

rhythms range from the microseconds of biochemical reactions, to the seconds of the heart cycle, to the 90 minute rapid eye movement cycle of dreaming, to the monthly menstrual cycle. The normal regularity of these various rhythms becomes apparent when there is disruption of the regularity because of disease, stress, or erratic external synchronization, as seen, for example, in *jet fatigue*.

The major 24 hour day-night cycle is referred to as *circadian* (circa: about; dies: a day). Rhythms shorter than 24 hours are defined as *ultradian*, and those longer than 24 hours are *infradian*. We will comment about the possible relationship between biological rhythms and psychopathology in the following chapter.

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NEUROBIOLOGICAL FACTORS IN MENTAL ILLNESS

HENRI BEGLEITER, PH.D.

For the better part of this century more people have been hospitalized for mental illness than for all other diseases combined. It is important to note that the reduction of patient populations in mental hospitals coincides with the introduction of various psychopharmacolog-

ical agents such as the tranquilizers and the antidepressants.

PSYCHOPHARMACOLOGY

Psychopharmacology (Figure 48.4) may be defined as the use of drugs in the treatment of

Generic Name	Trade Name	Manufacturer	Chemical Formula
I. MAJOR TRANQUILIZERS			
A. PHENOTHIAZINES			
Acetophenazine	Tindal	Schering	
Butaperazine	Repoise	A. H. Robins	
Chlorpromazine	Thorazine	Smith Kline & French (SKF)	
Carphenazine	Proketa-zine	Wyeth	
Fluphenazine	Permitil Prolixin	Schering Squibb	
Mesoridazine	Serentil	Sandoz	

Figure 48.4 Tranquilizing drugs. Modified from Chapter 29.1, "Tranquilizers," in *Modern Synopsis of Comprehensive Textbook of Psychiatry*, edited by A.M. Freedman, H.I. Kaplan, and B.J. Sadock. Williams & Wilkins, Baltimore, 1972, pp. 540-543. Published by permission.

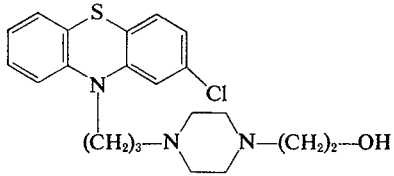
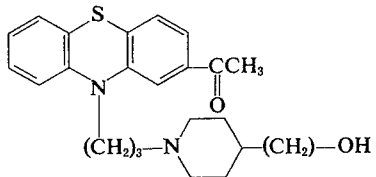
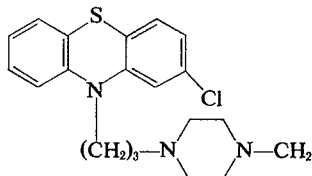
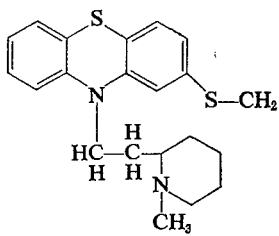
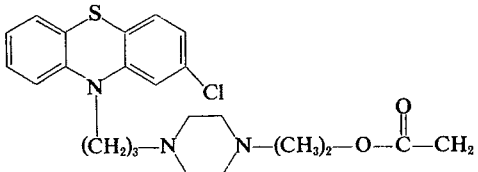
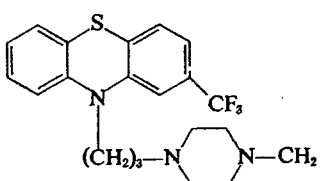
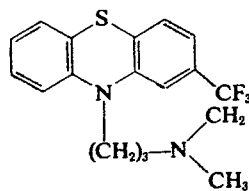
Generic Name	Trade Name	Manufacturer	Chemical Formula
Perphenazine	Trilafon	Schering	
Piperacetazine	Quide	Dow	
Prochlorperazine	Compazine	SKF	
Thioridazine	Mellaril	Sandoz	
Thiopropazate	Dartal	Searle	
Trifluoperazine	Stelazine	SKF	
Triflupromazine	Vesprin	Squibb	

