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Psychopharmacologic Drugs

Harold E. Himwich

The last few years have seen the increasing use of a new group of drugs effective for overactive psychotic patients and presenting interesting and important differences from procedures and drugs previously employed in the management of individuals with such behavioral disorders. In fact, in order to give an appropriate name to these drugs, it was necessary to invent a nomenclature. Many terms, all emphasizing one or another aspect of the actions of these drugs, have been devised. The one most frequently used is *tranquilizer,* indicating a sedative or calming effect without enforcement of sleep. Others are *ataraxic* (*1*), denoting peace of mind, and *neuroleptic* and *neuroplegic,* indicating diminutions in the intensity of nerve function. This group of drugs, however, may be regarded as an advance guard of a long-awaited pharmacologic attack not limited only to hyperactive disturbed patients, but also to be directed against other types of behavioral disorders. To this division of drugs the term *psychotropic* (*2*), or action on the mind, has been applied. *Neuropharmacologic* refers to the branch of pharmacology to which these drugs belong. The title *psychopharmacologic drug* (*3, 4*), possesses certain advantages, for it indicates a medicine which influences the mind by affecting its morphologic substrate, the brain.

The chief usefulness of the new drugs, which at present lies in the field of psychiatry, is being extended into the many medical and surgical specialties. It is true that a drug not only changes favorably the malfunction of the organ for which it is intended but also acts, perhaps to a lesser extent, on the entire body. Either indirectly, by their influence on the brain, or by their influence on the peripheral nerves, the new drugs exert potent effects on the viscera of the body, including the gastrointestinal tract and the cardiorespiratory system and the endocrine glands.

But the impact of these new drugs has extended far beyond their immediate practical use in the management of disease. They are also employed by the clinical investigator who is seeking to unravel the tangled skein of abnormal behavior as well as by the psychologist who delves into intricacies of accepted normal patterns. Neurochemists and neurophysiologists have taken advantage of the tranquilizers to use them as tools in their investigations and meanwhile are uncovering their physiological actions in the brain and elsewhere in the body. These studies, made on man and lower animals, permit an analysis of the structure and function of the central nervous system, impossible before. Not that the methods are new, but the tranquilization resulting from the application of these drugs has not been previously observed. Perhaps most important, the new drugs may aid in the production of a desirable change in our culture and remove mental disease from the field of mysticism and superstition. They may convince the public that mental disease is not a thing to be ashamed of and that it should be placed in the same category as any other disease which can be treated by medical means.

Clinical Aspects

At this time it is hardly necessary to emphasize the magnitude of the problem of mental disease. The title of Gorman's recent book, *Every Other Bed* (*5*), is suggested by the fact that half of the sickbeds in our country are occupied by mental patients. The financial requirements for the maintenance of these hospitals are correspondingly great. The money comes chiefly out of the taxpayers' pockets. Only comparatively wealthy families can bear the cost of maintaining one of their members in a private institution.

The growing population of our mental hospitals indicates that advances made prior to the advent of new drugs were not adequate to cope with the problem of mental disease. Much was left to be desired, therefore, from the therapeutic viewpoint. Psychoanalysis is a better weapon in the management of the neuroses than of the psychoses. Electroshock is a comparatively severe procedure, for electrodes are applied to the temples of the patient and a brief, measured current is passed through his brain. The patient becomes momentarily unconscious and undergoes a convulsion. Electroshock greatly benefits patients with depression and is of value in the management of excessively hyperactive patients to maintain the uneasy status quo which characterizes hospitals not using tranquilizing drugs. Insulin hypoglycemia appears to be more effective than electroshock for certain types of schizophrenia but requires highly trained physicians and is costly. In insulin hypoglycemia, the patients receive doses of insulin large enough to reduce the level of sugar in the blood. The brain is thus deprived of its chief foodstuff, and the patient sinks into coma. Another method for treating the distraught patient is to stupefy or anesthetize him with an adequate dose of one of the barbiturate drugs.

Though the immediate situation can thus be met, it is not necessarily followed by improvement in behavior. With the tranquilizing drugs, however, the patient is improved without significant interruption of consciousness—a highly desirable goal in the successful therapeutic process. Even if his manic excitement is extreme and if he must be given a correspondingly large dose, which renders him

The author is director of the research division of Galesburg State Research Hospital, Galesburg, Ill.

sleepy, he can be easily awakened and in general can go on with his prescribed hospital activities. With the new drugs, more patients have been returned to society from the state hospitals than with any previous therapeutic regime. We therefore seem to be entering a new era in the treatment of mental disease, and it remains to be seen how far this advance will take us.

Schizophrenia

What are the mental disorders to which these new drugs are applied? The field of mental disease is complex. It is not a case of a single mental disease. On the contrary, there are many categories, and each one includes several varieties. Schizophrenia is the chief disorder met with in our psychotic population. We do not know the cause of schizophrenia, and this makes it necessary to limit our attack on it to empirical methods. But this is not unusual in the history of medicine, for the majority of therapeutic successes were produced on an empirical basis; witness the use of quinine long before the plasmodium of malaria was discovered.

Because the origin of schizophrenia is not known, that disease must be characterized chiefly by its symptoms. These are many and varied and, in general, may be divided into four types, which may change and merge into each other. The clinical picture is therefore not constant, and at different times the signs of one or another of these four types predominate. One of the characteristics of schizophrenia is emotional blunting, and this is a prominent change in the *simple* type. The psychiatrist is quick to observe the diagnostic paucity of facial expression and regards it as an outward lack of emotional expression or affect. Some individuals with inadequate personalities, who lose one job after another, belong to this group of patients. Sometimes the patient wears a silly and inappropriate grin. If such a patient, like Mr. M. on one of our wards, exihibit restless hyperactivity, at least that aspect of his disorder can be corrected by a tranquilizing drug.

An abnormality of the thought process is another characteristic of schizophrenia and is developed most highly in the *hebephrenic* type. Sentences spoken may have meaning for the patient but to others are neither coherent nor logical. In the most serious distortion of the thought process, the spoken word ceases to assume sentence form and is called "word salad." Mrs. H. replies to all questions with the unintelligible statement "16-21 telephone pole." That phrase includes her usual conversational limits. After receiving a new experimental tranquilizer, she informed us, in well constructed sentences, that she was born in a small village, consisting of six homes, and that her home was situated near a telephone pole numbered 16-21.

Delusions or false ideas and hallucinations, or false sensory impressions, are characteristic of the *paranoid* type. Unlike the utterances of the hebephrenic, which cannot be comprehended by the physician, those of the paranoid patient are readily understood but reveal lack of relation to reality. Mrs. G., one of the patients in our hospital, has suffered intensely for a long time from well-developed delusions of a gigantic "crime ring" which is out to get her, even penetrating into the confines of the Galesburg State Research Hospital. Recently, when she was receiving a test drug, a new serenity was observed in her demeanor. When asked about the "crime ring," she smiled, made a deprecating gesture with her hand, and said it did not bother her any more. In fact, she doubted whether it existed. This is an evident amelioration and was maintained as long as the patient remained on this medication.

In general, hallucinations, which also occur in mental disease other than schizophrenia, yield more readily to these drugs than do delusions. Mrs. S. has placed cotton plugs in her ears for many years to shut out the voices that were so hostile and were giving her such a bad time. During a period in which she was receiving one of the test drugs, she came in for an interview without the cotton plugs in her ears. The voices no longer tormented her, or at least not to the same extent as previously.

In the *catatonic* type of schizophrenia there are marked distortions of motor activity. Stupor is one aspect, and whether with or without stupor, posturing and the assumption and maintenance of bizarre positions and mannerisms are observed. After one has raised the arm of such a patient, the patient may keep his arm up for a long time. When he walks he may change his direction by turning at right angles only. A catatonic may also go into a furor, a period of wild overactivity, and become highly destructive.

