reserpine, morphine, barbiturates, general anesthetics, etc.), while drugs which are associated with decreased brain acetylcholine activity cause excitation and convulsions.

The tricyclic antidepressants have definite anticholinergic effects and Fink has suggested that electroconvulsive therapy acts through the cholinergic nervous system.

Janowsky et al. have reported that the intravenous administration of physostigmine, an acetyl-cholinesterase inhibitor, will significantly reverse symptoms of mania, and under some

conditions induce symptoms of depression, including feelings of hopelessness and uselessness, lethargy, psychomotor retardation, social withdrawal, and irritability. They suggest that increasing acetylcholine activity will reduce mania and may induce depression. In an effort to integrate this view with the biogenic amine theories of affective illness, they have postulated the need for a critical balance between the cholinergic and the aminergic systems, with a relative preponderance of amines over acetylcholine in mania, and a relative preponderance of cholinergic activity in depression.

While there is no direct evidence to incriminate the cholinergic system in the genesis of affective illness, there is sufficient circumstantial evidence and preliminary experimental observations to indicate that this system does warrant further investigation.

## Neuroendocrine Studies

### Hypothalamic-Pituitary-Adrenal Function

The hypothalamus is a vital integrating and regulating center whose functioning may be disturbed in depression. Kraines has reviewed much of the evidence in favor of an abnormal hypothalamic

functioning in affective illness. This includes the findings that certain hypothalamic lesions are associated with mood disturbance; that an intense affective state can be induced by hypothalamic stimulation; that the hypothalamus is involved in the regulation of appetite, sexual activity, menstruation, and aggression, which are frequently abnormal in depressives; and that it is part of the link between the cerebral cortex and the neuroendocrine system. He suggested that depression results from a persistent, gradually intensifying inhibition of hypothalamic function. While it is probable that aspects of hypothalamic function are altered in depression, there is at this time insufficient evidence to support the hypothesis that this is the primary disturbance.

Patients with hyperadrenalism (Cushing's Syndrome) may be either euphoric or depressed, while patients with hypoadrenalism (Addison's Disease) have many symptoms suggestive of clinical depression. The administration of adrenocortical hormones for therapeutic reasons may be associated with symptoms of both depression or mania. Butler and Besser found that tests of adrenal and pituitary function did not distinguish between patients with Cushing's syndrome and patients with severe depression. Antidepressant

treatment and clinical improvement reversed the abnormal endocrine function in the depressed patients.

It is known that adrenocortical hormones do directly influence brain function. Cortisol is present in brain tissue and the concentration of cortisol in the brain is responsive to alterations in plasma cortisol levels.

Depressed patients do have a number of changes in adrenocortical function, which point to alterations in glucocorticoid production. These changes include an elevation in plasma 17-hydroxycorticosteroids, 11-hydroxycorticosteroids and cortisol, and in urinary corticosteroids and free cortisol. There is also an increase in the cortisol secretion rate. There is a report of an abnormal response to the metopirone test involving an increased excretion of 11-deoxycorticoids, suggesting an increase in ACTH secretion. Some, but not all, investigators have found alterations in the normal circadian rhythm of plasma cortisol.

Some, but not all, investigators have found a resistance to the normal suppression of plasma cortisol following dexamethasone

administration. Dexamethasone is a synthetic glucocorticoid which normally reduces endogenous ACTH release, with a subsequent lowering of plasma cortisol. Finally, it has been shown that the plasma cortisol response to an insulin hypoglycemia is impaired in depressed patients and returns to normal with recovery.

There is disagreement over whether these changes in adrenocortical function are simply a reflection of the "stress" of the illness or result from a more fundamental disturbance. It is known that a variety of stress experiences will cause an increase in adrenocortical activity, and it has been suggested that either the stress of hospitalization, the nonspecific stress of the illness, or perhaps fluctuations in emotional distress and turmoil in individual patients, are sufficient to account for the changes. An example of this might be the increase in urinary 17-hydroxycorticoids found in some depressed patients prior to suicide attempts.

Sachar has reported that apathetic depressed patients with little emotional arousal have no significant change in cortisol production, while anxious depressed patients have a moderate increase in cortisol, and psychotic depressed patients with severe anxiety have marked

increases. He suggests that the elevation in glucocorticoid output may reflect individual distress and pain with disruption of ego defenses, and that cortisol production returns to normal when the disruption passes, even though there may be no real alleviation of the depression.