Figure 48.4—Continued

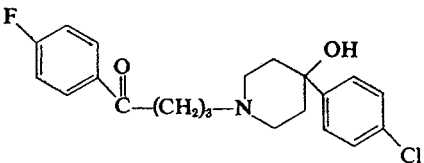
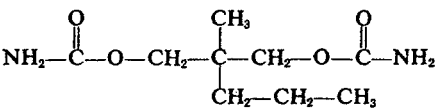
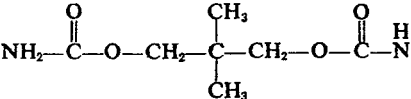
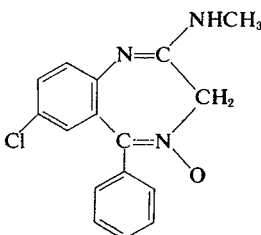
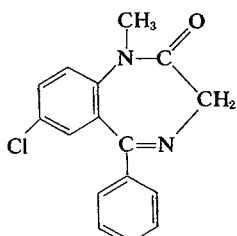
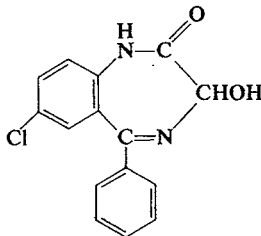
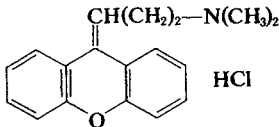
Generic Name	Trade Name	Manufacturer	Chemical Formula
B. BUTYROPHENONES			
Haloperidol	Haldol Serenace	McNeill Searle	
II. MINOR TRANQUILIZERS			
A. MEPROBAMATES			
Meprobamate	Miltown Equanil	Wallace Wyeth	
Tybamate	Tybatran Solacen	A. H. Robins Wallace	
B. BENZODIAZEPINES			
Chlordiazepoxide	Librium	Roche	
Diazepam	Valium	Roche	
Oxazepam	Serax	Wyeth	
Doxepin	Sinequan	Pfizer	

Figure 48.4—Continued

psychological and behavioral disorders, as well as the study of brain functions utilizing biochemical and behavioral methodologies. The importance of this approach is quite obvious when one considers that eventually only an extension of our knowledge concerning brain structure and functions can permit a better understanding of the causes of psychological disturbances. More than anything else in the history of psychiatry, the phenothiazines and related compounds have influenced the treatment outcomes of schizophrenic patients.

Major Tranquilizers

The *phenothiazine* derivatives, including chlorpromazine, form the most important group of major tranquilizers. They are widely used in the treatment of the psychoses and may also be used as a preanesthetic medication. Chlorpromazine blocks the uptake of norepinephrine (NE) into sympathetic nerve endings, blocks the release of NE from nerve endings, and also blocks alpha-adrenergic receptors. The phenothiazines induce a series of characteristic changes in animal behavior which are essentially dose-dependent. At very low doses they increase sociability in animals, while at medium doses they impair motor activity. At very high doses motor activity is drastically reduced or absent, and the animal is in a cataleptic state. The phenothiazines and the other major tranquilizers reduce exploration behavior in animals and markedly impair conditioned avoidance responses and learning.

The phenothiazines can produce extrapyramidal symptoms in humans. These tremors and spastic movements can be quite alarming and require close medical supervision. Phenothiazines also produce hypersensitivity reactions such as orthostatic hypertension, visual and retinal pigment changes, and photosensitivity.

Another class of major tranquilizers is the *rauwolfia* alkaloids of which reserpine is the most common. Reserpine is not as widely employed for clinical purposes as previously, but it still retains a degree of importance in experimental laboratory studies. Reserpine appears to interfere with the storage of serotonin, norepinephrine, and dopamine in the central nervous system (CNS). Reserpine and serotonin both contain an indole nucleus. The presence of this indole nucleus has led some researchers to

assume that serotonin mechanisms in the brain might be the basis for the action of reserpine.

The therapeutic indications for reserpine are rather similar to those of the phenothiazines. The behavioral effects of reserpine also resemble those observed with the phenothiazines. Reserpine decreases spontaneous motor activity, decreases exploratory behavior, and impairs conditioned avoidance responses and learning. In the management of schizophrenia numerous clinical reports have stated that reserpine was clearly less useful than the phenothiazines, so that this drug is currently not as widely employed as it used to be. In fact, reserpine is currently employed more frequently in the treatment of hypertension than in the management of psychosis. The single most undesirable side effect of reserpine is its inducement of a depressive state which can be quite severe.

The *butyrophenones* constitute a class of major tranquilizers which have been developed quite recently. They have not been as widely utilized clinically or experimentally. The behavioral effects of the butyrophenones are quite similar to those of the phenothiazines. Clinically, the butyrophenones show a phenothiazine-like activity that more closely resembles that of the most typical antipsychotic agents rather than being characteristic of sedative compounds of this class. The butyrophenones act upon the severity of psychotic symptoms in schizophrenic patients. However, the undesirable extrapyramidal symptoms are more frequently and intensely induced by the butyrophenones. For this reason the butyrophenones are not used as commonly as the phenothiazines in the treatment of schizophrenia. Conceivably, the antischizophrenic activity of the phenothiazines and butyrophenones, and their extrapyramidal side effects, might be attributable to interactions with dopamine receptors in the brain.

Minor Tranquilizers

The minor tranquilizers produce behavioral calm which is not the same as that produced by the major tranquilizers. The difference is not just in the degree of calm produced but in the quality of calm. The minor tranquilizers are used primarily in the treatment of psychoneuroses associated with chronic anxiety, phobias,

obsessive-compulsive behavior, and acute stress-induced anxiety. It should be noted that in contrast to major tranquilizers, minor tranquilizers have no effect on conditioned avoidance responses except at extremely high doses. In general, minor tranquilizers increase the rate of behavior normally suppressed by punishment.