Here we come to a very important use of tranquilizing drugs—namely, a calming action which is being applied to various kinds of destructive patients and not only to combative schizophrenics. Taking chlorpromazine and reserpine as examples, we find two different kinds of pharmacologic actions characteristic of this group of drugs. The first, which counteracts such symptoms of schizophrenia as dissociated thought, hallucinations, and delusions, has just been described. The second drug effect is of a different type and causes a general toning down of emotional reactions and physical activity. If the ability to correct the thought processes of the hebephrenic and the paranoid patients is regarded as a specific antipsychotic power of chlorpromazine and reserpine, then the use of these drugs to combat excessive activity may be considered a nonspecific result. As has been pointed out by Barsa, these two results do not necessarily occur together; either may be observed without the other (*6*). The calming action of the drug cuts across the diagnostic categories of mental disease, for it is employed in all types of overactive patients, irrespective of the diagnosis. It can even be given to an individual who has no behavioral abnormalities, and in such a normal person a reduction of activity and a diminution in the response to environmental stimuli will be noted.

Use with Hyperactive Patients

It must be remembered that patients with psychoses are sent to psychiatric hospitals most often because they display behavior which is not socially compatible. Psychotics who can carry on outside the hospital gates are not necessarily sent to such institutions. When a patient presents behavioral disorders that menace the life and limb of other individuals as well as his own, it is essential that he enter a hospital where he can be properly treated.

Types of hyperactive patients who secure benefits from this sedative influence include the manic, whose disorder is chiefly that of mood or affect, which is greatly elevated; the schizoaffective, in whom abnormal elation is associated with deterioration of mental abilities; and the patient with a toxic psychosis, as in delirium tremens. These patients have their hyperactivity and abnormally increased initiative reduced to more reasonable levels so that they cease to wear themselves out and are no longer a trial to the ward attendants and their fellow-patients. This is a tremendous advantage for hospitals with highly disturbed patients. Isolation rooms, where a dangerous patient was formerly incarcerated, are no longer required. Mechanical restraints, sedative wet packs, electroshock, and deep barbiturate medication are prescribed only infrequently. As a result,

many of these patients can now be liberated from physical restraints as well as from the psychological constraints of a locked ward. The ward doors have been opened, and privileges have been given to many patients, permitting them to traverse hospital halls and attend various therapeutic activities—recreational, occupational, and industrial. Thus, treatments have not only been made more humane, with greater benefit to the patient, but have also effected improvement in the staff morale of the mental institutions. A hospital atmosphere is being established in state institutions to an extent that was not previously possible. One now feels that a mental hospital is not a place for the expedient management of an intolerable situation but rather a treatment center for the amelioration of disease, like hospitals devoted to other kinds of disorders.

One patient will receive most benefit from a certain tranquilizing agent, and a second from another. This is not the place to compare the therapeutic efficacy of the various tranquilizers, especially in such an early state of their development, but it is obvious that some produce a deeper sedative action than others. Each of the accepted tranquilizing drugs, when given in adaquate dosage, is of aid to disturbed patients, but our experience (*7*) with hyperactive patients has been widest with chlorpromazine (*8*) and reserpine (*9*), drugs which have profound sedative or calming actions. But there is no way to foretell which drug will be most effective for a given patient, and therefore the psychiatrist should be prepared to employ any one in an emergency. Some, like azacyclonol (*7, 10*), can bring about better social adjustment, so that the atmosphere on the ward becomes friendlier, especially among patients who are only moderately disturbed. The choice of a tranquilizing drug must be decided empirically; the best one for a given patient can be found only by the process of elimination.

The most dramatic improvements are observed in the first acute attack or in the chronic patient who has developed an acute exacerbation of his disorder. At our hospital, however, tranquilizing drugs have also been found to exert marked benefit in patients with schizophrenia of long duration—that is, chronic schizophrenia, as documented in the case histories presented above. But the improvements were mainly seen in patients with obvious active schizophrenic processes—those who had hallucinations and delusions or who were hyperactive, agitated, and tense. Blocked, retarded, and apathetic schizophrenics are more difficult to help. This greater intractability of the so-called "burned-out" patients, who have survived a more active phase of their disorder and who seem free of schizophrenic symptoms and excessive physical activity, is also observed with previous methods of treating deteriorated, passive schizophrenics.

Similarly, senile patients who are irritable, quarrelsome, and apprehensive show greater improvements than patients who exhibit negativism, apathy, and withdrawal. It would appear that tranquilizing drugs are less valuable for the senile patient who does not display signs of agitation. For the same reason, depressions not accompanied by anxiety and tension are less apt to be ameliorated by a psychopharmacologic agent. The treatment of the passive patient is therefore more difficult. In individuals with hypertension, apparently free from behavioral abnormalities, the use of these drugs may lead to a worsening of the mental condition if the profound sadness of a depression is induced.

Psychoneuroses

Mental diseases milder than the psychoses are the psychoneuroses or neuroses, and in some forms of these disorders tranquilizing drugs are of value. In contradistinction to the psychotic patient, the neurotic acts, by and large, as if reality has the same meaning for him as for most people. He is not subjected to persecution by a "crime ring" and does not have other bizarre experiences. He suffers, however, from great anxiety, which may not be readily identified with any particular object. Yet this anxiety is expressed in bodily symptoms: palpitation, breathlessness, weakness of limbs, tremors and pains that plague him. For that reason, in some patients, the anxiety is associated with a particular organ: the heart, the lungs, or the stomach. Neurotics who must be active in order to escape their disturbing fears are usually not helped by tranquilizers. In contrast, those with internal tensions, who cannot sleep despite use of such sedative drugs as the barbiturates, often gain relief from a psychopharmacologic agent.

For the "Normal" Population

These drugs also exhibit decided usefulness for the members of our so-called normal population who are subjected to intolerable stress. A businessman with a demanding and unreasonable supervisor or a woman with insufficient funds to run her home according to her ideal standard can gradually build up an emotional impasse so that perspective is lost, as the darker side of the situation is increasingly magnified, until a state of panic may develop. Restoration to a more objective evaluation of the situation may be secured by psychotherapeutic discussions with a physician, and an important action of tranquilizing drugs is to render the patient more receptive to other kinds of therapy. In fact, at times a psychopharmacologic drug may be essential for a successful psychiatric interview. Ephemeral disturbances—for example, the anxiety and tension aroused by an impending surgical operation—can be pleasantly dissipated by a small dose of a tranquilizing agent.

Side Reactions

I have not mentioned the matter of occasional undesirable side reactions of the new drugs (*11*). In the first place, the drugs cause much less inconvenience than the mental disorder of the psychotic patient. Some patients can be managed by a temporary reduction of dosage—for example, a patient who exhibits an excessive fall of blood pressure. Others can be treated by a drug which counteracts the undesirable changes; a tremor of the hands resembling that of Parkinsonism can be relieved by an anti-Parkinson drug. Patients with brain injury are more likely to exhibit a convulsion than those with an intact organ (*12*). The production of lactation and menstrual changes by chlorpromazine and reserpine and the power of the latter to impair libido in the male are subjects for research. Fortunately, serious complications occur only rarely. A small number of patients develop jaundice, a sign of liver involvement. In some instances there may be a reduction of white blood cells. A failure in the formation of these cells is dangerous because it diminishes the resistance of the body to disease. But, on the whole, the treatment of thousands of psychotic patients with the new drugs has been relatively safe, because most are resistant to these side effects. This resistance, however, does not apply to neurotic patients, who seem more sensitive to side reactions and even on comparatively low dosage complain of fatigue, prostration, dizziness, and nausea.

