CHAPTER 1

Introduction and Theories of Affective Disorders

CHARLES B. SCHAFFER, GHANSHYAM N. PANDEY, KATHERINE M. NOLL, GRANT A. KILLIAN, and JOHN M. DAVIS

Neuropharmacology of Central Nervous System and Behavioral Disorders

ISBN 0-12-544760-4

I. INTRODUCTION

The symptoms of depression and mania have remained remarkably invariant both across different cultures (Zung *et al.*, 1975) and through time. Many hypotheses regarding the etiology of these symptoms have been proposed in terms of intrapsychic processes, reward or punishment-based learning, or biologically altered function of the nervous system. All these formulations have merit and can be supported by empirically derived evidence. This suggests that it should be possible to integrate these points of view, as it seems probable that they are all describing aspects of the same phenomenon.

However, it has also been recognized for some time that in depression, in particular, there is some heterogeneity both in terms of etiology and in presentation of symptoms. The primary common ground for this group of dysfunctions is that they have as their most significant symptom an alteration in mood, and so they are currently called affective disorders (AD).

Depression is now recognized as the most common psychiatric disorder seen in clinical medicine. Approximately 5% of the population suffers from this disorder at any given time. Some patients suffer from episodes of both depression and mania, the "lifetime" incidence of this disorder being about 1% of the general population. These disturbances are characteristically regarded as a disturbance in mood or affect. During the past two decades, progress made in the areas of pharmacology and genetics have provided new and illuminating information concerning the biology of mood disorders.

II. AFFECTIVE DISEASE SIGNS AND SYMPTOMS

A constellation of symptoms usually accompanies a primary major depressive order. There is usually diminished ability to experience pleasure, as well as feelings of sadness. The patient is no longer interested in hobbies or pleasurable activities, and usually reports a decrease in his sex drive, a decrease in appetite with weight loss, and sleep disturbance. Psychomotor functioning can also be affected resulting in slowing down of thought processes, speech, and

body activity. The depression is frequently accompanied by somatic complaints which may reach the extreme form of somatic delusions. Lowered self-esteem may result in repetitious self criticisms and even a delusional sense of incompetence. The depression may show a diurnal variation with more discomfort in the morning compared to the evening. Severely depressed patients report a feeling of hopelessness and helplessness which should warn the clinician of impending thoughts of death or suicide.

III. UNIPOLAR VERSUS BIPOLAR DISORDERS

Unipolar disorder as opposed to bipolar disorder is characterized by episodes only of depression, while bipolar disorder manifests both manic and depressive episodes. The manic periods are characterized by markedly euphoric or irritable mood, racing thoughts and speech, and increased energy resulting in behavior or motor activity which may have potentially destructive consequences. Other symptoms which can be seen during a manic episode are distractability, grandiosity, insomnia, and a full-blown psychotic picture including hallucinations, delusions, and thought disorganization which can appear similar to a schizophrenic decompensation. The Research Diagnostic Criteria for mania disorder can be seen in Table I. The bipolar form of affective disorder is characterized by the first episode of depression or mania appearing at an earlier age than the first episode in unipolar depression.

IV. NATURAL HISTORY

It therefore would be important to know such information as age of onset, past number of episodes, level of functioning between episodes, course of symptomatology during each episode, and presence or absence of any external precipitating factor which may have played a role in promoting the episode. Affective patients tend to have a good recovery between episodes. Understandably, input from family members and close friends is invaluable, especially if the patient presents such a severe clinical state that elicitation of the history from the patient is difficult if not impossible.

V. GENETIC INFLUENCE

A careful survey of first degree family members (father, mother, siblings, and children) may indicate that the patient is genetically predisposed to develop affective disorder. Genetic transmission of affective disorder should be

TABLE I

Manic Disorder[a]

A. One or more distinct periods with a predominantly elevated or irritable mood. The elevated or irritable mood must be a prominent part of the illness and relatively persistent, although it may alternate with depressive mood. Do not include if apparently due to alcohol or drug intoxication.

B. If mood is elevated, at least three of the following symptom categories must definitely be present to a significant degree (four symptoms if mood is irritable). (For past episodes, because of memory difficulties, one less symptom is required.)
   1. More active than usual—either socially, at work, sexually, or physically.
   2. More talkative than usual or feel a pressure to keep talking.
   3. Flight of ideas or subjective experience that thoughts are racing.
   4. Inflated self-esteem (grandiosity, which may be delusional).
   5. Decreased need for sleep.
   6. Distractibility, i.e., attention is too easily drawn to unimportant or irrelevant external stimuli.
   7. Excessive involvement in activities without recognizing the high potential for painful consequences, e.g., buying sprees, sexual indiscretions, foolish business investments, reckless driving.

C. Overall disturbance is so severe that at least one of the following is present:
   1. Meaningful conversation is impossible.
   2. Serious impairment socially, with family, at home, at school, or at work.
   3. In the absence of (1) or (2), hospitalization.

D. Duration of manic features at least one week (or any duration if hospitalized).

E. None of the following, which suggest schizophrenia, is present:
   1. Delusions of being controlled or of thought broadcasting, insertion, or withdrawal.
   2. Nonaffective hallucinations of any type throughout the day for several days or intermittently throughout a 1-week period.
   3. Auditory hallucinations in which a voice keeps up a running commentary on the patient's behaviors or thoughts as they occur, or two or more voices conversing with each other.
   4. At some time during the period of illness had more than 1 week when no prominent depressive or manic symptoms were inhibited, but had delusions or hallucinations.
   5. At some time during the episode had at least 1 week when no prominent manic symptoms were exhibited but had several instances of formal thought disorder.

[a] Adapted from Research Diagnostic Criteria (RDC) and from Spitzer (1975).

suspected if first degree relatives have had a disorder with similar symptoms and natural history. In some instances patients with first episodes of affective disorder may present symptoms which are not clear-cut diagnostically, and the presence of affective disorder in first degree relatives may help confirm a diagnosis. Unipolar patients tend to come from unipolar families; bipolar from bipolar families. The work by Perris (1966, 1973a,b) suggests that bipolar illness involves a separate genetic determinant; he found that patients with bipolar disorder had 16.35% of first degree relatives with evidence of both depression and

mania, whereas only 0.8% of first degree relatives manifested depression only. This was compared to only 0.5% of first degree relatives of unipolar patients having bipolar disease, and 10.6% with significant clinical unipolar depression. Some studies have shown a relationship between affective disorders and ABO blood type (Rinieris *et al.*, 1979).

Winokur and associates (1971) have found that unipolar depressed patients may be divided into two theoretical subgroups according to the pattern of family disorders. In one group, Depressive Spectrum Disease, there is an early onset of depression before age 40, a greater incidence of affective disorder in first degree female relatives, and a high frequency of alcoholism and/or antisocial personality in first degree male relatives. In the second type, Pure Depressive Disease, the onset of depression is after age 40, affective disorder incidence is roughly equal in male and female first degree relatives, and there is a paucity of alcoholism or antisocial personality in the family history. Although patients with either disorder have similar presenting depressive symptoms, the family history data infers that there may be a different genotype and hence biological abnormality in the two unipolar disorders. In recent years a subgroup of patients hospitalized only for depression, but having a history of episodes of subclinical hypomania or drug-induced mania, have been designated as Bipolar II on the basis of certain similarities to Bipolar patients on dimensions such as augmenting–reducing (Buchsbaum *et al.*, 1971). Finally, researchers have found suggestive evidence that patients with affective disorders tend to respond to the same antidepressant medication which has produced therapeutic effects in blood relatives with depression, and there are also genetic influences on rate of drug metabolism.