The *meprobamates* were used originally as the most efficacious antianxiety agents. Meprobamate induces great reduction in motor activity and as such is a potent muscle relaxant. It never induces narcosis or the appearance of extrapyramidal effects as caused by the major tranquilizers. The major clinical use of meprobamate is to induce mild sedation to reduce psychic tension and anxiety. The most undesirable effects of meprobamate are ataxia, somnolence, and psychic confusion. It has been demonstrated that meprobamate can induce tolerance as well as physical and psychological dependence.

In recent years a new class of compounds was introduced. The *benzodiazepines* are minor tranquilizers which have gained enormously in popularity in the treatment of anxiety reactions. The use of benzodiazepines (chlordiazepoxide, diazepam, oxazepam, doxepin) results in a significant decrease in aggressive behavior accompanied by an increase in sociability. These drugs act primarily on the limbic system of the brain without major impairment in arousal. Low doses of benzodiazepines do not impair motor behavior. They possess anticonvulsant properties, and may be used (diazepam) to block the convulsions in status grand mal epilepsy.

The major clinical indications for benzodiazepines are for anxiety, conversion syndromes, and in the treatment of psychosomatic complaints such as dermatitis or diarrhea of psychogenic origin. Chlordiazepoxide has also been widely used in the management of alcohol withdrawal, delirium tremens, and acute alcoholic hallucinosis. All of the benzodiazepines can be used to attenuate a patient's fears about stressful situations. They are commonly used and abused in general medical practice. Heavy and continuous use of benzodiazepines results in psychological and physical dependence which may culminate in hallucinations and withdrawal symptoms. Other undesirable effects of

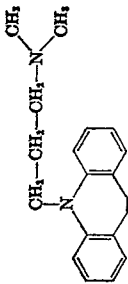
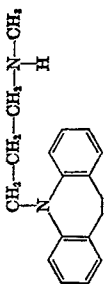
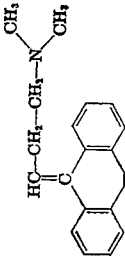
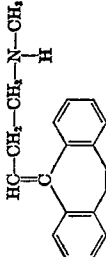
the benzodiazepines include somnolence, ataxia, disorientation, and hypotension.

Antidepressant Drugs

The antidepressant compounds (Figure 48.5) such as the *monoamine oxidase inhibitors* (MAOI) and the *tricyclic antidepressants* (TCAD) do not really qualify as stimulants since in normal animals and man they have little tendency to produce overt signs of CNS stimulation. They are used primarily in the treatment of depression or affective disorders. The first MAOI (isoniazid) was discovered by accident. It was being used in the treatment of tuberculosis, and a euphoric state was observed subsequent to the administration of isoniazid. The behavioral effects of the MAOI are neither very intense nor clearly observable in normal animals. In psychiatry the most important use of MAOI is in the treatment of depression. Today the MAOI are rarely used because of a number of dangerous side effects. They are strongly contraindicated in cases of hepatic or renal damage. They may elicit cardiac failures and cerebrovascular disturbances. Patients on MAOI therapy should be warned about taking other drugs. MAOI can interact with other drugs in dangerous ways. They potentiate the effects of most sympathomimetic amines such as amphetamine. Tyramine is a sympathomimetic found in cheeses which may react with MAOI to produce death.

The tricyclic antidepressants have largely replaced the MAOI in clinical practice. The tricyclic antidepressant, imipramine, has few effects in most normal animals or in normal man, yet it is one of the most effective compounds in the treatment of psychotic depression. The biochemical effect of tricyclic antidepressant in the brain implies that a greater quantity of catecholamines is present at adrenergic receptors. A series of clinical studies has indicated that the tricyclic antidepressants are most effective in those forms of depression that are objectified by the patient with accompanying physical discomfort, insomnia, and loss of appetite.

As in the case with MAOI, problems can result in the interaction between the tricyclic antidepressants and other drugs. For example, imipramine can potentiate the effects of amphetamine and other sympathomimetic amines. Many other side effects of imipramine

Antidepressants	Generic Name	Trade Name	Formula
A. IMIPRAMINE-TYPE DRUGS (iminodibenzyl derivatives, tricyclic antidepressants, dibenzazepines)	Imipramine	Tofranil	
	Desipramine, desmethylimipramine	Norpramin Pertofrane	
	Amitriptyline	Elavil	
	Nortriptyline	Aventyl	