It is apparent, then, that state hospitals have been placed on a much better basis by the use of the tranquilizing drugs, especially in the management of highly disturbed patients. The same, however, can-

not be said of psychiatrists whose private practice is concerned chiefly with neurotic patients. But it is also true that many patients who were formerly sent to a mental institution can now be treated outside the hospital gates. Some psychotic individuals can continue to lead productive lives and need not go to a psychiatric hospital at all. During the acute phase, they may be controlled by tranquilizing drugs in a general hospital and later may be maintained outside the hospital on appropriate doses of these medicines. On the other hand, apathetic psychotics who are not in conflict socially but who are rather withdrawn, inactive, and without signs of agitation, usually cannot be raised to a higher adaptive level. They are still the despair of the psychiatrist. In evaluating the present clinical position of the psychopharmacologic drugs, it must be understood that the production of tranquilization, though a desirable end in itself, also aids other forms of therapy. A potent factor in the successful treatment of a patient with disorganized or disturbed behavior is a satisfactory relationship with a psychiatrist, and an important result of tranquilization is the facilitation of such a beneficial relationship.

Neurohormonal Changes Caused by Reserpine and Chlorpromazine

A lead for the pharmacologic attack on schizophrenia comes from a study of indole-containing substances. Not only serotonin but also the tranquilizer reserpine and the psychotomimetic lysergic acid diethylamide (LSD) contain the indole nucleus (see Fig. 1). The idea that indoles are associated with schizophrenia is not new (*13*). In a similar vein, suggestions have been made that serotonin plays a part in brain function (*14*). A clinical analysis of this problem became available in 1954 with the paper of Hoffer, Osmond, and Smythies (*15*). These experimenters knew that an adrenaline solution which had become pink after standing in the light for a long period of time had exerted psychotomimetic effects. They also drank a solution containing impure adrenochrome and succumbed to its influence to the extent of revealing schizophreniclike changes in their behavior. They therefore thought that the pink solution might contain a breakdown product of adrenaline, similar to adrenochrome in being indolic in character, and pointed out that some indole-containing substances affect behavior adversely. Thus, again we have the suggestion of the pathogenic importance of indole-containing substances. However, it should be pointed out that not all such compounds evoke aberrant behavior. Moreover, drugs with entirely different chemical structures—for example, hashish—are psychotomimetic in action. Nevertheless, it is instructive to examine the effects of serotonin.

The experiments of Welsh (*16*) showed that in the clam *Venus merceneria* the accelerator nerve of the heart, for which serotonin is the chemical mediator, is inhibited by LSD. Gaddum and Hameed (*17*) have demonstrated the antagonism of LSD to the peripheral action of serotonin in mammals and wondered whether or not this antagonism might not also apply in the brain. Woolley and Shaw (*18*) made the bold hypothesis that LSD produced behavioral abnormalities by interfering with the physiological actions of serotonin in the brain. According to these investigators, LSD is enough like serotonin to be taken up by the serotonin receptors in the brain, yet is different to the extent that LSD fails to evoke serotonin effects.

The Rockefeller workers used the lock-

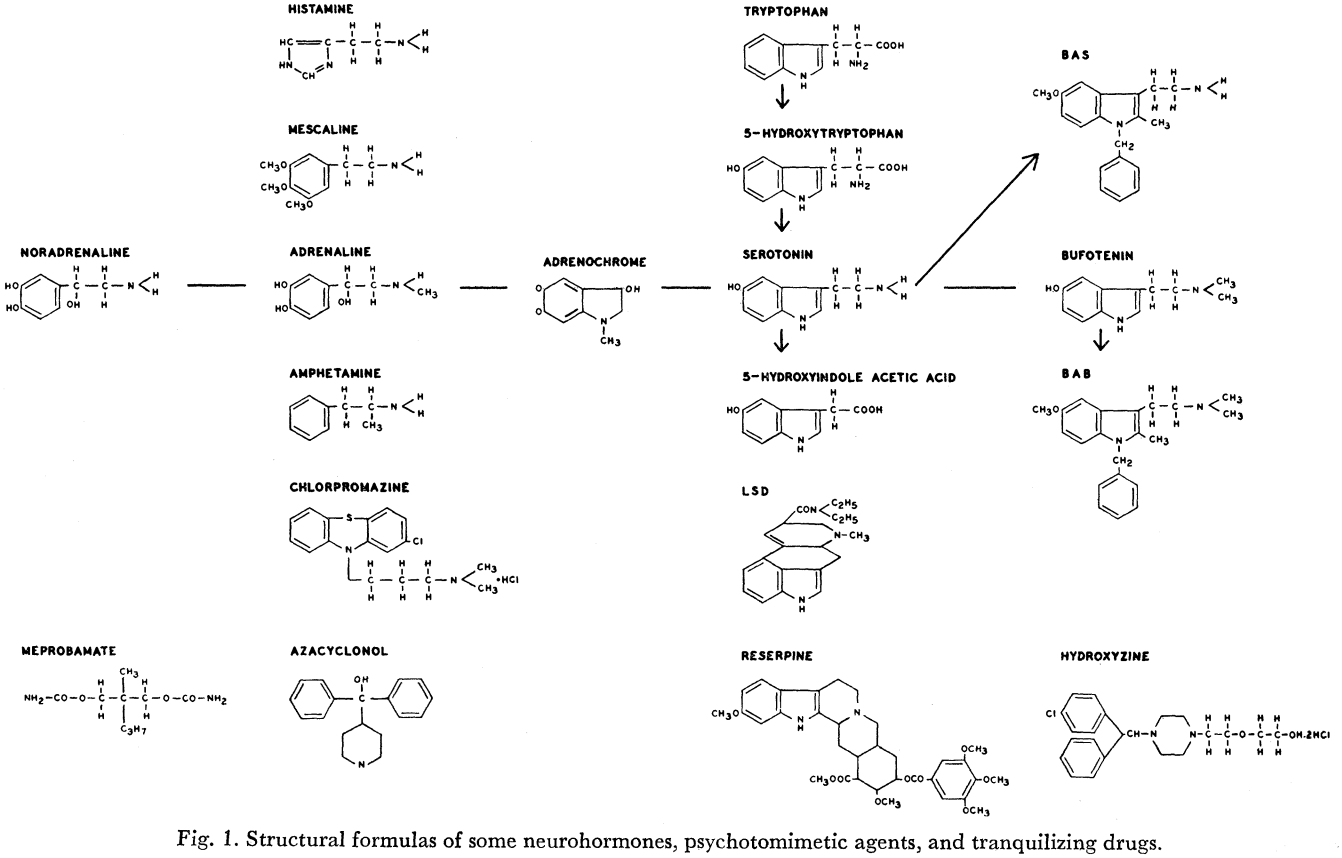


Fig. 1. Structural formulas of some neurohormones, psychotomimetic agents, and tranquilizing drugs.

and-key analogy: LSD could be introduced into the same lock as serotonin but, in contrast, could not be used to turn the lock. This suggested, of course, that mental aberrations are produced by an inadequate amount of serotonin at its site of action, the receptors with which serotonin combines. But it is also possible that there may be an excessive concentration of serotonin in some forms of mental disease, and in a later paper these workers showed that LSD could also act like serotonin and, for example, increase the effects of that brain hormone to raise the blood pressure of anesthetized dogs (*19*). Costa (*20*), in our laboratory, found that LSD can either diminish or increase the effects of serotonin, depending upon its concentration. The serotonin-evoked contraction of a rat uterus is antagonized by LSD in a solution containing 1.0 microgram per liter but is facilitated by that psychotomimetic agent when its concentration is reduced to 0.2 microgram per liter or less. The latter result suggests that an excess of serotonin, rather than a deficiency, is a disturbing factor in mental disease. In the present status of these investigations it is not possible to decide between these two alternatives. In fact, both may be correct, but each may apply to different kinds of abnormalities.