Other investigators have argued that changes, such as the abnormal response to dexamethasone, indicate a disturbance of the normal hypothalamic control over adrenal function which *may* contribute to the genesis of the illness. This dysfunction may involve the limbic system which exerts a regulatory effect on the hypothalamus.

Alterations in *ketosteroid* metabolism, including a reduction in urinary ketogenic steroids, in 11-deoxy-17-ketosteroids (especially dehydro-epiondrosterene) , and in the urinary C19 compound, androstenol (with normal 17 ketosteroids), have also been reported. Morning plasmatestosterone concentration was found to be normal in a preliminary study of male depressives. There is a report of an elevation in 11-oxy-17-ketosteroids, as compared with the n-deoxy-17-ketosteroids, in a group of eight male depressed patients. Values returned to normal with clinical improvement. These preliminary

findings suggest the possibility of a disturbance in androgen metabolism in depression.

Epidemiological studies of depression have drawn attention to its association with endocrine state and change. Depression is more common in females than in males (a male.-female ratio of 0.69); this may only apply to recurrent depressive illness, rather than to manic-depressive illness, and is more likely to occur at times of life associated with endocrine changes: premenstrually[3] , postpartum, and during the involutional period. There are also conflicting reports of depression occurring in women receiving oral contraceptives.

In addition to the possibility that these endocrine changes may in themselves contribute to the development of mood changes, there are important functional links between them, biogenic amines, and electrolytes. For example, progesterones increase monoamine oxidase activity, while estrogens may decrease Further, biogenic amines play a critical role in hypothalamic control of endocrine function.

**Thyroid**

There is some circumstantial evidence pointing to a possible

association between thyroid function and affective illness. Hypothyroid patients often have features of clinical depression, together with symptoms of an organic confusional state. Measures of thyroid function, such as protein-bound iodine and ankle reflex time, have not produced any conclusive findings in depressives.

L-tri-iodothyronine (T3) and thyroid-stimulating hormone (TSH) have been reported to accelerate the antidepressant effects of imipramine and of amitriptyline in female patients, an effect which has been attributed to the action of thyroid hormone in increasing the sensitivity of adrenergic receptors.

There are also reports that the intravenous injection of thyrotropin-releasing factor (TRF) will produce a temporary symptomatic relief in some depressed patients. TRF is the hypothalamic polypeptide which, *inter alia,* stimulates the release of TSH from the pituitary. There was also less of an increase in plasma TSH levels in the depressed patients than in normal control subjects in response to TRF. It has been suggested that the antidepressant effect of TRF may be due to a central action rather than its effect on the thyroid gland.

### Growth Hormone

The release of growth hormone from the pituitary gland is also under hypothalamic regulation and is believed to involve dopamine and possibly other biogenic amines. The capacity of the pituitary to release growth hormone into the bloodstream after such stimuli as L-DOPA, or apomorphine administration, insulin hypoglycemia, or soon after sleep onset, provides another measure of the hypothalamic-pituitary functional state. There are initial reports of deficiency in the release of growth hormone after L-DOPA administration, during sleep, and in response to insulin hypoglycemia in depressed patients. findings must await confirmation in larger studies involving age-matched control subjects.

## Electrolyte Metabolism

Electrolytes play a crucial role in the maintenance of the resting potential across the cell membrane, in the transmission of electrical impulses within the nervous system, and in the changes associated with synaptic excitation and inhibition. In addition, they have a critical role in the metabolism of the biogenic amines and are involved in the mechanisms that govern the release, re-uptake, and storage of amines

from the neuron. Thus, alterations in the concentration or distribution of certain cations can profoundly affect neuronal functioning through either a direct action on cell membrane activity and electrochemical potential or by altering biogenic amine metabolism. Changes in the ratio of one cation to another are probably very important. For example, the passage of norepinephrine across the membrane is believed to involve a carrier with a high affinity for the amine at the outer neuronal membrane surface (where sodium concentration is high and potassium concentration is low), and a low affinity for the amine at the inner surface (where potassium concentration is high and sodium concentration is low). Alterations in sodium-potassium concentrations and of their ratio to each can thus alter norepinephrine metabolism. The maintenance of the normal ionic gradient is an active process governed in part by (Na + K) Mg adenosinetriphosphatase (ATPase). Further, the transport of norepinephrine into the storage granule involves a carrier system with an affinity for sodium at the low concentration found intraneuronally.