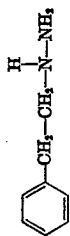
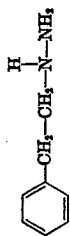
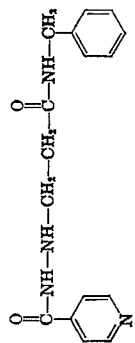
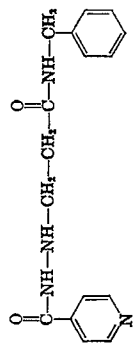
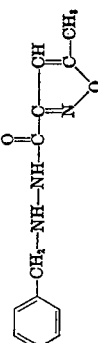
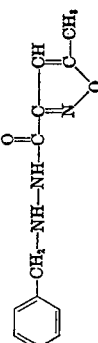
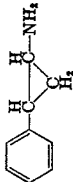
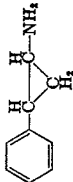
B. MONOAMINE OXIDASE INHIBITORS			
Phenelzine	Nardil		
Nialamide	Niamid		
Isocarboxazid	Marplan		
Tranylepromine	Parnate		

Figure 48.5 Antidepressant drugs. Modified from Chapter 29.2, "Antidepressant drugs," in *Modern Synopsis of Comprehensive Textbook of Psychiatry*, edited by A. M. Freedman, H. I. Kaplan, and B. J. Sadock. Williams & Wilkins, Baltimore, 1972, pp. 550 and 551. Published by permission.

are atropine-like, including dry mouth, constipation, tachycardia, blurred vision, and urinary retention. In some patients signs of CNS overstimulation do occur. Hypomanic excitation or toxic confusional psychosis can also occur.

In the early 1960's it was reported that *lithium* carbonate was a useful drug for treating the manic phases of cyclical affective disorders. This was a very useful finding for, although the tricyclics and the MAOI's were quite successfully used for treating depressive phases, the manic phases were generally unresponsive to these drugs. The several effects of lithium depend upon the ability of this compound to substitute for sodium and potassium ions, altering the organic balance of these ions, and acting as their antagonist under various conditions.

While lithium appears to be a most effective drug in the treatment of manic depressive disorders, it should be noted that it also possesses some degree of toxicity. Mention should be made of slight tremor, diarrhea, vomiting, tininitus, ataxia, and blurred vision. Subsequently there may be muscle spasms, convulsive episodes, and possible death caused by an irreversible renal damage. Such dangers make frequent evaluation of plasma lithium concentrations indispensable during the course of treatment.

NEUROBIOLOGICAL RESEARCH

Biochemistry of Schizophrenia

The possibility that schizophrenia has a genetic basis with probably a biochemical abnormality has been widely discussed in the literature and has been suggested in a number of reports. It would be encouraging if an obvious biological characteristic of schizophrenia were evident. To this date, studies indicate that while there is most likely some genetic component, the search for biochemical aberrations has not been successful. In spite of the large number of abnormal chemical findings which have been reported in schizophrenia, few have been independently confirmed. This may easily be attributed to the operation of an inordinate number of uncontrollable variables which are present in the experimental or clinical studies of schizophrenia. It should be noted that the research described here should not be viewed as

providing definitive answers. Rather, various experimental findings representing selected lines of scientific inquiry have been used to illustrate the constructive avenues in this research area.

Evidence suggesting an abnormality in schizophrenia plasma has a rather long and quite controversial history. The most extensive work dealing with an *immunological abnormality* in the blood of schizophrenics has been carried out by Heath and his associates at Tulane University. They have isolated a substance, called *taraxein*, which they claim produces abnormal EEG activity from implanted electrodes in the septum of monkeys. They also state that taraxein produces numerous behavioral abnormalities in various animals, including schizophrenic-like behavior in human volunteers. Therefore, they conclude that schizophrenia is an immunological disease in which taraxein reacts with certain antigenic foci in the brain. The evidence with regard to an abnormal plasma in schizophrenics is certainly far from conclusive at the present time. Most of the effects reported have not been thoroughly replicated, and none have been shown to be properties of plasma which are characteristic of schizophrenia. Certainly more controls are needed to determine to what extent these plasma abnormalities are caused by institutionalization, stress, or possible dietary factors.

In 1952 Osmond and Smythies established similarities between the structure of catecholamines and that of the hallucinogen mescaline. They proposed that *transmethylation*, the adding of a methyl group, was an important process in the metabolism of catecholamines. Several methylated derivatives of catecholamines produce symptoms similar to those of schizophrenia. This raised the question of whether some abnormal metabolite of the catecholamines, particularly a methylated metabolite, might possibly produce symptoms of schizophrenia, especially under stress, when catecholamines are supposedly produced in greater quantities. This concept gained credence following the observation that feeding methionine, a methyl group donor substance like MAOI, could in many cases exacerbate psychotic symptoms. Although these results have been replicated by a number of investigators using betaine instead of methionine, it is not

definitively established whether the researchers had merely imposed a new transient toxic psychosis on schizophrenic patients. Although the transmethylation theory has gained in popularity, there is no direct evidence from methyl donor feeding experiments that abnormal or excessive methylation occurs.