Reserpine, which is so valuable in the management of combative destructive patients, reduces the concentration of serotonin in the body (*21, 22*). Furthermore, only those *Rauwolfia* alkaloids which are tranquilizers have this depleting action in the stores of serotonin (*23*). According to one explanation, the competition between the drug and serotonin displaces the latter from its receptors and, as a result, the neurohormone is eliminated from the depots in the brain and other parts of the body. Restoration of serotonin to normal levels is protracted. After a single dose of reserpine was injected into a rabbit, the brain serotonin was depressed to 10 percent of normal within 4 hours and remained at this low level for 36 hours, after which it rose slowly over a period of 6 days before premedication values were attained (*22*). Following the administration of reserpine, the concentration of that drug in the brain increased rapidly to a brief maximum, but in contrast to the long-enduring depletion of serotonin (*24*), reserpine diminished speedily and was practically undetectable in the brain in about 4 hours. These results with reserpine, obtained by a fluorometric method, are in agreement with the concept that reserpine produces pharmacologic effects indirectly by its influence upon the serotonin content of the brain. But other observations (*25*) with a more sensitive technique, employing isotopically labeled reserpine, disclosed that the radioactive material is extractable from the brain *as reserpine* up to 48 hours after its injection. The long presence of reserpine in the brain does not necessarily exclude the theory that reserpine acts through an indirect mechanism that involves serotonin, but it is in accord with the idea that reserpine acts as such.

Additional evidence that reserpine releases serotonin has been adduced by Valcourt (*26*), who observed two groups of patients, one schizophrenic and the other mentally defective, at the Galesburg State Research Hospital. A significantly increased urinary excretion of 5-hydroxyindoleacetic acid occurred during the first day of the administration of 4 milligrams of reserpine. Apparently, when serotonin does not attain its binding site, it is rendered vulnerable to the amine oxidase enzyme and is metabolized to form 5-hydroxyindoleacetic acid (Fig. 1).

Even if it is proved that serotonin is important to the function of the mind, its action is not a simple one, for that hormone may serve in other ways. Because serotonin can cause smooth muscle—the type of muscle in the walls of arteries and of viscera—to contract, it is thought to be a factor in the production of high blood pressure and in the motility of the gastrointestinal tract. Only 1 percent of the serotonin content of the body is found in the brain (*27*). Most of it occurs in the spleen and especially in the gastrointestinal tract containing the specialized cells of the enterochromaffin system, which secrete serotonin (*28*). A tumor of these cells, called malignant carcinoid, is associated with abnormally high levels of blood serotonin and with an increased excretion of its metabolic product, 5-hydroxyindoleacetic acid, in the urine (*29*). Behavioral changes are absent, perhaps because of the relative impermeability of the brain to serotonin (*30*).

The similarities between serotonin, an indole amine, and the catechol amines, noradrenaline and adrenaline, are important. These similarities are not limited to their areas of distribution in the brain (Figs. 2, 3), which in general reveal high concentrations in various subcortical areas and low ones in the cerebral cortex and cerebellum (*31, 32*), nor are their resemblances confined to their chemical structures (Fig. 1), which dis-

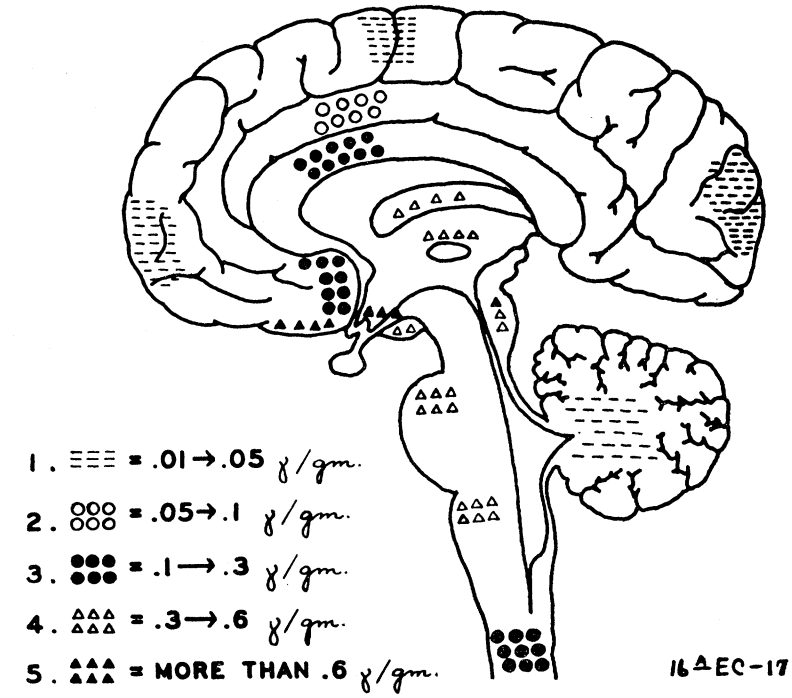


Fig. 2. Serotonin content of the human brain. The areas with the highest concentration of serotonin, an indole amine, include the hypothalamus. A lower level is observed in the mammillary bodies, fornix, thalamus, and medulla oblongata. Serotonin is found in the cingulate gyrus, hippocampus, and amygdaloid nucleus in greater concentrations than in the neocortex or cerebellum, which contain the least amounts. [Costa and Aprison (*32*)]

close that adrenaline can be oxidized to form an indole amine, adrenochrome, and that the latter, plus the appropriate side chain, yields serotonin.

Most striking is the discovery that reserpine exerts an action on noradrenaline and adrenaline similar to that previously disclosed for serotonin—that is, it empties their stores wherever they occur in the body. Even more significant is the observation (*33*) that the curve for the time relationships for the release of these substances from the brain and the reestablishment to premedication values follow each other closely. Though the results are not the same when different methods for the determination of noradrenaline are used, yet in general there is agreement in the rapid release (*34*) from the brain and the slow return to normal values. It is obvious, then, that the releases of these amines are closely associated phenomena. Either the amines combine with the same receptor, though not necessarily with the same prosthetic group, or the discharge of one amine initiates the liberation of the other.

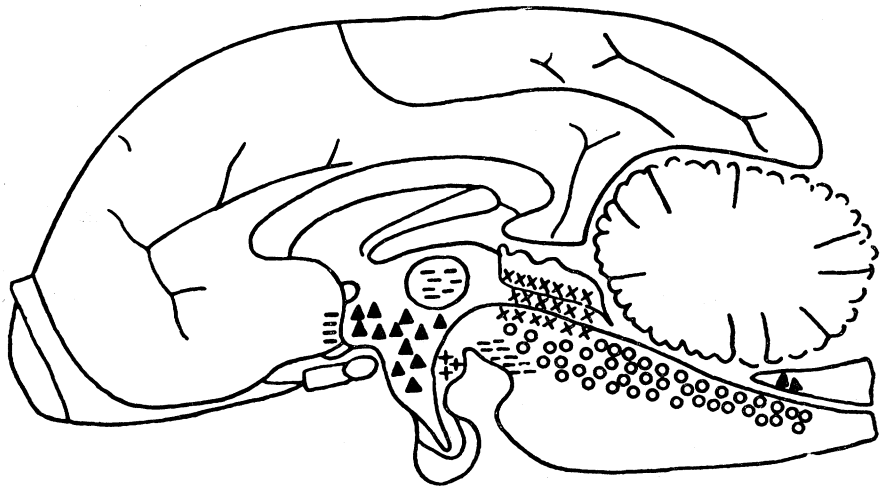


Fig. 3. Medial sagittal section of a dog's brain, showing the distribution of noradrenaline in micrograms per gram of fresh tissue: ▲, 1.0 μg/g; +, > 0.4 and < 1.0 μg/g; ○, > 0.3 and < 0.4 μg/g; –, > 0.2 and <0.3 μg/g. In the dog brain, the catechol amines, noradrenaline and adrenaline, are at their highest concentration in the hypothalamus; then, in decreasing amounts, in the mammillary bodies and the reticular formation. Still lower concentrations are observed in the neocortex and cerebellum. [Vogt, *J. Physiol. (London) (31)*]