VI. EFFECTS OF PHARMACOLOGIC AGENTS ON NEUROTRANSMITTER SYSTEMS IN AFFECTIVE STATES

In the 1950s clinicians observed that certain medications that were known to affect the biogenic amine levels in the central nervous system also influenced affective states in patients (Schildkraut, 1965; Bunney and Davis, 1965). This observation helped to stimulate research to elucidate the connection between central amines and affective disorders. It also led to the discovery of new pharmacologic properties of drugs. For example, lithium was found to alter biogenic amines at several different levels.

A. Reserpine

Reserpine, the active component of *Rauwolfia serpentina*, has been used in the medical profession for several decades in the treatment of hyperten-

sion. Fifteen percent of those receiving reserpine were observed to experience a mood alteration which was quite similar to the depression seen in psychiatric patients suffering from a primary depressive disorder (Bunney and Davis, 1965; Jensen, 1959; Lemienuxt *et al.*, 1956). Furthermore, it was noted that most patients who experienced an episode of depression while taking reserpine had prior history of similar depression not caused by reserpine usage (Ayd, 1958). The depression induced by reserpine in these patients generally resolved spontaneously a few weeks after reserpine was terminated; in some instances, the depression persisted and required drugs or electroconvulsive therapy (ECT) for treatment.

Reserpine affected the biogenic amine system in the brain by impairing storage in the nerve ending granules of serotonin (5-HT), dopamine (DA), and norepinephrine (NE), leading to depletion of these amines as they are degraded by mitochondrial monoamine oxidse (MAO) to inactive metabolites when they are unprotected in the cytoplasm.

B. α-Methyl Dopa

α-Methyl dopa, another commonly used antihypertensive medication, has also been observed to cause clinical depression in some patients. This medication was found to produce "false transmitters," α-methyl-dopamine and α-methyl-noradrenaline, which displaced the natural biogenic amines from storage granules in the terminals of nerve endings and hence produced deficiency of biogenic amines at the neurotransmitter synapses. This was further evidence that depression was caused by a deficit in central nervous system amine transmitter systems.

C. Monoamine Oxidase Inhibitors

In the 1950's, clinicians fortuitously observed that the antituberculosis medication, iproniazid, had a mood-elevating effect on patients receiving it for treatment of tuberculosis. It was noted that one of the pharmacologic properties of this agent was to inhibit the enzyme monoamine oxidase (Zeller *et al.*, 1952). Later this drug as well as other monoamine oxidase inhibitors (MAOI) were used in the treatment of depressed patients and found to be effective in alleviating symptoms of depression. The MAOIs inhibit the mitchondrial enzyme which deactivates the biogenic amines 5-HT, NE, and DA through the process of deamination, thus raising brain levels. The pharmacology of the MAOIs is discussed later in this volume.

In recent years researchers have speculated that measuring the levels of MAO inhibition in platelets may provide an accessible peripheral method or window to MAO inhibition in the brain. This theory has led to attempts to correlate MAO

inhibition in platelets with therapeutic response (Robinson *et al.*, 1977; Chang *et al.*, 1977). Our laboratories have found that therapeutic response to the MAOI agent phenelzine takes place only after the level of platelet MAO inhibition has reached 90–95%. Thus, if these assay methods are available, one can achieve the optimal therapeutic dose by aiming towards a platelet MAO inhibition level of 90% or greater.

Monoamine oxidase inhibitors were the first antidepressant medications to be use in a clinical setting. These agents are generally felt to be less effective than the tricyclic antidepressants and seem to be more efficacious in certain subgroups of depressed patients such as those who do not respond to tricyclics or those who are considered to be chronic or "atypical" depressives. Theoretically the MAOIs should be similar in efficacy to the tricyclics because they are equally effective in raising central neurotransmitter levels of both 5-HT and NE. Some speculate that the poor track record of MAOIs compared to tricyclics is the result of failure to reach optimal levels of MAO inhibition.

D. Tricyclic Antidepressants

Attempts to synthesize a new antipsychotic medication structurally related to chlorpromazine produced imipramine, a member of the family of tricyclic medications that was found to be more effective as an antidepressant. It was not useful in the treatment of schizophrenia. This family of drugs has the property of blocking presynaptic reuptake of NE and 5-HT (but not DA), at pharmacologic doses, thus creating more NE and 5-HT available in the synaptic cleft (Maas, 1975).

The effect on mood associated with reserpine, α-methyl-dopa, MAOIs, and the tricyclic antidepressants suggested that the biological common denominator of depression may be related to an actual or relative deficiency of NE or 5-HT in neuronal synaptic clefts in the brain. This amine hypothesis of affective disorders has produced a theoretical framework which has stimulated research involving the specific defects in patients suffering from mood disorders.

VII. LABORATORY ABNORMALITIES IN SOME FORMS OF DEPRESSION

A. Catecholamines

The findings that essentially all CNS NE is metabolized to 3-methoxy, 4-hydroxyphenylglycol (MHPG) has stimulated research strategies that attempt to locate biological markers and subgroups of affective disorders. The MHPG produced as a breakdown product of norepinephrine in the brain can easily cross

the blood–brain barrier because of its high lipid solubility, and is ultimately excreted in the urine. Although other tissues outside the central nervous system involve the use of norepinephrine as a neurotransmitter, metabolic products of norepinephrine from these origins include vanillylmandelic acid (VMA) and normetanephrine (NMET) as well as MHPG (Maas and Landis, 1971; Karoum *et al.*, 1974). Practically all of the VMA, NMET, and NE found in the urine of nonhuman primates originates from periphal sources of norepinephrine production (Maas *et al.*, 1973). Studies using isotope tracers in humans reveal that about 80% of MHPG excreted in the urine originates from NE metabolism in the brain (Ebert and Kopin, 1975). Studies of the arterial–venous difference across the brain in man suggest that about 63% of MHPG has its origin in the brain (Maas *et al.*, 1979).

Certain investigators postulated that assessment of the quantity of MHPG in samples of urine collected from depressed patients over 24 hours might reflect an abnormality in norepinephrine functioning in the brain of these patients. Indeed, Maas and co-workers (1968, 1973) found that, although depressed patients excreted normal amounts of urinary VMA and NMET, both depressed men and women excreted significantly lower amounts of urinary MHPG. Other investigators have found that decreased urinary levels of MHPG seem to occur in a subgroup of patients suffering from depression (Beckmann and Goodwin 1975; Schildkraut, 1973; Casper *et al.*, 1977). Patients suffering from psychotic depressions have been shown to have low cerebrospinal fluid (CSF) homovanillic acid (HVA), the DA metabolite thought to reflect central DA turnover (Meltzer *et al.*, 1976; Papeschi and McClure, 1971). These findings imply that, while the metabolic turnover of NE in the periphery seems to be normal in depressed patients, the low urinary MHPG may indicate that NE and/or DA in the brain are decreased. This phenomenon reflects only a turnover abnormality, and other research strategies involving neuroendocrine systems were pursued to confirm a truly functional defect in the neurotransmitter systems of depressed patients.

B. Neuroendocrine Strategies of Assessing Function of Catecholamine Systems

Physiologists have established that neurotransmitter systems such as the NE system play an important role in regulating the release of polypeptide-releasing factors originating in the hypothalamus into the hypophyseal-portal system (Jones *et al.*, 1976). These releasing factors govern the release from the pituitary of several hormones including growth hormone (GH) and adrenocorticotropic hormone (ACTH). Thus one could indirectly assess the function of neurotransmitter systems with a neuroendocrine research strategy by measuring the plasma levels of these hormones in depressed patients.