A related line of inquiry has elicited much interest recently. In 1962 Friedhoff and Van-Winkle reported that they had identified dimethoxyphenylethylamine (*DMPEA* or "*pink spot*") in the urine of schizophrenic patients. Since *DMPEA* is quite similar to the hallucinogenic compound, mescaline, this finding suggested that schizophrenics were in fact producing an *internal hallucinogenic toxic substance*. It should be noted that drugs such as phenothiazines used in the management of schizophrenia are known to interfere with *DMPEA* determinations. Furthermore recent investigations have uncovered the presence of pink spots in a urine extract obtained from Parkinson patients. Therefore, it appears that while *DMPEA* may be present in small amounts in schizophrenic patients, it is by no means obvious that this compound is unique to schizophrenia.

Indoleamines such as serotonin have been implicated in a number of diseases which are often accompanied by severe mental disturbances. Tryptamine excretion may have special significance in schizophrenic patients before a period of exacerbation. Increase in urinary tryptophan metabolites has also been observed subsequent to methionine administration, and it has been suggested that the conversion of tryptamine to its hallucinogenic methylated derivative may possibly occur. The work of Himwich at Galesburg Hospital seems to implicate some indoleamines in various aspects of abnormal behavior in animals. These results appear to implicate a *dysfunction in phenylalanine and/or tryptophan metabolism* in the psychoses.

In recent years, a less direct, but possibly more heuristic approach has been adopted in the search for the biochemical abnormalities in schizophrenia. One aspect of schizophrenia with possible biochemical implications is the response of schizophrenics to antipsychotic agents such as the phenothiazines. If the actions of these drugs derive from effects on the

functional abnormalities in schizophrenic patients, then a better understanding of these drug mechanisms might possibly elucidate abnormalities in the brains of schizophrenics. It has been suggested that the therapeutic action of antipsychotic compounds is related in some way to a blockade of dopamine receptors in the brain. Carlsson and Lindquist have reported that the phenothiazines block catecholamine receptor sites, whereupon a message is conveyed by means of neuronal feedback to the cell bodies. These speculations have been confirmed in studies showing that phenothiazines and butyrophenones do indeed accelerate catecholamine synthesis in proportion to their clinical efficacy.

Recent reports by Stein and his associates appear to extend this line of investigation. Several pieces of biochemical evidence suggest that *6-hydroxydopamine* is the aberrant metabolite associated with schizophrenia. This compound is an autooxidation product and metabolite of dopamine. *6-hydroxydopamine* induces a marked and long-lasting depletion of norepinephrine. When injected intraventricularly into the rat brain, *6-hydroxydopamine* similarly causes a prolonged or permanent depletion of brain catecholamines. It is important to note that chlorpromazine, the drug of choice in the treatment of schizophrenia, antagonizes the norepinephrine-depleting action of *6-hydroxydopamine*. Chlorpromazine is an inhibitor of the neural norepinephrine uptake process; hence it has been assumed that chlorpromazine prevents the depletion of peripheral norepinephrine by limiting the access of *6-hydroxydopamine* to the noradrenergic nerve terminals. The drug may well exert its central antipsychotic effect by the same mechanism. Stein and his colleagues have shown that intraventricular injections of *6-hydroxydopamine* caused marked and long-lasting deficits in brain self-stimulation and other rewarded behaviors in the rat. They postulate that schizophrenia is also best characterized by a deficit in goal-directed behavior and a marked deficit in the capacity to experience pleasure. This, they state, may be due to an *impairment of the noradrenergic reward system*. They further demonstrated that the behavioral deficits, as well as the depletion of brain norepinephrine induced by *6-hydroxydopamine*, are prevented

by prior treatment with chlorpromazine in rats.

Since damage to central adrenergic neurons can be estimated by measuring the dopamine- β -hydroxylase (DBH) in various regions of the brain, they set out to conduct postmortem studies from the brains of schizophrenic patients and normal controls. They found a significant reduction in the DBH activity of the schizophrenic group in all brain regions examined. Their findings are consistent with the hypothesis of impaired noradrenergic "reward" pathways in schizophrenia. Since these results are quite recent, replications have not yet been reported and final assessment is still premature.

Although it would not be accurate to state that a definitive understanding of the biochemical aberrations of schizophrenia has taken place, substantial progress has nonetheless been made. Of the various biochemical approaches to the study of schizophrenia, the investigation of brain neurotransmitter interactions with antipsychotic agents appears to be most productive. One enormous difficulty in this area of research is the fact that the crucial process of diagnosis is based entirely on subjective estimates. A schizophrenic population certainly seems to contain several disease entities overlapping with one another. Their inadequate separation and objective identification not only give rise to inexact diagnosis but make any kind of laboratory research much more difficult than in more definable disease conditions.

Biochemistry of Affective Disorders

In recent years there has been a gradual accumulation of evidence suggesting a relationship between the affective disorders (depression-mania) and brain biogenic amine metabolism. It has been reported that drugs which cause depletion and inactivation of norepinephrine centrally produce sedation or depression, while drugs which increase or potentiate brain catecholamines are associated with behavioral stimulation and generally exert an antidepressant effect in man. These findings led to the *catecholamine hypothesis of affective disorders*. This hypothesis states that depressions are associated with a relative deficiency of catecholamine (particularly norepinephrine) at functionally important adrenergic receptor sites in

the brain. Elation or manic phases may be associated with overproduction of these amines.