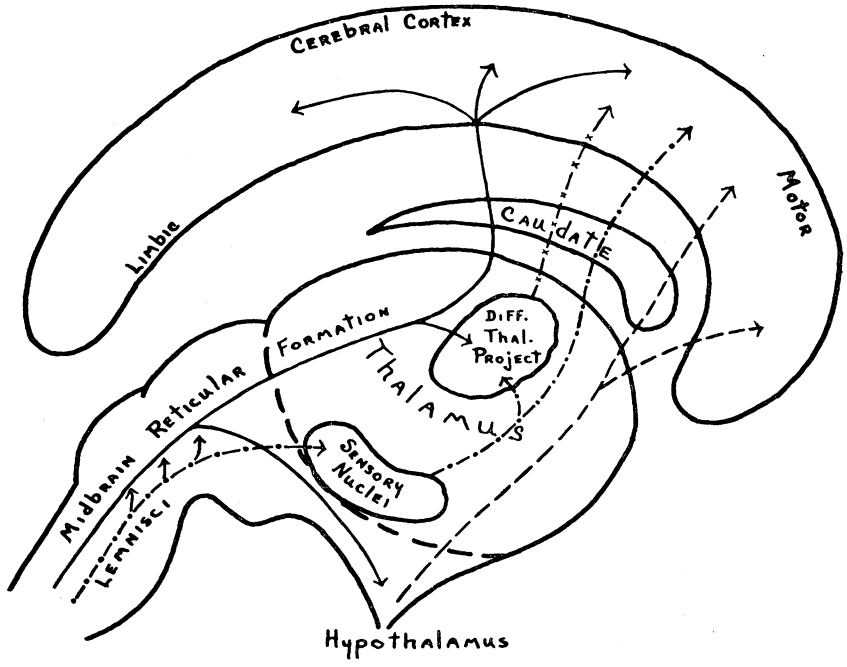
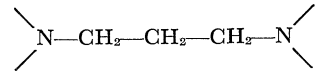


Fig. 4. Mesodiencephalic activating system. Stimulation of the organism evokes impulses which travel by way of the lemnisci to the thalamic sensory nuclei and then to cortical sensory areas. The lemnisci send collateral nerve fibers to the midbrain reticular formation, and by these fibers impulses advance in the reticular formation to the diffuse thalamic projections and arouse the cerebral cortex. Collaterals bearing stimuli from the midbrain reticular formation pass to the hypothalamus, which in turn sends impulses to the cerebral cortex. [Himwich, *J. Nervous Mental Disease (3)*]

One action of reserpine, therefore, involves closely allied substances which may be included in the term *biogenic amines*. Can such a conception be applied to chlorpromazine? An examination of the structure of chlorpromazine (Fig. 1) reveals two chief portions, the phenothiazine nucleus and a side chain



Suggestions arise from an examination of both portions of the chlorpromazine molecule. If the phenothiazine nucleus portion is depicted in three dimensions instead of two, it closely resembles the indole nucleus, as observed in serotonin as well as in reserpine. It does not seem, however, that chlorpromazine acts in the same manner as reserpine, for chlorpromazine does not empty the depots of serotonin and the catechol amines. Another lead comes from the examination of the side chain, which is contained in many successful phenothiazine derivatives (*35*). As has been pointed out by Gyermek and others (*35, 36*), the same side chain occurs repeatedly in substances which depress the effects of amines. It must not be forgotten that the phenothiazines belong to the group of antihistaminic drugs and can usually inhibit actions evoked by histamine (Fig. 1). In fact, such a side chain will interfere with the effects of other biogenic amines, including noradrenaline, adrenaline, and serotonin. Chlorpromazine shares with these biogenic amines a side chain of similar construction, and perhaps chlorpromazine attaches itself to the same binding site as do these amines.

If such a generalized action may be attributed to chlorpromazine, the study of the chemical substrates of behavior becomes even broader than the indole viewpoint suggested by the pharmacologic action of reserpine and renders every biogenic amine a fit subject for investigation in the field of behavior. But even these broad possibilities do not account for the chemical aspects of tranquilizers not included in the reserpine and chlorpromazine groups. As an ex-

ample, we may cite the experiments of Costa, who showed that the peripheral effects of serotonin were blocked not only by reserpine and chlorpromazine but also by azacyclonol (20). Moreover, meprobamate, hydroxyzine, benactyzine, and many other drugs, each with different chemical constitutions, are effective in various degrees against one mental condition or another. Until the chemical advances catch up with the clinical advances, some of the manifestations can be followed in the form of changes in nerve function.

Neurohormonal Equilibrium

Marrazzi and Hart (*37*) propose a theory, depending upon an equilibrium between various hormones, that may account for results with diverse types of tranquilizers. They contrast the stimulating effects of acetylcholine, a chemical mediator of the nerve impulse across the synapse, the junction between two nerves, with the inhibiting action of adrenaline, amphetamine, mescaline, and LSD. The latter group depresses and may even stop the transmission of the nerve impulse from one nerve to the next. Marrazzi and Hart also report that tranquilizing drugs —reserpine, chlorpromazine, and azacyclonol—prevent the inhibitory effect of mescaline on the transmission of the nerve impulse. They regard the signs of psychosis as release phenomena, results of the removal of normal restraints. Their experimental work also discloses that the depressant influence of serotonin is more potent than that of adrenaline, amphetamine, mescaline, or LSD. They therefore suggest that mental derangement is caused by an imbalance between such inhibitory substances as serotonin and the chemical transmitter of the nervous impulse, acetylcholine.

It is known that acetylcholine is active in the function of several cerebral areas, including the mesodiencephalic activating system, which is discussed in the succeeding section of this article (*38*). In a way, this conception is somewhat like that of Pfeiffer and Jenney, that an increase of acetylcholine may exert an antischizophrenic effect, for raised concentrations of that neurohormone should antagonize the action of serotonin to block the transmission of the nerve impulse (*39*). But it is not impossible that a dearth of acetylcholine is associated with one type of abnormal behavior, perhaps psychosis, and that an excess of acetylcholine is an accompaniment of another type, neurosis. Jacobsen (*40*) has suggested that the action of Benactyzine to block acetylcholine may serve a beneficial effect in disturbances associated with supernormal concentrations of acetylcholine (*41*). Benactyzine exerts little influence on schizophrenic patients but has been termed an antiphobic drug because it is effective against abnormal fears and reduces the emotional reactivity to stress.