1. Growth Hormone

When hypoglycemia is induced by insulin, GH is released into the peripheral system. The fact that NE receptor blockers such as phentolamine reduced the amount of GH produced by insulin-induced hypoglycemia is strong evidence that the NE neurotransmitter system plays an important role in insulin-induced GH release. This belief is supported by the evidence that in depressed patients there is less GH secreted compared to normal controls when hypoglycemia is induced by insulin (Mueller *et al.*, 1969; Sachar *et al.*, 1971). This is an indirect indication that central NE function is hampered in some patients suffering from depression. Such a measurement of GH response may provide more of a direct indication of NE neurotransmitter function than the measurement of turnover rate of NE by such methods as assessment of urinary MHPG. Recently, investigators nave shown that those patients who have a decreased GH response to an insulin challenge also excrete less urinary MGPH (Garver *et al.*, 1975). Both of these findings in the same depressed patients provide stronger evidence that a central NE abnormality exists in at least some patients with affective disorders.

2. Cortisol

Studies of laboratory animals have helped to elucidate the role of the neuroendocrine system in the production of cortisol. Cortisol secretion from the adrenal glands is stimulated by ACTH, which is released from the pituitary under the regulation of corticotropin-releasing factor (CRF) originating from the hypothalamus. It has been shown that activation of central NE inhibits release of CRF (Jones *et al.*, 1976). Thus, through the above mentioned chain of events, a defect in the functioning of central NE activity might ultimately result in increased release of cortisol into the peripheral circulation. Indeed, the plasma level of cortisol is continuously elevated in some depressed patients (Carroll, 1979). In a majority of these patients, the administration of extraneous dexamethasone partially or completely fails to lower plasma cortisol levels. These findings imply that, in a subgroup of depressed patients, there is a diminished ability by the NE central neurotransmitter system to inhibit CRF. In addition, an increase in plasma cortisol would stimulate hepatic production of the inducible enzyme tryptophan pyrrolase, and this would result in the metabolism of tryptophan being shunted away from 5-HT into the kynurenine pathway (Lapin and Oxenkrug, 1969; Mangoni, 1974). This would significantly reduce the amount of tryptophan available to the CNS, and availability of tryptophan is the rate-limiting step in the production of 5-HT. Presently, researchers are attempting to ascertain if those patients who have abnormally elevated plasma cortisol levels also manifest lower GH responses to insulin-induced hypoglycemia and have lower than normal urine levels of MHPG. There is also evidence that physostig-

mine, which increases central acetylcholine (ACh) levels, can produce the cortisol regulation abnormality of escape from dexamethasone suppression of cortisol release, an abnormality found in depressed patients. Since there are several different transmitters which govern the control of cortisol secretion and several components involved in this process, it is doubtful that the cortisol abnormality would point its finger at a single transmitter. Clearly the fact that there is a cortisol deficit is consistent with abnormalities in the control of cortisol by transmitters such as NE, 5-HT, and Ach. This evidence is not enough at this time to implicate a single transmitter.

3. Luteinizing Hormone

In recent years, it has been found that a subgroup of depressed women have lower than normal levels of luteinizing hormone (LH) (Sachar, 1974). Although neuroendocrine regulation of LH has not been defined as well as that of other neuroendocrine hormones, certain laboratory evidence suggests that NE plays an important role in regulating the release of LH.

C. Evidence for Central Serotonin (5-HT) Abnormality in a Subtype of Depression

Much of the same evidence exists for serotonin (5-HT) as for NE, in that reserpine, tricyclics, and MAOIs all alter 5-HT. Thus, it is relevant to see if 5-HT synthesis is decreased in depression. One method of measuring the turnover of central 5-HT is the measurement of 5-hydroxyindole acetic acid (5-HIAA), the major metabolite of brain 5-HT metabolism, in the cerebrospinal fluid (CSF). During the past several years the data concerning quantities of this metabolite in the CSF in depressed patients has been collected.

Some studies find a decrease in 5-HIAA in CSF while others do not. No studies find depressed patients to have elevated 5-HIAA. Overall, combining data from the studies, depressed patients have a reduction of 5-HIAA to about two-thirds of normal (Ashcroft *et al.*, 1966, 1973; Bowers *et al.*, 1969; Coppen *et al.*, 1972; Dencker *et al.*, 1966; Goodwin *et al.*, 1973; Goodwin and Post, 1975; McLeod and McLeod, 1972; Papeschi and McClure, 1971; Roos and Sjöström, 1969; Subrah-manyam, 1975; Van Praag and Korf, 1971; Van Praag *et al.*, 1973). Similarly, after probenecid, a drug which inhibits CSF 5-HIAA transport and elevates levels, some studies find 5-HIAA to be reduced (Sjöström and Roos, 1972, Van Praag *et al.*, 1973) and others find no change (Bowers, 1974; Goodwin *et al.*, 1973). The findings of studies of brain 5-HT or 5-HIAA in postmortem suicide are essentially similar to those of CSF. Some researchers find low levels in the presumably depressed suicides; others find no change, and no study finds elevated levels. Specifically, several studies found low levels of

5-HT in the brains of suicide victims (Shaw *et al.*, 1967; Pare *et al.*, 1969; Lloyd *et al.*, 1974), but no significant difference was found by Beskow *et al.* (1976), Bourne *et al.* (1968), and Cochran *et al.* (1976). Similarly, Bourne *et al.* (1968), Pare *et al.* (1969), and Beskow *et al.* (1976) found suicides to have low brain 5-HIAA. Cerebrospinal fluid 5-HIAA reflect spinal cord as well as brain 5-HT, and autopsied tissue studies must be qualified by the many uncontrolled variables in such a situation, i.e., effects of cause of death on both experimental and control groups, various types of postmortem changes, uncertainty of diagnoses of depression (in that not all suicide victims are depressed). Taken together, this data does suggest that there is a general trend for there to be low levels of these indices of 5-HT in at least some depressed patients.

Asberg and associates (1976) have recently published findings which may help to clarify conflicting data in this area. A bimodel distribution of 5-HIAA levels in the CSF of depressed patients was found by Asberg. The group with higher levels was similar to the normal distribution of control subjects, and 29% of the depressed group of patients had levels of 5-HIAA which fell within the range of the lower mode. This finding indicates that a subgroup of depressed patients have decreased turnover of 5-HT. This bimodal distribution could explain the conflicting reports in previous studies. The frequency of substantial numbers of patients in the lower mode could be highly variable when only a few subjects are studied in each clinical trial.

Some clinical researchers, stimulated by the possibility that a central 5-HT deficiency may cause some patients to have depressions, have attempted to test this hypothesis by treating depressed patients with such 5-HT precursors as tryptophan and 5-hydroxytryptophan (5-HTP). The reports from these studies have been equivocal. Apparently such precursor loading increases the amount of 5-HIAA in the CSF (Dunner and Goodwin, 1972). Van Praag has found that 5-HTP is effective in depressed patients who initially had low 5-HIAA in their CSF (Van Praag and Korf, 1971). He found, however, that it is less effective in patients with normal CSF 5-HIAA (Van Praag and Korff, 1971; Van Praag *et al.*, 1973). Another study found 5-HTP reduced in depression; however, this could not be predicted from CSF 5-HIAA (Takahashi *et al.*, 1975). Also, not all studies produce a positive finding (Mendels and Frazer, 1975). These results give support to the theory that only a certain subgroup of depressed patients have decreased central 5-HT turnover. The success of such a treatment in a sample of depressed patients would depend on the relative distribution of patients with low and normal central 5-HT functioning in the population sample. This suggests that studies of precursor-load treatment of depression using L-tryptophan or 5-HTP should be re-examined to determine if this treatment was effective in roughly one-third of the patients treated, the proportion suggested by Asberg *et al.* (1976) to have low central 5-HT turnover. This proves to be the case in the study by