Chemical methods for the estimation of catecholamine tissue concentrations have shown that norepinephrine is localized in brain areas such as the hypothalamus and the limbic system, brain areas which are concerned with emotional behavior. There is indeed good evidence to support the thesis that the antidepressant effects of both the MAOI and the tricyclic antidepressant drugs are mediated through the catecholamines, and that, by possibly different biochemical mechanisms of action, both of these classes of drugs increase the active catecholamines at adrenergic receptor sites. It is interesting to note that reserpine, a drug which induces depression, also depletes animal brains of catecholamines. The reversal of reserpine sedation by tricyclic antidepressants has been amply demonstrated, and has been shown to depend upon the availability of catecholamine stores and the rate of release of these stores by reserpine. A number of studies have shown that clinically effective doses of MAOIs decrease vanillylmandelic acid (VMA), the major urinary metabolite of norepinephrine and epinephrine. Schildkraut and his associates have found that VMA excretion is decreased in depressed patients during treatment with antidepressant drugs.

Some investigators have challenged the catecholamine hypothesis, pointing out that much of the evidence is indirect and could easily implicate other neuroregulatory agents as well. Some researchers have speculated that serotonin may be an important substance involved in the determination of mood changes. Recent physiological and pharmacological evidence supports the long-standing observation that depression does not at all represent a single homogeneous entity. An effect of genetic factors on the response to antidepressant drugs has also been reported recently. It is quite feasible that the catecholamine hypothesis of affective disorders may ultimately be confirmed for certain clinical subgroups of depression, and not for other clinical subgroups. Whatever the ultimate outcome, the heuristic value of this hypothesis has provided many lines of investigation for the researcher, and has given hope for the development of better treatment modalities for depressive illness.

ELECTROPHYSIOLOGY AND PSYCHOPATHOLOGY

Evoked Potential

In an effort to discover the physical bases for psychiatric disorders, a great deal of interest and attention has been focused on electrophysiological techniques to elucidate the nature of various psychopathological dysfunctions. A wealth of evoked potential data on normal subjects has been accumulated, thus providing a rich background against which pathology can be examined. In recent years, evoked potential research has been applied to the area of psychopathology with some success in discriminating between normal and pathological groups. In this chapter, I will not attempt to present an exhaustive review of the literature, but rather to outline briefly the major trends of research.

Differences in amplitudes of evoked potentials have been obtained between normal and psychiatric groups. Taken at face value, this would imply less activation or arousal in the patient group. However, since the signal-averaging process (described in the previous chapter) adds responses algebraically, the more similar successive wave forms are to each other, the larger the resultant responses, while more variable wave forms would cancel each other out. Schizophrenics have been found to exhibit lower evoked potential amplitudes as a result of high variability of response. This finding suggests greater background "noise" in schizophrenics, which is indicative of greater distractibility and an inability to focus attention. The highest variability in evoked potential responses has been reported for low intensity stimulation. This will be discussed in more detail later in the chapter, when we deal with intensity-response gradients.

Callaway and his co-workers have systematically investigated evoked potentials in schizophrenic patients, and have described their inability to establish "sets." "Set" in this study refers to the strategy adopted for categorizing sensory inputs and directing action. Schizophrenics have a tendency to develop multiple, unarticulated, minor sets, known as *segmental sets*. Thus the differences in potentials evoked by two trivially different tones were used to assess the degree of preoccupation with ordinarily disregarded details. Using a correla-

tional statistical procedure, they found that schizophrenics manifested a reduced similarity between averaged responses evoked by two tones, while controls had similar evoked potentials to both tones. However, these findings were later explained in terms of the greater variability of responses exhibited by schizophrenics, rather than their persistent concentration on minor details, as their responses are found to differ even when they are presented with the same stimuli. Thus, it has been concluded that the major distinguishing characteristic of the evoked potentials of schizophrenics is their moment to moment variability and general inconsistency in responding to identical stimulus situations. Furthermore, evoked potential variability among schizophrenics is highest in those patients displaying the most variable and incorrect perceptual performances. This variability in brain responding decreases with increased improvement in the schizophrenic's condition.

The well known concept of the cortical excitability cycle in neurophysiology depends on amplitude measures of cortical potentials. Typically it is based on the observed phenomenon that the amplitude of a potential evoked by a second stimulus varies as a function of the temporal relationship to a potential evoked by a first stimulus. Recovery time experiments use paired stimuli to investigate brain reactivity and study the effect of changing the time interval between the two stimuli of the pair. The degree of recovery is conventionally the ratio of the magnitude of the second response (R_2) relative to the first (R_1), or R_2/R_1 . The change in reactivity with respect to the interstimulus interval is the *recovery function* or *excitability cycle*.