Further, the effectiveness of the cation lithium in the treatment and prophylaxis of various phases of manic-depressive and depressive illness has stimulated additional interest in ionic metabolism in

depression. The interested reader is referred to several recent reviews describing the physiology of electrolyte metabolism and their role in brain function.

### *Sodium*

Depressed patients are reported to have an increase in sodium retention, followed by an increased excretion of sodium on recovery yijg correlation between exchangeable body sodium and clinical improvement has been shown to be close. For example, Gibbons found that sixteen depressed patients who were successfully treated with electro-convulsive therapy had a mean decrease in exchangeable body sodium of 209 mEq, which represented an almost 10 percent reduction in their total exchangeable body sodium. In contrast, eight similar patients also treated with electroconvulsive therapy who did not improve had no significant alteration in exchangeable body sodium.

Similar changes have been found in association with relatively minor mood changes in normal subjects. For example, there is a report of an association between transient periods of depression of mood and a decrease in urinary sodium excretion in a group of normal subjects.

Coppen and Shaw suggested that the extra sodium was mainly being retained in the “residual sodium” compartment (comprised of intracellular sodium and exchangeable bone sodium). They also found an increase in residual sodium in manic patients. However, the method they used for the calculation of residual sodium is relatively imprecise, and their results remain unconfirmed.

It is possible that the sodium retention may result from an increase in cortisol production, and a significant correlation between sodium and water retention and elevated urinary 17-hydroxycorticosteroids has been found.

A logical consequence of these findings has been the effort to directly measure intracellular sodium in depressed patients.

Mendels et al. found erythrocyte sodium concentration to be relatively normal in hospitalized male depressives. Further, the depressed patients who improved with lithium treatment tended to have an increase in erythrocyte sodium concentration over time (in association with lithium administration), whereas the patients who did not respond to lithium tended to have little change (or even a

decrease) in erythrocyte sodium concentration.

There is also a report that patients who responded to lithium had a significantly greater increase in twenty-four-hour exchangeable sodium that did nonresponders. These findings have led to the suggestion that depressed patients who show an increase in intracellular (or exchangeable) sodium during lithium therapy are more likely to improve than patients who do not show these changes. These findings indicate that there is a difference in the cell membrane function governing electrolyte transport between the lithium responders and nonresponders. This requires further investigation.

An alternative strategy has involved the measurement of the rate of entry of sodium from plasma into the cerebrospinal fluid. This measure may provide an indication of the retention and rate of turnover of sodium by the central nervous system. While there are conflicting reports, the consensus of several investigators'" is that there is a decrease in the rate of entry of sodium into lumbar fluid for depressed and manic patients, in comparison with either control subjects or recovered depressed or manic patients. There was no significant difference between manic and depressed patients.

### *Potassium*

No consistent significant changes in potassium have been found in depression or mania. Studies of exchangeable potassium, potassium balance, and of plasma and erythrocyte potassium concentrations, have produced essentially normal findings. There is an unconfirmed report of a decrease in intracellular potassium in depression, which persisted after clinical recovery.

### *Magnesium*

Magnesium is important for nervous system activity, serving *inter alia* as a necessary cofactor in the ATPase system which regulates ion and perhaps biogenic amine flux across the neuronal membrane. There are reports that depressed patients have elevated or reduced plasma magnesium concentrations, and of increased plasma and erythrocyte magnesium concentrations in both depressed and manic patients. Nielson found no significant differences in erythrocyte magnesium concentrations between depressed and manic patients. Some of these findings are difficult to interpret and additional carefully controlled studies, as well as measures of ionized (unbound) magnesium, will be important in clarifying whether or not there is an

important alteration in magnesium metabolism in depression.