Takahashi *et al.* (1975) where individual data are reported. Some evidence for the effect of L-tryptophan is provided by Coppen *et al.* (1967, 1976), Broadhurst (1970), Kline and Shah (1973), and MacSweeney (1975). However, other work failed to replicate this finding, and found tryptophan ineffective (Carroll *et al.*, 1970; Bowers, 1970; Gayford *et al.*, 1973; Murphy *et al.*, 1974; Herrington *et al.*, 1974; Farkas *et al.*, 1976). Moller *et al.* (1976) found that patients with lower levels of plasma tryptophan showed a rapid remission of depression when treated with tryptophan. This treatment proved superior to ECT by the twenty-first day; a striking finding in view of the fact that ECT is generally thought to be most uniformly effective treatment for depression. Tryptophan has also been reported to potentiate the antidepressant effect of cloimipramine (Walinder *et al.*, 1976) and of MAOIs (Coppen *et al.*, 1963, 1967; Glassman and Platman, 1969). Two of the studies found a statistically significant effect, while the other found a trend in this direction. Prange *et al.* (1974) and Murphy *et al.* (1974) also treated mania successfully with L-tryptophan. In patients recovering from depression with MAOI, addition of *para*-chlorophenylalanine (PCPA) which would inhibit 5-HT synthesis specifically produced a return of depression, a finding which also implies a role for low 5-HT in the patient's depressive disease (Shopsin *et al.*, 1975, 1976).

D. Effects of Tricyclic Antidepressants on Depression

Maas *et al.* (1972) were the first to report that a subgroup of depressed patients who had low levels of 24-hour urine MHPG before treatment selectively responded better to imipramine. Later Schildkraut (1975) noted that the urinary MHPG levels were higher in a group of depressed patients who responded to treatment with amitriptyline when compared to a group who did not respond. Recently, the work of Beckmann and Goodwin (1975) has helped to substantiate these earlier findings by also showing that patients with low urinary MHPG showed good clinical response to imipramine and little or no response to amitriptyline. Conversely, these authors found that patients with normal or higher levels of excreted MHPG responded to amitriptyline and had a poor response to imipramine. These findings are highly suggestive that there are at least two major types of depressive disorders: one that responds to imipramine, and the other to amitriptyline.

Table II summarizes the differential ability to block the reuptake of central nervous system amines by imipramine and amitriptyline and their respective active metabolites (Maas, 1975). The major therapeutic effect of imipramine is actually produced by its metabolite desipramine which blocks the reuptake of NE into the central presynaptic NE neurons. Amitriptyline behaves somewhat differently when given in therapeutic doses, for it is converted to its metabolite nortriptyline at a slower rate than that of the breakdown of nortriptyline to its

TABLE II

Summary of Effects of Various Antidepressants on the Blockade of Uptake of Biogenic Amines[a]

Drug	Biogenic amine		
	Serotonin	Norepinephrine	Dopamine
Amitriptyline	++++	0	0
Nortriptyline	++	++	0
Imipramine	+++	++	0
Desipramine	0	++++	0

[a] From Maas (1975). Copyright 1975, American Medical Association.

inactive metabolite. For this reason plasma levels of amitryptyline are usually the same or higher than those of nortriptyline (Maas, 1975). In this case, amitriptyline, the parent compound, is the most important agent in blocking the reuptake at the presynaptic terminal. Thus, there is strong evidence from these clinical research findings for the existence of two main types of unipolar depressions. The major abnormality in the first type is a decrease of NE reaching NE neuron receptors. Those patients with NE deficiency show low levels of MHPG in the urine and respond best to imipramine and most probably desipramine. The second major group of patients would most likely have decreased levels of 5-HIAA in the cerebrospinal fluid, normal or high levels of urinary MHPG, and selectively better clinical response to amytriptyline.

E. Cholinergic Effects in Mania

Janowsky *et al.* (1972a,b) first postulated that the cholinergic system might be involved in modulating the noradrenergic system in depression. If this two-factor hypothesis were true, then high NE and low ACh levels (or function) would be associated with mania, and low NE and high ACh with depression. To test this theory they administered physostigmine to manics, since physostigmine is known to increase brain ACh function. No changes in effect were found in patients who received the neostigmine, a similar drug which acts only peripherally. For a 1–2 hr period after patients received physostigmine, their manic state was converted to a state of psychomotor-retarded depression (Fig. 1).

The patients were initially in a typical manic state exhibiting such symptoms as rhyming, punning, and rapid movements and thoughts. After the physostigmine injections, the patients began to slow down: appeared lethargic, felt drained, and had less energy. Many patients reported a marked reduction of thought process and content. Many felt depressed, whereas others felt only retarded, but not necessarily depressed.

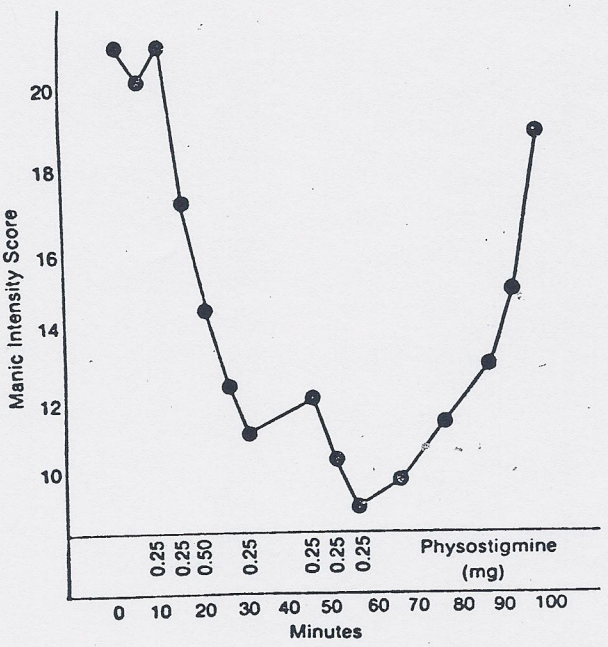

Figure 1. Time course of change in Biegel-Murphy manic intensity scale for patients receiving 2 mg of physostigmine. From Janowsky *et al.*, 1973.

Physostigmine seemed to act specifically on the "rate disturbance" aspects of mania, that is, on the level of motoric behavior and the rate of psychomotor activity. Affect and ideational content were altered less consistently. This is consistent with the effect of ACh in mediating the behavioral response of extinction through lack of reinforcement in animals postulated by Carlton (1963).

Evidence that the antimanic effect of physostigmine is mediated by a muscarinic mechanism is provided by the observation that physostigmine's effect normally lasts about 2 hr, and if iv atropine is administered, the physostigmine effect disappears within minutes of the injection. This is illustrated schematically (Fig. 2).

Physostigmine produces some dissociation between different affective symptoms in that it has a more pronounced effect on the rate of behavior than on its content. The specificity of its antimanic effect depends on what is considered to be the essence of manic disease. If psychological content (i.e., grandiosity) is considered the essence of manic depressive disease, then physostigmine would have relatively less specificity. If the rate disturbance (i.e., being speeded up, rhyming and punning, and rapid thoughts) is considered central to mania, physostigmine's ability to influence these disturbances is quite specific.

F. Cholinergic Effects in Depression

Physostigmine also exacerbates depression in patients who have pre-existing depression (Janowsky *et al.*, 1974). Oral choline administered to patients with tardive dyskinesia produced profound depression in 50% of the cases (Tamminga *et al.*, 1976). We have also seen profound depression in two patients treated with physostigmine while in a tetrahydrocannabinol (THC)-induced high (Ed Yousef *et al.*, 1973). We have found that patients with pre-existing depressive symptomatology manifest substantially more depression than patients without pre-existing affective symptoms when treated with physostigmine. Schizoaffectives (depressive phase) showed over six times more depression than "pure" schizophrenic patients without affective symptoms (Janowsky *et al.*, 1974).