Charles Shagass has applied this technique to the study of psychopathology in order to uncover deviations in central nervous system reactivity in patient groups. He found that certain groups of psychiatric patients have depressed somatosensory recovery curves, whereas other psychiatric patients are indistinguishable from those of non-patients. Recovery functions obtained to intense stimuli were found to be depressed in the psychiatric categories of schizophrenia, personality disorders, and psychotic depressions, particularly in the early phase up to 20 milliseconds; on the other

hand, patients with anxiety, neurotic depressions, or psychophysiological reactions do not have recovery curves different from those of non-patients. However, it became apparent to the researchers that the intensity used to determine recovery functions was a critical factor. When weaker stimuli were used, it was found that patients exhibiting reduced recovery with intense stimuli displayed supernormal recovery to weak stimuli. Shagass has suggested that the processing of weak and strong stimuli is dependent on different mechanisms, thus accounting for these differences in central nervous system excitability.

Therefore, it would seem that in studying the relationship between psychopathology and evoked potentials, the *intensity-response gradient* is critical in determining the resultant differences between normal and psychopathological central nervous system functioning. An investigation of this factor has been systematically undertaken in Monte Buchsbaum's laboratory, as a direct application of the work of Petrie to evoked potential research. Petrie developed a personality perception continuum based on individual differences in the perception and processing of incoming sensory stimuli. In order to tap differential responsivity she used the Kinesthetic Figural Aftereffect Test (KFA), and distinguished two different types of individuals at the extremes of the continuum, namely *augmenters*, who tend to amplify sensory stimulation, and *reducers*, who tend to attenuate stimulations. Augmenters tend to overestimate size, overreact to pain, overrespond to high intensity stimulation, and tolerate sensory isolation well. Reducers, on the other hand, tend to do the reverse—underestimating size, responding to intense stimulation less acutely, and tolerating deprivation poorly.

The processing of different stimulus intensities was further investigated by Buchsbaum's group using cortical evoked potential indices. In most individuals, the evoked potential amplitude has been found to have a direct relationship to the intensity of stimulation, within a moderate range of stimulation. KFA augmenters exhibit an exaggerated increase in evoked potential amplitude with increasing stimulus intensities, whereas subjects who perceived high stimulus intensities as less intense (as measured by KFA scores) also manifested

decreases in their visual evoked potential amplitudes. In order to measure the extent of the relationship between stimulus intensity and evoked potential amplitude, Buchsbaum devised an index, taking the slope of the co-vari-
ance between these two variables. A high slope is indicative of augmentation, whereas a low or negative gradient indicates evoked response reduction.

In a series of studies in Buchsbaum's laboratory, this technique was used to assess patients with psychiatric disorders. It was found that bipolar (manic-depressive) patients exhibited extreme augmentation, regardless of whether they were in their manic or depressed phase, whereas unipolar (depressed) patients did not show this extreme responsiveness, tending to exhibit corresponding reductions in their evoked potential amplitudes. A further investigation of bipolar depressed patients indicated that their augmentation is caused by their unusually slight response to the dimmest intensity flash, thus creating an ascending intensity-response gradient. It can be concluded from these results that bipolar depressed patients may be overattenuating sensory experiences to weaker stimuli. Bipolar depressives exhibit a greater degree of augmentation because they not only underrespond to weak stimuli, but also display an exaggerated increased responsiveness to stimuli at the highly intense range. Schizophrenic patients were found to differ from normal controls only with respect to their variability scores, particularly in the two dimmest flash intensities.

Evoked potentials seem to be most susceptible to attentional factors at the lower portion of the stimulus intensity continuum, and schizophrenics show their greatest dysfunction with respect to weak sensory stimulation. Thus it can be concluded from all the foregoing approaches to the study of schizophrenia, that when attentional factors are important in determining evoked potential configurations, those of schizophrenic patients will be most deviant from those of normals.

While evoked potential techniques have been successfully applied to the area of psychopathology, it is still too early to assess the practical usefulness of these methods for clinical purposes. Thus, great caution is suggested in interpreting the results obtained, and it remains for

future research, with refinements in techniques and methodology, to determine to what extent this approach will be of practical value in establishing an objective index of psychopathology.

Sleep and Dreaming

With the development of sophisticated techniques for studying sleep, scientists have begun to investigate the possible sleep disorders of schizophrenia and depression. In the normal individual there is a remarkable consistency in the pattern of sleep, even though there is quite a bit of variability from individual to individual. Recent work with geriatric subjects indicates that there are sleep changes which are the result of age. With the passage of years, the continuity of good sleep tends to be increasingly broken by transient awakenings. The proportion of deep sleep decreases and so does the total amount of sleep.