### *Calcium*

Calcium plays an important role in several aspects of neuronal function. Thus, studies of calcium metabolism are potentially important. Methodological problems have impeded work in this area in that the measurement of total plasma calcium does not provide a reliable index of the functional or ionized portion. At the time of writing, no reliable studies of ionized plasma calcium have been conducted in depressed patients. There are reports of an increased calcium retention with a reduction in urinary calcium excretion in depressed patients in association with clinical improvement. These investigators suggested that there might be some alteration in calcitonin activity in depression.

## Psychophysiological Studies

A variety of psychophysiological measures have been studied in depressed patients on the assumption that they provide a measure of brain function or nerve conduction. Studies of the *resting encephalographic pattern* in depressed patients have not produced any

significant findings, except for the suggestion of a nonspecific "electrophysiologic instability." Studies of the *sleep electroencephalogram* have attracted the most attention. In general, most depressed patients have a reduction in actual sleep time, an increased frequency of wakening through the night (especially in the last third of the night) and a reduction in delta-wave sleep (Stages 3 and 4). In addition, the depressed patient takes longer to fall asleep, wakes significantly earlier in the morning, and has an increase in Stage 1 sleep and in drowsiness. jn ruost respects, sleep appears to be lighter and more susceptible to disruption by external stimuli.

Reports of changes in Stage 1 Rapid Eye Movement (REM) sleep or dreaming sleep are not as consistent. There were a number of initial reports of a reduction in Stage 1 REM sleep during depression. However, more recent careful longitudinal studies show an increase in the amount of Stage 1 REM sleep in some depressives. There is also evidence of an increased pressure to achieve REM sleep, which is reflected by a reduced latency to the first REM period of the night in some patients.

There is considerable variation in the sleep pattern from night to

night and from patient to patient, which may be the result of differences in diagnostic category, severity of the illness, or fluctuations in clinical state from day to day.

There is evidence that some of the abnormal sleep features revert to normal, prior to complete clinical improvement. A notable exception to this is delta-wave sleep, which may continue below normal values after clinical improvement, although it does eventually reach control values. Several patients whose sleep was studied on an intermittent basis for one or two years after clinical recovery developed abnormal changes in their sleep pattern while asymptomatic. Several weeks later, these patients relapsed. If this finding were confirmed, it would indicate that there are important alterations in brain physiology *prior* to clinical manifestation of the illness.

It is known that the biogenic amines, and perhaps acetylcholine, histamine, and other possible central neurotransmitters, play an important role in the mediation of sleep. Attempts are being made to relate the postulated role of these substances in the control of sleep with their hypothesized involvement in the affective disorders.

*Alpha suppression* in response to stimuli is reported to be more persistent in depressed patients than controls. A prolongation of the recovery phase of the *cortical evoked potential* beyond the normal 20 milliseconds has been noted in psychotically depressed patients. These two findings suggest the possibility of an increased activity of the reticular activating system.

Two patterns of abnormality in the *auditory evoked cortical response* in depressed patients have been reported: hyper-recovery and hypo-recovery. The former patients may have increased CNS excitability whereas the latter may have decreased excitability. There is some preliminary evidence that these two patterns of recovery are associated with the presence or absence of a positive family history of affective disorder, as well as with a different response to chemotherapy.

Perez-Reyes used intravenous sodium pentothal to determine the inhibition threshold for the galvanic skin response (GSR), and the sleep threshold. He found significant differences between neurotic depressives, psychotic depressives, and control subjects, suggestive of a "basic difference" in CNS activity among the three groups. He

suggested that the neurotic depressives have an increased central excitatory state, a decreased central inhibitory state, or a combination of both. In contrast, the psychotically depressed patients may have a decreased central inhibitory state or a combination of both.

Most of the findings from these studies of psychophysiological function (with the exception of the sleep studies) must be regarded as preliminary. Further, it is difficult to come to any clear conclusion as to their significance, in view of our limited understanding of the multiple mechanisms involved in their mediation.

## General

Investigators have studied a number of the biological parameters in depressed patients, and in a few instances also proposed specific theories. These remain very limited findings, which are still to be confirmed and whose significance is uncertain. As such, they will only be noted in summary form here.

a) Alterations in glucose utilization.

b) An increase in blood acetaldehyde levels.

c) An increase in plasma triglycerides and cholesterol.

d) An elevation of residual motor activity (muscle tension) termed “hyperponesis.”

e) A reduction in salivation.-

f) Proposal to divide monoamines into excitant and depressant types with abnormalities in balance between two types.

g) A defect in the normal rhythmic homeostatic mechanism which may underline at least some forms of manic-depressive illness and which may involve some abnormal “switch mechanism.”