Modestin and his co-workers (1973a,b) studied 24 depressed patients, 4 manic patients and 40 nonpsychotic, nondepressed patients using 1.25–1.5 mg physostigmine and neostigmine (iv). These studies had a double blind, crossover design. Physostigmine induced some lessening of mania. Physostigmine produced a substantial increase in depressive symptomatology when administered specifically to depressed patients, whereas neostigmine did not.

Cholinergic factors may play a secondary role in affective disease. Choline and physostigmine can produce depression in some normals but not all normals.

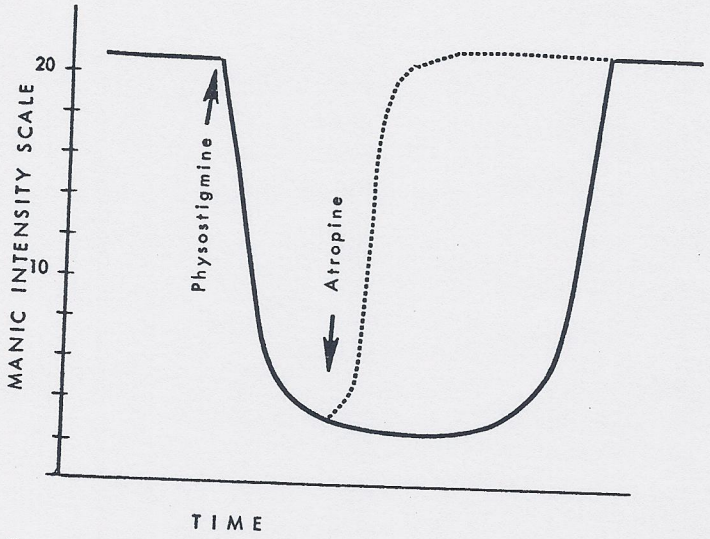

Figure 2. Hypothetical response curve: reversal of mania. With physostigmine blockage of physostigmine effects by atropine. Extremely manic patients respond to I.V. physostigmine by becoming depressed. Several hours later when physostigmine effects wear off, the manic symptoms reappear. If I.V. atropine is given, the mania reappears rapidly.

Of course, perhaps depression could have occurred in all subjects had a high enough dose of the cholinergic agent been used. Cholinergic factors may play an important role in mania and depression as they do in Parkinson's disease, but this role may be to modulate a defect in another system. Our emphasis would be to stress the balance between transmitters rather than adopting a single transmitter-single disease approach.

VIII. BIOLOGICAL THEORIES OF MANIA

It is tempting to assume that the major biological defect in manic states is an excess of biogenic amines, particularly NE. Several authors have demonstrated that in patients who rapidly cycle from mania to depression, urinary MHPGs were lower during the depressed phase and higher during the manic state (Jones *et al.*, 1973). The higher measurement of urinary MHPG during mania however is a relative increase because MHPG levels are actually normal during manic episodes. Interestingly, in cases of mixed depression and mania, urinary levels of MHPG are generally reduced. In other words, clinical depression correlates fairly well with decreased MHPG, while mania presents a less clear-cut picture.

Another strategy of testing whether mania is a result of excess NE in the central nervous system is to administer medications which diminish or block NE and to observe whether the symptoms in mania are improved or resolved. Fusaric acid is a dopamine-β-hydroxylase inhibitor, which decreases central NE, and this medicine has not been found to be effective in treating symptoms of mania (Sack and Goodwin, 1974). α-Methyl-*para*-tyrosine, which blocks catecholamine synthesis earlier at the tyrosine hydroxylase step, has a weak effect in treating manic episodes (Brodie *et al.*, 1971). It should be noted though that manipulation of tyrosine hydroxylase also decreases central DA as well as NE. There is some evidence that the DA pathways may be involved in mania. There are reports of patients suffering from Parkinson's disease who become hypomanic when treated with L-dopa (Murphy *et al.*, 1973). L-Dopa is primarily converted to DA with substantially less increase in NE. Moreover, it is well known that the antipsychotic medications, which are DA-blocking agents, are effective in reducing manic symptoms. Even more intriguing is the growing existence that manic symptoms can be decreased by cholinergic stimulation. Janowsky *et al.* (1973a,b) successfully reduced manic symptoms temporarily by giving intravenous physostigmine which, due to its anticholinesterase inhibitor properties, elevates central nervous system ACh synaptic action. The above findings indicate that the mechanisms by which mania is produced are probably more complicated than the involvement of just one amine neurotransmitter system. It could be that manic symptoms result from imbalances of more than one neurotransmitter system in the brain. In other

words, mania may be a result of a DA excess or over-functioning resulting from either a decrease in cholinergic activity or to an actual DA hyperactivity or excess. In summary, despite the strong evidence that depression is associated with decreased NE in the central nervous system, there are indications that mania may be due to a defect resulting in a relative or absolute predominance of central dopamine systems.

IX. THE USE OF LITHIUM TREATMENT FOR BIPOLAR AFFECTIVE DISORDER

Cade (1949) first reported the effectiveness of lithium salts in the treatment of acute manic patients. Subsequently other investigators found that lithium was also effective in the prophylactic treatment of both depression and mania. Lithium may decrease the amount of NE at the postsynaptic receptor by increasing presynaptic NE uptake, or by diminishing the sensitivity of postsynaptic receptors (Colburn *et al.*, 1967; Forn and Valdecases, 1971).

X. ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT) is an important therapeutic modality for the treatment of severe depression. Despite the fact that ECT has been proven beyond a doubt by controlled studies to be efficacious, its use continues to be controversial. It is especially indicated in depressed patients who are highly suicidal or in delusional depressives (Glassman *et al.*, 1975). There have been some studies attempting to elucidate the effect of careful ECT on the central neural transmitter systems. Some studies have shown that during treatment with ECT, urinary MHPG increases, probably reflecting an increase turnover in NE (Schildkraut, 1975). ECT benefits Parkinsonian symptoms, as well as depression, in patients with both diseases, a finding suggesting that it increases catecholamine synthesis (Dysken *et al.*, 1976).

XI. SLEEP DEPRIVATION

Recently sleep researchers have reported that rapid eye movement (REM) sleep deprivation brings therapeutic benefits to some depressed patients (Vogel, 1975). Some sleep investigators suggest that those patients who experience REM pressure have increased activity of central NE. Moreover, some studies have found that depressed patients who neither respond to REM depriva-

tion nor have REM rebound tend to be nonresponsive to therapy with imipramine, a medication which selectively blocks NE reuptake (Vogel *et al.*, 1975).

XII. MEMBRANE ABNORMALITIES IN AFFECTIVE ILLNESS

According to the biogenic amine hypothesis of affective illness, a dysfunction of neurotransmitter amines may be associated with some forms of manic depressive illness. The dysfunction could be caused by several processes such as biosynthesis, metabolism, transport, or amine receptor sensitivity. The observation that accumulation of lithium in red cells of patients with bipolar illness is higher than in normal controls has provided some evidence in support of membrane theories of affective illness. It has also been suggested that aminergic receptor responses in patients with affective illness may be altered.

XIII. LITHIUM TRANSPORT IN HUMAN RED CELLS

Several investigators have suggested that changes in the transport of cations may be associated with manic depressive illness. Coppen (1967), Coppen *et al.* (1966), and Coppen and Shaw (1963) observed a decrease in intracellular sodium in patients who had recovered from depression. It has been suggested that there is significantly less sodium pump activity in red blood cells of bipolar patients than in the cells of normal controls. Lithium treatment increases the activity of the enzyme ATPase which is associated with the transport of Na^+ and K^+.