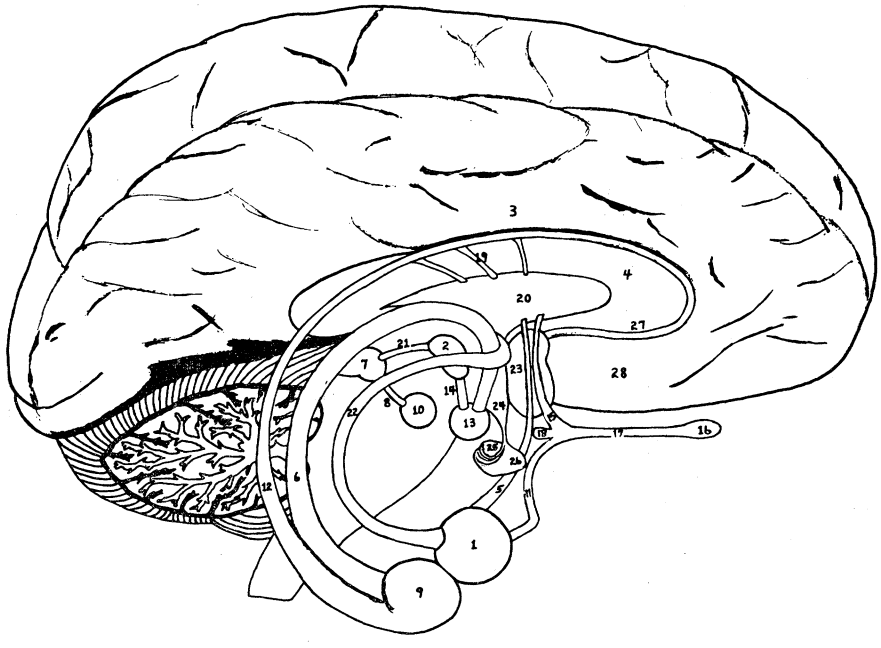


Fig. 5. Semidiagrammatic section of human brain. 1, amygdala; 2, anterior nucleus of thalamus; 3, cingulate gyrus; 4, corpus callosum; 5, diagonal band of Broca; 6, fornix; 7, habenula, a nucleus of the thalamus; 8, habenulopeduncular tract; 9, hippocampus; 10, interpeduncular nucleus; 11, lateral olfactory stria; 12, longitudinal stria; 13, mammillary body; 14, mammillothalamic tract; 15, medial olfactory stria; 16, olfactory bulb; 17, olfactory tract; 18, olfactory tubercle; 19, perforating fibers; 20, septum pellucidum; 21, stria medularis; 22, stria terminalis; 23, subcallosal gyrus; 24, hypothalamus; 25, posterior pituitary gland; 26, anterior pituitary gland; 27, caudate nuclei in depth of brain; 28, septal region. [Adapted from "Physiology and Pharmacology of Emotion," *Scope* 4, 1 (1955)]

Anatomic Sites of Action

Differences between the pharmacologic actions of depressant drugs like the barbiturates and of the tranquilizers are mentioned above in the section on "clinical aspects." An important cause for the diverse effects of these two different kinds of drugs is disclosed by an examination of their sites of action. It is well known that every drug may affect many parts of the body, but it must also be emphasized that some areas, usually the important ones for the therapeutic results, are more susceptible than others. Take, for example, the barbiturates, which in general act most strongly on the later-developed parts of the brain—the cortex of the cerebral hemispheres—and least so on the more primitive medulla oblongata, containing vital centers for the control of heart rate, respiration, and blood pressure. Because of their pronounced effects on the cerebral cortex, barbiturates depress functions of the cortical regions concerned with the analyzing mechanisms of vision, audition, and other perceptive functions—the fine coordination of motor movements as well as thought and memory. Though the tranquilizers also affect functions ascribed chiefly to the cerebral cortex, their most potent actions are exerted on the subcortical structures regarded as parts of the anatomic substrate of emotion: the midbrain reticular formation, the hypothalamus, and the components of the rhinencephalon (Figs. 4, 5).

The viewpoint expressed in this article is that the tranquilizing drugs pick out, for their main sites of action, these three cerebral areas, all connected with each other and with the cortex. It would seem that the visceral functions, related to the emotions, were correlated chiefly by the reticular formation in the lower vertebrates. It is also probable that, later in the evolutionary process, other centers in the hypothalamus and especially in the rhinencephalon took over much of the emotional aspect of behavior.

A more detailed description of the

midbrain reticular formation reveals that it is an ancient cerebral area, well developed even in the Amphibia, as has been shown by the work of Herrick on the tiger salamander (*42*). In that animal, the midbrain reticular formation probably serves as an important integrating mechanism, coordinating muscular and visceral activities in accordance with the sensory information evoked by changes in the environment. We owe the elucidation of the basic physiology of the reticular formation in mammals and primates to Moruzzi, Magoun, and their students (*43*). These workers showed that the midbrain reticular formation acts in conjunction with the diffuse thalamic projections (Fig. 4), as ascribed by Jasper (*44*). Thus, the phyletically older midbrain reticular formation is united functionally with the later-developed diffuse thalamic cortical projections, and the two together form the mesodiencephalic activating system (*38*). This does not mean that the mesodiencephalic activating system is independent of the rest of the brain. On the contrary, its midbrain reticular component probably receives a varying number of stimuli by way of collateral nerve fibers from the lemnisci (Fig. 4). There are therefore two parallel systems. One carries information by way of the lemnisci and the paths of the sensory thalamic nuclei to the cortex, where the messages are analyzed for specific information on the kind of stimulus, its point of application, and similar relationships to the organism. In the other system, the mesodiencephalic activating system, nerve impulses ascend in the reticular formation to the thalamic nuclei, which then send other impulses to the cortex by way of the diffuse thalamic paths. The mesodiencephalic activating system thus affords the emotional cloak which accompanies some kinds of stimulation of the body.

The parts played by the hypothalamus and the rhinencephalon will be considered below, but with this background we can proceed with the psychopharmacologic analysis of the functions of the mesodiencephalic activating system, which has been shown to be sensitive to members of the reserpine group of drugs, to chlorpromazine and other phenothiazine derivatives, and to azacyclonol. A clue to the effect of these drugs on this system is afforded by the electroencephalograph, for stimulation and inhibition are each accompanied by characteristic brain-wave patterns. Those associated with inhibition of the reticular formation are also observed, with rest or light dozing in the human being or animal, and are shown on the left side of Fig. 6*A*. They are characterized by high-amplitude slow waves and spindles of rapid waves. The latter are most prominent in the motor cortex, as is seen in records obtained from a rabbit. This type of activity continues until the animal is exposed to auditory, tactile, or painful stimuli, when rapid low-amplitude waves, particularly in the cortex, appear, while a slower regular rhythm develops in the hippocampus. On the right side of Fig. 6*A* is seen such an alerting or arousal pattern (*3, 45*). On the other hand, when chlorpromazine is given, the reticular formation is blocked and no longer shows the alerting response (Fig. 6*B*). This inhibition of the reticular formation does not prevent impulses evoked by a painful stimulus from traversing the lemnisci (Fig. 4), and awareness is thus achieved by way of the cortical mechanisms, but the severity of the associated distressing emotional accompaniment of the stimulus is greatly mitigated.

A clinical example is seen in the use of chlorpromazine for the treatment of the intractable pain associated with inoperable cancer. Surely the patient is aware of the pain, but it has been largely robbed of its harrowing emotional accompaniment. It is not impossible that a patient disturbed by painful hallucinations and upsetting delusions can be similarly rendered relatively free of emotional upheavals. The ability of chlorpromazine to reduce the emotional reactions to painful stimuli is probably due to the depression of the reticular formation. Though azacyclonol is not capable of blocking the pain response, it can prevent and correct the alerting of the electroencephalogram caused by the psychotomimetic drugs, LSD and mescaline (*46*). In contrast to chlorpromazine, reserpine, in adequate doses, activates the mesodiencephalic activating system and produces the alert pattern (*47*). It is significant, therefore, that reserpine, despite its tranquilizing action, is not of use in the management of pain. Perhaps the greater sedative effect of chlorpromazine is due to its ability to depress the midbrain reticular formation.

But the fact that reserpine does not inhibit the mesodiencephalic activating system indicates that there are other centers important for tranquilization. We therefore turn next to the consideration of the hypothalamus, which is known to be a part of the brain containing patterns for coordinating visceral functions, increases of blood pressure, heart rate, and respiration in order to support muscular activity. This integration of visceral and muscular activities is especially essential in emergency situations, originally referred to by Cannon as the "fight or flight" reactions (*48*). This part of the brain, therefore, organizes the visceral manifestations which are overactive in disturbed patients. It would seem probable that the depression of this mechanism acts to mitigate this type of overactivity. The earliest research done on reserpine and chlorpromazine indicated that these drugs inhibited hypothalamic structures, particularly those of the posterior hypothalamic nuclei which regulate the sympathetic nerves to the viscera and blood vessels (*49*).

The action of reserpine can be explained in part by a depression of the sympathetic representation in the hypothalamus (*50*), which leaves parasympathetic activity unopposed and thus accounts for the fall in heart rate, drop in blood pressure, constriction of pupils, and the increased intestinal motility frequently observed in patients receiving that drug. These physiological changes are signs of acetylcholine activity. Acetylcholine is not only associated with the chemical transmission of the nerve impulse in parasympathetic nerves to the various organs but also with transmission within the central nervous system. With reserpine, however, the increased effects of acetylcholine may be due to the failure of the opposing effects of adrenaline and noradrenaline. As we have seen in a previous section, this failure may be the result of the emptying of the catechol amine depots by reserpine, in the brain and elsewhere in the body. As a consequence of this depletion, stimuli impinging on the hypothalamus fail to evoke responses from the cerebral representation of the sympathetic nervous system (*51*). It is also probable that, because of the exhaustion of the adrenaline and noradrenaline deposits in the peripheral sympathetic nerves, these nerves, too, cannot react, and thus the central effects of that drug are accentuated.