**Manic-Depressive and Recurrent Depressive Illness**

Among the many efforts that have been made to divide depressed patients into meaningful subgroups, one of the more promising involves the distinction between manic-depressive illness and recurrent depressive illness. This distinction is made on the basis of whether or not the patient has a previous history of mania, or has only a history of recurrent depressive episodes. The terms “bipolar” or “biphasic” illness and “unipolar” and “uniphasic” illness have been applied.

When depressed patients are divided according to this classification, a number of potentially important differences have been found. Biphasic depressed patients (in contrast with uniphasic depressed patients) have, in addition to a previous history of manic episode(s), the following distinctive features: A different genetic history with a high incidence of biphasic illness in first-degree relatives; a more equal frequency of the illness in males and females; an alteration in erythrocyte catechol-o-methyl-transferase levels (in female patients); an increased frequency of pacing, physical complaints, and anger; an increased likelihood of responding to lithium carbonate; an increased likelihood of developing symptoms of psychomotor activity after the administration of L-DOPA or of developing a manic response to tricyclic antidepressants; lower urinary 17-hydroxycorticosteroids; more frequent augmentation with increased stimulus intensity on cortical evoked potential; reduced platelet monoamine oxidase activity; an earlier age of onset; a more frequent history of postpartum depression; and a lower sedation threshold.

Thus, it is reasonable to proceed on the assumption at this time that these may be separate conditions.

## Relationship Between Depression and Mania

Many investigators regard mania and depression as representing opposite ends of the affective spectrum—the bipolar concept of manic-depressive illness. This is implied in the catecholamine hypothesis of affective illness, which postulates a relative deficiency of norepinephrine in depression and a relative excess in mania. However, there are a number of observations which suggest the possibility that depression and mania share a number of important features and that their relationship may not be bipolar. These observations include: Symptoms of depression are frequent in manic patients; steroid therapy may precipitate either depression or elation; depression and mania both occur in Cushing's Syndrome; total body water and intracellular water concentration are altered in both manic and depressed patients; CSF 5HIAA are low in both manic and depressed patients; CSF tryptophan concentration is low in depressed and manic patients; sleep changes in hypomanic and depressed patients have many features in common; erythrocyte COMT activity is reduced in both mania and depression; sodium transfer into the CSF is reduced in both depressed and manic patients; plasma and RBC magnesium concentrations are reported to be elevated in both mania and

depression; electroconvulsive therapy is an effective treatment for both manic and selected depressed patients; lithium carbonate is effective in the treatment of manic and some depressed patients; phenothiazines are useful in the treatment of manic and of some selected depressed patients.

These observations, of course, do not prove that mania and depression are the same. Clearly, they have many important features that distinguish between them. However, it is also apparent that it may not be correct to regard them as bipolar states, and that the eventual unraveling of the biological features of these two conditions may reveal a certain important communality. This concept has been discussed in more detail elsewhere.

## Conclusion

Complex interrelationships exist between the metabolic systems discussed here. It seems likely that a meaningful hypothesis of the biology of depression must eventually account for this. Such interrelationships include the critical effect of the electrolytes in the synthesis release, re-uptake, and storage of biogenic amines; the effect

of changes in hypothalamic function on pituitary adrenal activity, which in turn can alter electrolyte distribution and metabolism (and thus affect amine metabolism); alterations in catecholamine metabolism affecting hypothalamic function; changes in the (Na+K) ATPase system as a result of alterations in cortisol metabolism, with a consequent effect on both electrolyte and amine activity, and the central role of cyclic AMP in so many neuroendocrine and amine activities, amongst others. Research is only beginning to explore the implications of these and other interactions for an understanding of the biology of affective illness.

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## *Notes*

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2 Recently, there have been reports that probenecid may itself influence brain tryptophan-serotonin

metabolism, thus complicating interpretations of these findings.8 Also, the varying rates of absorption and blood levels of probenecid could distort the results with big variations in its effects from subject to subject.

3 The premenstrual mood changes may be associated with changes in electrolyte and water distribution.