The suggestion of a defect in the transport of monovalent cations in patients with affective illness has prompted investigators to examine whether a defect in the transport of lithium, a monovalent cation used in the treatment of mania, is associated with manic depressive illness. It was observed by several investigators that the levels of lithium in red cells of patients treated with lithium was considerably lower than plasma (Na^+-like distribution) and that a large interindividual variation was observed in the distribution ratio of lithium between red cells and plasma (commonly referred to as Li^+ ratio) in patients treated with Li^+. The Li^+ ratio has been related to clinical response to lithium therapy (Casper *et al.*, 1976; Rybalski *et al.*, 1976; Mendel *et al.*, 1973), clinical diagnosis (Pandey *et al.*, 1979a), and side effects of lithium therapy (Hewick and Murray, 1976). Several investigators have studied the mechanisms of Li^+ transport in human red cells in order to determine the factors which cause such interindividual variations in the lithium ratio. It is possible that the factors which regulate lithium transport in human red cells may be related to the factors which regulate behavior.

At least four distinct pathways of lithium transport have been elucidated and characterized in human red cells. Of these, the most important pathway which is

operational under physiologic conditions and is responsible for the interindividual variations observed in the lithium ratio is the Li^+–Na^+ exchange pathway operated by a Li^+–Na^+ countertransport mechanism (Haas *et al.*, 1975; Pandey *et al.*, 1976, 1978; Duhm and Becker, 1977). This pathway, which is insensitive to ouabain, can drive Li^+ against its electrochemical potential by an oppositely directed electrochemical potential gradient for Na^+ (Haas *et al.*, 1975). This uphill movement of Li^+ is inhibited by phloretin, furosamide, quinine, and quinidine and does not require the presence of cellular ATP (Pandey *et al.*, 1978; Sarkadi *et al.*, 1978). This unidirectional ouabain-insensitive movement is stimulated by Na^+ on the trans side and inhibited by Na^+ on the cis side of the membrane. Among various cations tested (e.g., K^+, Rb^+, Cs^+, Ca^{2+}, Mg^{2+}), Na^+ was the only one found to have this role. Na^+-dependent fluxes also are inhibited by phloretin, furosmide, quinine, and quinidine and do not require the presence of ATP. The similar characteristics of downhill and uphill Li^+ transport stimulated by Na^+ suggest that both are mediated by the same process. They also suggest that the phloretin-sensitive counterflow pathway is mediated by a carrier molecule through a tightly coupled Li^+–Na^+ exchange mechanism.

Pandey *et al.* (1979a) observed a significant inverse correlation between Li^+ transport mediated by Li^+–Na^+ exchange mechanism and Li^+ ratio observed *in vivo* and suggested that alterations in Li^+ transport mediated by this pathway cause interindividual variations in the Li^+ ratio. Patients who had reduced Li^+ transport mediated by this pathway had a high Li^+ ratio *in vivo*, and those patients who had normal or higher Li^+ transport mediated by this pathway had lower *in vivo* Li^+ ratio. These studies not only helped in the understanding of mechanisms involved in the transport of lithium but also resulted in the development of *in vitro* methods which could accurately predict Li^+ ratio *in vivo* and thus provided simpler procedures for studying membrane characteristics in patients and normal controls without administering Li^+ to these subjects.

Preliminary evidence was provided by Lyttkens *et al.* (1973) showing that bipolar patients have higher Li^+ ratios compared to normal controls. These reports were not confirmed probably because of the difficulties associated with the administration of Li^+ to control groups and due to a large variability observed in the lithium ratio *in vivo*. With the development of *in vitro* methods it became possible to compare a larger number of controls with the patients. We recently compared Li^+ ratio *in vitro* and other parameters of Li^+ transport mediated by Li^+–Na^+ exchange pathway in a group of patients with bipolar illness and in Normal controls. The mean Li^+ ratio *in vitro* (0.29 ± 0.13 S.D.) observed in 22 patients with bipolar illness was significantly higher as compared to 88 normal controls (0.23 ± 0.07), as shown in Table III.

Net uphill and downhill Li^+ efflux from red cells of bipolar patients was also significantly higher as compared to normal controls. Sodium-dependent downhill Li^+ efflux in bipolar patients was higher as compared to normal controls, but just

missed the level of significance. Since these measurements of lithium transport are primarily mediated by the Li^+–Na^+ exchange pathway, these results suggested a reduction in the Li^+ transport through these mechanisms and suggested that the observed elevation of the Li^+ ratio both *in vitro* and *in vivo* is caused by a defect in one of the moieties of Li^+ transport, i.e., Li^+–Na^+ exchange.

These results indicate that there is no one-to-one relationship between bipolar illness and abnormalities of Li^+ transport; not all bipolar patients have high Li^+ ratios and deficient counterflow. In a recent study, we found that some patients in other diagnostic groups, such as schizophrenia, also have high Li^+ ratios and deficient counterflow. On the other hand, the average for bipolar patients differs from that for normal controls. More importantly, there is substantial heterogeneity within the bipolar groups with respect to Li^+ transport. This finding is consistent with the data of Rybakowski (1977) which indicate that bipolar patients with first-degree relatives who have a history of affective illnesses, have a higher mean Li^+ ratio than those with no family history. Frazer *et al.* (1978) have also reported heterogeneity of bipolar patients, those with lower schizoid indices having significantly higher Li^+ ratios on the average than patients with higher schizoid indices. The results suggest that it would be useful to characterize patients with high Li^+ ratios and deficient Li^+ efflux, regardless of their diagnosis, by means of a range of biochemical, clinical, and pharmacologic parameters.

The significance of these observations is poorly understood at this time. The Li^+–Na^+ exchange system pathway in the absence of Li^+ is associated with a Na–Na exchange system. This system can accept Na^+ and/or Li^+, but no other cations which have been tested. Although the presence of such a system in the central nervous system has not been demonstrated, it can be speculated that in the brain such a system can probably achieve the transport of other physiologically active cations such as Ca^{2+} and positively charged neurotransmitters, and a defect in this transport system could alter the distribution, and thus the effect of such substances.

XIV. GENETIC FACTORS AND LITHIUM TRANSPORT

The reports that a large interindividual variation in the Li^+ ratio is observed in patients during Li^+ treatment (Mendels and Frazer, 1973; Casper *et al.*, 1976) suggested that genetic factors may be responsible at least in part for such observed differences. Preliminary evidence for genetic control of the Li^+ ratio was provided by the twin-study method carried out by Dorus *et al.* (1974, 1975). The Li^+ ratio was first determined *in vitro* by incubation, in a plasmalike medium containing 1.5 m*M* LiCl, of red cells obtained from normal monozygo-

tic (MZ) and dizygotic (DZ) twin pairs. The Li^+ distribution ration between erythrocytes and the medium was determined after 24 hr of incubation. In their first study, Dorus *et al.* (1974) determined the Li ratio *in vitro* in ten MZ and seven DZ twin pairs. The intrapair differences in the Li ratio were significantly smaller in the MZ twin pairs than in the DZ twin pairs. In a subsequent study (Dorus *et al.*, 1975), Li^+ was administered to MZ and DZ twin pairs for 7 days, and the Li^+ was determined *in vivo* and *in vitro*. The variance in the Li ratio, *in vitro* and *in vivo*, in DZ twin pairs was significantly greater than that in MZ twin pairs. These results gave preliminary evidence of genetic control of the Li^+ ratio.