Sleep studies of depressed patients have established that the subjective reports of these patients about insomnia were indeed corroborated by a greater number of awakenings throughout the night. Depressed patients also show an increase in Stage 1 and Stage 2, which are most like waking EEG, whereas Stage 3 and Stage 4 are markedly decreased. While the total time spent in REM sleep is also altered in depressed patients, both an increase and a decrease in REM time have been reported. Acutely depressed patients commonly report a temporary increase in REM time. The 90 minute cycle normally observed in healthy subjects may often be changed to a 30 minute cycle in the depressed patient. These sleep cycles have usually a very regular sequence, proceeding from wakefulness, to light and fast wave sleep, to deeper and slow wave sleep, with a reemergence of faster patterns followed by a REM phase. In the normal subject there are four or five such cycles, while in the depressed patient 10 or more such cycles may be observed. It is clear that in depressed patients the recurrent cycles of sleep stages are shortened considerably, resulting in a restless sleep often interspersed with awakenings. In general, the more severe the depression, the greater the tendency toward these sleep abnormalities.

It has been reported that the manic phase of the bipolar manic-depressive disorders is char-

acterized by reduced total sleep with a reduction in the absolute amount and percentage of REM sleep. Since these patients sometimes continue in a manic state for months at a time, it might be postulated that there exists a reduced REM sleep pressure, or reduced need for REM sleep, in mania. The reduced need for REM sleep is probably related to the often noted reduced need for sleep in general in mania.

The relationship between sleep disturbances and schizophrenia has not yielded clear-cut results. Originally it was reported that differences in REM sleep parameters did not exist between schizophrenic patients and normal subjects. However, Feinberg and his colleagues did report significantly less REM time in schizophrenics ill less than one year, compared to those ill two years or longer. They also reported that some actively ill schizophrenics had extremely short REM latencies, i.e. the time it takes for the first REM to occur from the point at which the person falls asleep. Furthermore, they reported that hallucinating schizophrenics had more eye movements during REM sleep than non-hallucinating schizophrenics, although both of these groups of actively ill patients had fewer eye movements than the control groups. There was a striking variability among patients, in both the amount of time spent in the various sleep stages and the degree to which these stages were either organized or disorganized. In some patients REM sleep was very fragmented and frequently interrupted by Stage 2 sleep.

Longitudinal studies of schizophrenic patients have revealed that there are times in the course of the schizophrenic illness when sleep in general and REM sleep in particular seem highly abnormal in one way or another. There is indeed no question that the acute phase of a florid schizophrenic psychosis is accompanied by profound alterations in the sleep patterns. REM sleep often is the most profoundly affected, usually in terms of reduced times and abnormally low or high frequency of eye movements. Finally, it has been shown that, in contrast to normals, schizophrenics do not respond to REM deprivation with an increased pressure for REM sleep. Therefore it appears reasonable to look at possible relationships between normal REM mechanisms and possible malfunction-

tions of these mechanisms for a better understanding of the schizophrenic process.

Biological Rhythms

Biological rhythms can be defined as biological events which are amenable to frequency synchronization by an environmental event, but which persist in the absence of that *synchronizer*. For example, the light-dark cycle is the environmental event or "timekeeper" that synchronizes circadian (24 hour) rhythms through the hypothalamic-pituitary and the adrenal steroid systems. "Night people" differ from "day people" in using a different part of the light-dark cycle to synchronize their circadian rhythms. In the complete absence of external synchronizers, a rhythm may drift, gaining or losing a few minutes each day, a situation known as *free running*.

Charles Stroebel has hypothesized that a free running condition may be responsible for certain forms of insomnia, as well as certain psychosomatic symptoms. Abnormal biological rhythms have also been implicated in various regressive, psychotic behaviors, as well as in accident proneness. In addition, the response to drugs and to infection varies during a 24 hour period, the greatest sensitivity occurring around 3 to 4:00 A.M. Insulin reactions are the greatest at this time, and heart attacks and asthmatic episodes occur most frequently at this time. Other research, particularly by Aschoff, has indicated that both day-workers and night-workers make the greatest number of errors around this same time.

We are only just beginning to systematically investigate the possible relationships between abnormalities in biological rhythms and the various syndromes of psychopathology. Nevertheless, this new science of chronopsychophysiology seems to hold considerable promise for the future. To quote Charles Stroebel:

"Except for the catecholamine hypothesis for affective disorders, the replication status of virtually every physiological correlate or explanation of mental disorder is uncertain at present. Findings in the original laboratory are only rarely confirmed in a second setting. . . . Some major source of previously unidentified variance must be present in these studies to account for the discrepant findings. The ubiquitous nature of rest-activity disturbances in human emotional illness, coupled with their ap-

pearance as a common denominator in most models of psychopathology, clearly make biological rhythm variation a possible candidate for the missing variance."^{*}

SUGGESTED READINGS

See previous chapter, "Brain and Behavior: A biological approach."

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^{*} From Stroebel, C. F. Chronopsychophysiology. In *Comprehensive Textbook of Psychiatry*, edited by A. M. Freedman, H. I. Kaplan, and B. J. Sadock, ed. 2, vol. 1, p. 173. Williams & Wilkins, Baltimore, 1975. (Quoted by permission.)