In a way, the pharmacologic actions of chlorpromazine may be compared with those of reserpine, for both exert central and peripheral effects. It is true that both drugs inhibit the hypothalamus, but chlorpromazine also depresses peripheral sympathetic nerve centers which help to regulate blood pressure, and this is a second reason for the observed decreases of arterial pressure. But chlorpromazine also exerts a similar impairment on peripheral parasympathetic

nerves which usually slow heart rate, and therefore in patients receiving chlorpromazine the heart rate is characteristically rapid. Both peripheral results may be ascribed to interference with the action of acetylcholine in the transmission of the nerve impulse and therefore may be compared with the central operation of chlorpromazine to block the reticular formation (*52*).

Pathfinding Experiments

The discussion on the parts of the brain affected by chlorpromazine and reserpine will now be extended to include those which were highlighted by the pathfinding experiments of Klüver and Bucy (*53*). These workers removed the temporal lobes of monkeys, thereby changing these difficult creatures into remarkably tame animals. These primates also exhibited increased oral and sexual proclivities. Objects of all kinds were repeatedly introduced into the mouths of the animals being tested, and males, especially, attempted sexual intercourse frequently, whether or not the animal chosen for these relations was of the appropriate sex or even of the same species.

The temporal lobe includes some structures belonging to the rhinencephalon, which was first regarded as a unified system by Papez (*54*), in accordance with the schema presented semidiagrammatically in Fig. 5. When the hippocampus is stimulated it gives rise to impulses which initiate the Papez circle. These impulses are transmitted from the hippocampus (No. 9, Fig. 5), through the fornix (No. 6), to the mammillary bodies of the hypothalamus (No. 13). From that area they continue to the anterior thalamic nuclei (No. 2) and attain the cortex of the brain in the cingulate gyrus (No. 3). The functional circle is completed in fibers leaving the cingulate gyrus and returning to the hippocampus.

Again the phyletic point of view is enlightening. When the first air-breathing vertebrates—the amphibians and especially the reptiles—left the oceans for the land, they developed areas of the brain important for smell, the olfactory bulb (No. 16) and the olfactory tract (No. 17). The olfactory tubercle (No. 18), which receives impulses from the midbrain reticular formation, supplies an indirect connection between the latter and Papez' circle. The term *rhinen-*

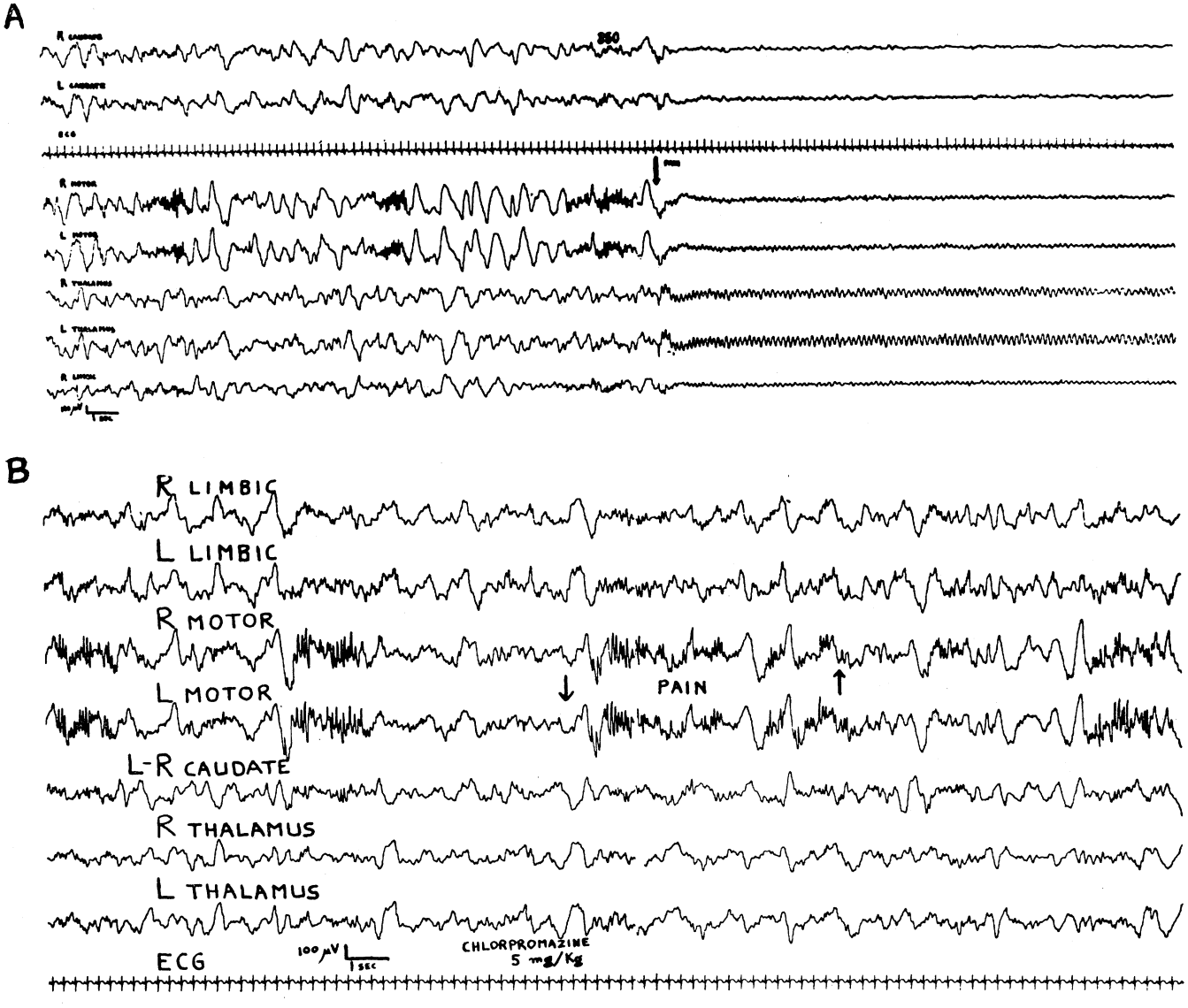


Fig. 6. Alert pattern evoked by pain and prevented by chlorpromazine. (*A*) Bilateral leads are taken from various cerebral structures: on right side, electroencephalographic control pattern of resting rabbit; on left side, the effects of pinching rabbit's leg. (*B*) Change produced by chlorpromazine (5 mg/kg) in electroencephalographic pattern in response to pain. Note the absence of the alerting reaction to pain. [Himwich, *J. Nervous Mental Disease* (*3*)]

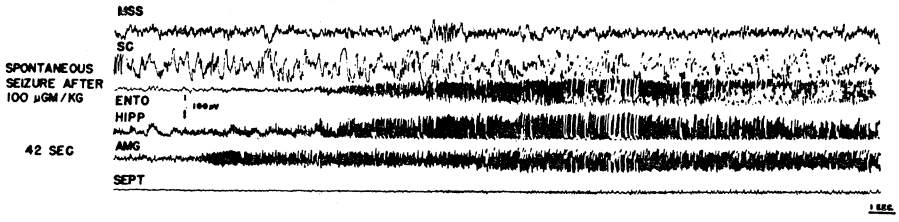


Fig. 7. Effect of reserpine (0.1 mg/kg) on brain waves; records of spontaneous rhinencephalic seizures initiated in the amygdala. [Killam and Killam, *Brain Mechanisms and Drug Action* (*63*)]

cephalon originates in the primarily olfactory functions of the bulb and of some of the amygdaloid nuclei (No. 1). These structures are connected, in turn, to others which have been adapted in higher animals to emotional activities. These include the remainder of the amygdaloid and septal nuclei (No. 28). Finally, the latter areas contact Papez' circle in the hippocampus, and awareness of emotional reactions is attained by way of the cingulate gyrus (*55*). Even today, in man, emotion and olfaction are closely associated, and this is so despite our mores, which in general require restriction of body odors.