To evaluate the degree of this genetic control, Dorus *et al.* (1980) studied the Li^+ ratio in members of normal families. In 291 members of 120 families, they observed that parent–offspring and sibling–sibling correlations were significantly different from 0, but not significantly different from 0.5. If a quantitative trait is under complete polygenic control, theoretically the expected correlation for relatives who have, on the average, one-half of their genes identical by descent (e.g., in parent–offspring and sibling–sibling pairs) is 0.50. There were no significant differences in the magnitude of the correlations between brother–brother, brother–sister, and sister–sister pairs. Similarly, there were no significant differences in the correlations between mother–son, mother–daugher, father–son, and father–daughter pairs, suggesting that sex chromosome effects do not play a major role in determining the distribution of lithium. These results thus indicate that autosomal genetic factors contribute substantially to the interindividual variation observed in the Li^+ ratio. It is not yet known, however, whether a single gene locus with a major effect or a number of gene loci with additive effects are involved.

The evidence that an abnormality of Li^+ transport in human red cells, resulting in a high Li^+ ratio, is inherited was provided in a study (Pandey *et al.*, 1977) of the family of a patient who had a high Li^+ ratio *in vivo*. This patient also had high Li^+ ratio *in vitro*, and the Li^+ transport mediated by the Li^+–Na^+ exchange pathway (Li^+–Na^+ counterflow) in his red cells was almost absent. The Na^+–Na^+ exchange system was also found to be deficient in the red cells of this patient. Several members of his family, including his father, had Li^+ transport characteristics similar to his own, thus suggesting that a deficient Li^+ transport in red cells mediated by the Li^+–Na^+ exchange pathway can be inherited. Similar results in several additional families have been reported by (Pandey *et al.*, 1979a).

XV. AFFECTIVE ILLNESS AND ADRENERGIC RECEPTOR SENSITIVITY

In recent years there have been suggestions, reinforced by Ashcroft *et al.* (1972) of a receptor defect in affective illness. Receptor sensitivity, particu-

TABLE IV

Percent Conversion of Total [^{3}H]Nucleotides to [^{3}H]cAMP in Intact Human Leukocytes[a]

Diagnostic Group	Basal[b]			PGE_1 (10^{-5} M)			NE (10^{-4} M)[c]			IP (10^{-4} M)[d]		
	N	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
Normal subjects	26	0.25	0.02	26	1.77	0.18	26	0.42	0.04	21	0.68	0.06
Unipolar depressed patients	21	0.29	0.03	21	1.34	0.12	19	0.20	0.03	17	0.31	0.05
Bipolar patients with mania	9	0.24	0.02	9	1.54	0.26	9	0.28	0.04	8	0.40	0.05
Schizophrenic patients	30	0.27	0.02	29	1.48	0.21	30	0.26	0.05	26	0.51	0.08

[a] The percent conversions in the presence of NE, IP, or PGE_1 are those observed with the addition of these drugs over the basal activity and have been refered to as stimulated activity.

[b] Percent conversion when no test drugs were added to the incubation mixture.

[c] NE stimulation differed significantly between the groups, $F(3, 80) = 4.14$, $p < .009$, and between normal subjects and patients, $F(1, 80) = 10.08$, $p < .002$.

[d] IP-stimulated activity differed significantly between groups, $F(3, 68) = 4.59$, $P < .006$; for normal versus patients, $F(1, 68) = 10.08$, $P < .002$; for normal subjects versus depressed patients, $F(1, 68) = 12.61$, $P < .001$; and for schizophrenics versus depressed patients, $F(1, 68) = 4.04$, $P < .05$.

group was not significantly lower compared to the normal control group. Bipolar patients also ;had a significantly lower IP-stimulated leukocyte adenylate cyclase activity compared to normal controls. In a recent report, Extein *et al.* (1979) also observed a significant reduction of IP-stimulated leukocyte adenylate cyclase in the unipolar depressed group as compared to normal controls, and found that the total binding of [^{3}H]DHA was significantly reduced in depressed patients compared to normal controls. The original finding of decreased β-adrenergic receptor sensitivity in depressed patients and bipolar patients reported by Pandey *et al.* (1979c) thus appears to have been replicated by another group. These findings may thus imply a decrease in β-adrenergic receptor sensitivity in affective illness. Whether such changes are related to the changes in brain, and are secondary to the onset of illness, is not clear and remains to be investigated further.

XVI. ANTIDEPRESSANT TREATMENT AND ADRENERGIC RECEPTOR SENSITIVITY

The therapeutic effects of the known antidepressants have been attributed to their ability to alter the functional levels of biogenic amines by their effects on amine metabolism, amine uptake or release, or amine turnover. It has also been suggested that the therapeutic effects of the antidepressants may be related to their ability to alter amine receptor sensitivity. In order to test this hypothesis, effects of chronic and acute antidepressant treatment on NE- and IP-stimulated adenylate cyclase, and on binding of radiolabeled ligands which bind to adrenergic receptors, have been studied in rat brain by several investigators. Some of these observations, which not only may be helpful in understanding the mechanism of action of antidepressants but may also be helpful in understanding the etiology of affective illness, are described briefly in this section. Details may be seen in other chapters in this book.

It was reported by Frazer *et al.* (1974) that chronic treatment with imipramine caused a reduction in NE-sensitive adenylate cyclase in rat cerebral cortex. Vetulani *et al.* (1976a,b; Vetulani and Sulser, 1975) reported that chronic treatment with several classes of antidepressants caused a reduction in the NE-stimulated increase in cyclic AMP production in the rat limbic forebrain. Such effects were observed with nialamide, which is a monamine oxidase inhibitor; and electroconvulsive therapy (ECT) which probably cause synthesis and release of amines. These observations have led to the suggestion that antidepressant treatments have a common effect of reducing NE-sensitive adenylate cyclase, probably caused by an alteration in adrenergic receptor sensitivity. However, iprindole is an effective antidepressant, although its effects on the catecholamine system are not clear since it is neither an uptake nor an MAO inhibitor, but decreases NE-sensitive cyclase in the rat brain.

Further evidence that the reduction in NE-sensitive adenylate cyclase in rat brain is in fact related to a decrease in β-adrenergic receptor sensitivity is provided by binding studies with labeled β-adrenergic antagonists. Banerjee *et al.* (1977) reported that chronic treatment with desmethylimipramine, doxepin, and iprindole caused a significant reduction in β-adrenergic receptor sensitivity in rat cerebral cortex. Sarkadi *et al.* (1978) and Wolfe *et al.* (1978) reported similar results on chronic treatment with these antidepressants. Bergstrom and Kellar (1979) and Pandey *et al.* (1979b) reported that treatment with ECT caused significant reduction in β-adrenergic receptor sensitivity in rat brain. Pandey *et al.* (1979b) also reported that similar reduction in β-adrenergic receptor sensitivity was observed by treatment with Wellbatrin, another antidepressant drug whose mode of action on catecholamines is not clear. Whereas treatment with antidepressants results in a decrease in β-adrenergic receptor sensitivity, the sensitivity of α-adrenergic receptors is not changed (Bergstrom and Kellar *et al.*, 1979). Furthermore, it is reported by Minneman and associates (1979) that this reduction in receptor sensitivity is primarily associated with β_1-receptors and no change is observed with β_2-receptors.

These observations have led some investigators to suggest that depressive illness is associated with hypersensitive β-adrenergic receptors and that treatment with antidepressants decreases the sensitivity of these receptors. Data from human studies are not entirely consistent with this hypothesis. However, studies under clinical situations have been carried out with peripheral tissues, and it may be difficult to extrapolate these findings to the events occurring in the brain. Although these studies do not provide definitive answers concerning the role of adrenergic receptors, either in the etiology of affective illness or in elucidating the mechanism of action of antidepressant drugs, they at least suggest a relationship between adrenergic receptor sensitivity alterations and affective illness during treatment with antidepressants. It is hoped that further developments in receptor technology and pharmacolgy will help in providing some answers to these questions.

Another related aspect is the mechanism by which antidepressant drugs cause a reduction in β-adrenergic receptor systems in rat brain. Treatment with ECT causes increased release and turnover of NE and possibly of DA in various areas of the rat brain. Tricyclic antidepressants, on the other hand, inhibit reuptake of biogenic amines in synaptosomal preparations, and drugs such as pargyline and phenelzine inhibit monoamine oxidase activity. These antidepressants have different modes of action on the biogenic amine system; however, all increase the biogenic amine concentration in the postsynaptic area, and reduce the sensitivity of β-adrenergic receptors and the responsiveness of adenylate cyclase to NE, as reported by others and presented here. Furthermore, Deguchi and Axelrod (1973) and others have suggested that continued exposure of adenylate cyclase-coupled β-receptors to elevated levels of agonists lowers the sensitivity of the receptors;

we might therefore assume that loss of β-adrenergic receptor sensitivity on chronic treatment with antidepressants is caused by overexposure of postsynaptic β-adrenergic receptors to elevated levels of NE. However, iprindole has no significant effect on reuptake, release or turnover of catecholamines and it is not certain whether it increases the levels of NE in the synaptic cleft; like other antidepressants it reduces β-adrenergic receptor sensitivity and decreases NE responsiveness of adenylate cyclase. Therefore, as suggested by Banerjee *et al.* (1977) other mechanisms may also be involved in the development of the reduction in β-adrenergic receptor sensitivity.

XVII. TRANSMITTER BALANCE AND AFFECTIVE DISEASE

Current biological theories of mental disease are single transmitter, single disease theories. Yet most biological functions are controlled by homeostatic systems involving a balance between regulatory systems, such as the sympathetic and parasympathetic control of peripheral autonomic functions. Parkinsonian symptoms provide one paradigm of how two transmitter systems interact. Parkinsonian symptoms are controlled by a balance between dopamine and acetylcholine (ACh). In Parkinsonian patients, drugs which increase ACh (or direct injections of ACh into the CNS) can worsen Parkinsonian symptoms. Alternatively, anticholinergic drugs benefit Parkinsonian symptoms. Similarly, administration of neuroleptics to schizophrenics can produce Parkinsonian side-effects by blocking DA receptors. Dopa, through its conversion to DA, also benefits Parkinsonian symptoms.

XVIII. THEORETICAL MODELS OF AFFECTIVE DISTURBANCE

A number of theories of the affective disorders based on the neuropharmacologic aspects of these disorders have been proposed over the years. The earliest were those suggested by the empirically observed action of the antidepressant drugs. These were the single-amine hypotheses. The Catecholamine Hypothesis, favored by American researchers, stated essentially that depression resulted from a deficit in catecholamines at CNS synapses and mania from an excess. European researchers favored the Indoleamine Hypothesis, which stated that depression resulted from a lack of 5-hydroxytryptamine (5-HT) at central serotonergic synapses, a hypothesis rejected by Schildkraut and Kety (1967) in that 5-HT appeared to act as an inhibitory transmitter in the CNS (an assertion

which continues to be supported; cf. Haigler and Aghajanian, 1977), and depressed patients do not appear to lack inhibition.

As both hypotheses continued over time to accumulate supporting evidence, several authors began to suggest that there might be more than one biochemically distinct form of affective disorder, but with the same symptoms, as suggested in Akiskal and McKinney's (1973) Final Common Pathway Hypothesis. Davis (1975) argued that no single-amine hypothesis could adequately account for the data on neuropharmacologic factors in affective disorder, and that it would be much more reasonable to assume that more than one transmitter system is involved in the changes seen in these disorders, perhaps by means of a disturbance of an equilibrium between transmitter systems.

The Permissive Hypothesis of bipolar affective disorder proposed by Prange *et al.* (1974) is a complex transmitter model taking into account and integrating information from both the Catecholamine and Indoleamine Hypotheses. These authors reasoned, on the basis of the fact that they found L-tryptophan to be an effective treatment for mania as well as depression, that a 5-HT deficit is the underlying condition in bipolar affective disorder, which permits the appearance of symptoms in response to an overlying alteration in catecholamines (with catecholamine elevation producing mania and a reduction in catecholamine function producing depression).

Considerable animal research has been directed toward the elucidation of the relationships between neurotransmitters and behavior, and this information would seem to be relevant to the study of affective disorders. Animal research has indicated that any given cell in the nervous system receives a vast number of inputs from other neurons, each of which is basically excitatory, making the cell more likely to develop an action potential, or inhibitory, making an action potential less probable. In a similar fashion, some aspects of behavior or motivation seem to depend on the reciprocal relationship of brain systems acting to enhance or suppress certain behaviors. Many of the behaviors studied in this way in animals are among those observed to be altered in the affective disorders, and so it would seen reasonable to use animal models both to study psychopathology and to make inferences about human neurochemistry from these studies.

With the recent surge of interest in the effects of motivation on human behavior and their applicability to both the etiology and treatment of psychopathology, a number of behavioral formulations concerning the etiology and maintenance of the symptoms of depression have been proposed. Probably the most straightforward of these is that of Lewinsohn and his co-worker (Lewinsohn and Atwood, 1969). They reason that the depressed person has deficient social skills and emits few reinforceable behaviors, so that the behavioral deficit seen in depression is a function of lack of reinforcement. Costello (1972) observes, however, that depressed people behave as though *all* of their instrumental be-

haviors were undergoing extinction, and not just those socially reinforced. He suggests that such a general effect on behavior might be biologically mediated.

Another behavioral explanation for the depressed person's improverishment of instrumental responses is that this phenomenon is mediated by negative reinforcement and punishment. The best known and most studied of these is Seligman's concept of Learned Helplessness (1975), which postulates the experience of a significant amount of inescapable aversive stimulation causes animals or humans to learn that they are helpless to control the contigencies in their lives. They then stop emitting instrumental behaviors, as they believe that their behavior has no effect on what happens to them. Seligman and his colleagues have recently elaborated this theory further (see Abraham *et al.*, 1978) for humans by proposing that individuals will be particularly likely to become depressed if they have the cognition that their inability to escape the aversive event(s) is internal, global, and stable. A virtue of this formulation for research is that it provides an animal model of depression which appears to be consistent with research on the same phenomena in humans (Maier and Seligman, 1976).

Probably the most serious argument against the learning theories of the etiology of depression is that the presence of the actual contingencies of reward or punishment proposed to give rise to the symptoms of depression often cannot be found in the afflicted individual's environment. This suggests that the change in contingencies might exist within the individual; not in the environment but in the individual's perception of the environment. To be consistent with this argument, it would be necessary to show changes in nervous system chemistry which would be consistent with the perceptions behavior theorists reason produce depression—inability to perceive positive reinforcement, heightened ability to perceive negative reinforcement or punishment, or both. These changes, which would be most likely to be changes affecting the function of neurotransmitters, should also correlate with other nonbehavioral changes associated with the affective disorders.

A neurotransmitter model which would integrate the existing data on neurotransmitter alterations (NE, DA, 5-HT, and ACh) in the affective disorders, the apparent heterogeneity of the affective disorders, the relationship between the CNS chemistry of the affective disorders and the symptoms and behavior of affected individuals, and the learning theories of depression, is that proposed by K. J. Noll (unpublished research, 1978). This model deals with the equilibrium between excitatory and inhibitory neurotransmitter effects in the brain systems mediating positive reinforcement (experienced as pleasure) and negative reinforcement or punishment (aversive experiences), and the equilibrium between these two brain systems as it affects behavior. Research on animals has suggested that these two systems share 5-HT as an inhibitory transmitter (Poschel and Ninteman, 1971), whereas the excitatory transmitters mediating positive reinforce-