The part of the brain concerned especially with emotional experience and the one least understood is the rhinencephalon, which is also called the limbic system or the visceral brain (*56*). It must be noted that not only tranquilization but also the reverse reaction of rage was observed when the more forward portions of the rhinencephalon—the septal area and olfactory tubercle—were removed, and similar effects were also reported after the extirpation of the amygdaloid nuclei, the hippocampus, and the fornix (*57*). Lesions of the septal region alone were also found to produce rage (*58*). Bilateral extirpation of the amygdaloid complex and the adjacent pyriform lobe rendered animals easily disturbed (*59*). Many workers, however, have observed placidity and emotional unresponsiveness following the bilateral removal of the amygdala and hippocampus (*60, 61*).

Though these results are apparently contradictory, at present the consensus is veering towards Klüver and Bucy's original conclusions because the pacifying effects of these extirpations are the more frequent findings. With either result, these experiments disclose relationships between the rhinencephalon and the emotional state. From this viewpoint both observations are useful, and in that case the nature of the response may depend on other factors—for example, the immediate social environment, whether or not it is hostile, and whether the animal is being provoked or treated in a friendly fashion. The general reaction characteristic of the animal is also important, for the effects of the operation may be superimposed on an excitable animal, easily aroused, or on a calm and phlegmatic one. Analyses have been made to explain these discordant results (*61, 62*), but for our purposes these reactions serve to point out the type of physiological activity of these parts of the brain, and they afford a basis for the appraisal of the effects of drugs upon them.

Killam and Killam report (*63*) spontaneous, seizurelike waves in the rhinencephalon of a cat following the administration of reserpine. These seizures appeared first in the amygdala (*AMG,* Fig. 7) and then spread to the hippocampus (*HIPP*) and to other rhinencephalic structures, including the entorhinal cortex (*ENTO*) and septum (*SEPT*). However, the neocortex, (*MSS* and *SC*) remained free of such abnormalities. Furthermore, Sigg and Schneider noted that electrically evoked, seizurelike waves in the amygdala were facilitated and prolonged by reserpine without necessarily involving neocortical areas (*64*).

Preston's observations (*65*) with chlorpromazine are similar in some respects to those of the Killams with reserpine, for he reports that the amygdaloid complex is readily stimulated by chlorpromazine at a time when the activity of the neocortex, including the motor cortex which regulates voluntary muscular movements, is unchanged. The electroencephalographic alterations evoked by single daily injections of chlorpromazine to a cat (10 mg/kg of body weight) for a period of 5 days showed that 20 hours after the last injection there was no obvious effect in the neocortex (*LG* and *MC,* Fig. 8), while the amygdaloid nuclei (*AMG*) revealed spiking.

Thus, the amygdala is the part of the brain most susceptible to both drugs. Rather surprisingly, this amygdaloid hyperactivity was associated with tranquilization. With this dose of chlorpromazine, well within the human therapeu-

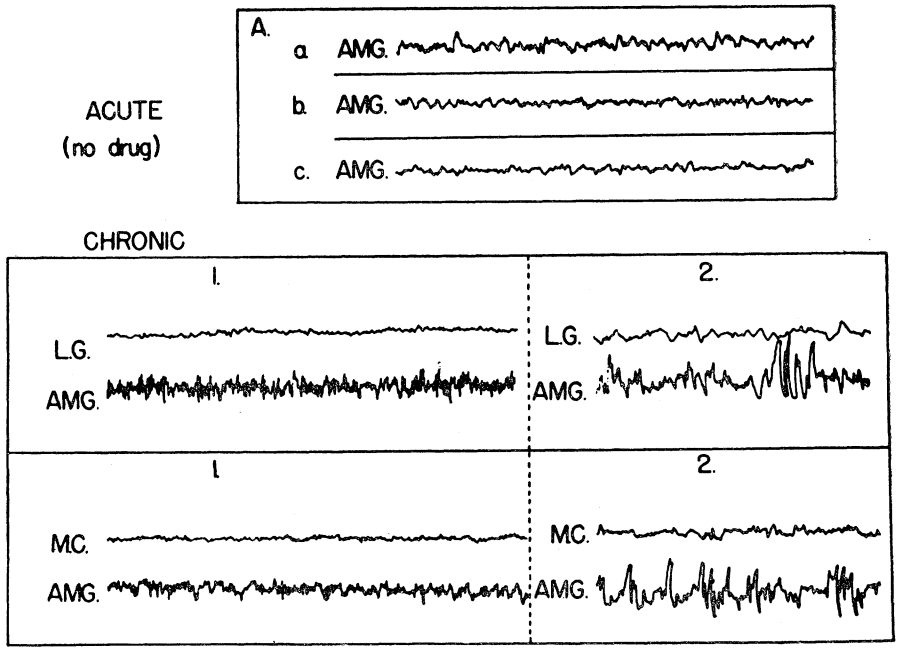


Fig. 8. Comparative effects of chlorpromazine on the amygdala and cerebral cortex. (*A*) Spontaneous activity recorded from the amygdala in three different cats: (1) Records from two cats after a single daily injection of chlorpromazine, 10 mg/kg, for 5 days; (2) spontaneous activity recorded at a later time in the same experiment after 10 mg/kg of chlorpromazine had been injected. Hyperactivity is present in amygdala but not in the neocortex. [Preston, *J. Pharmacol. Exptl. Therap.* (*65*)]

tic range, a cat will not pounce upon a mouse placed in its cage but, instead, acts with apparent indifference. Though the convulsive brain waves disclosed in the amygdala were accompanied by a transformation in the behavior of the cat, overt signs of motor activity were not apparent in such animals. In general, it is known that the rhinencephalon is more easily excitable than is the neocortical mantle of the cerebral hemispheres (*66*). With larger doses of chlorpromazine (*65*), which however do not exceed those administered to badly disturbed patients (*67*), the electrical hyperactivity spreads from the amygdala (*AMG*, Fig. 9) to other rhinencephalic structures, the septum (*SEPT*) and the hippocampus (*HIPP*). But only when the disturbance extends to neocortical motor areas are the characteristic violent muscular contractions of a major epileptic seizure observed. Perhaps a similar process, the initiation of seizure activity in the amygdala and its spread through the rhinencephalic structures and then to the motor cortex, can explain the convulsive seizure sometimes seen in patients taking reserpine and chlorpromazine (*12*). Penfield has suggested that the phenomena of psychomotor epilepsy may originate in a seizure discharge in the amygdala spreading in the centrencephalic system (*68*). The pharmacologic effects of these two drugs may be compared with the observations of Andy and Akert (*69*), who stimulated the hippocampal formation of a cat electrically and noted that, when the hippocampal discharge was propagated to include the amygdala, the cat was not affected by the presence of the mouse, an apathy which was prolonged for a short period of time after the discharge was completed and which was then replaced by an attack upon the little victim. But there is more than one method by which similar kinds of behavioral results may be obtained. Tranquilization of disturbed psychotic patients can be achieved with meprobamate (*70*), which is neither a phenothiazine derivative nor a reserpine-like drug (Fig. 1). Unlike these tranquilizers, meprobamate does not alter brain wave activity of the amygdala when it is administered in small doses which, however, depress the undulations exhibited by the thalamus (*71*). Though the amygdala does not seem to be a site of activity for meprobamate, yet some portion of the rhinencephalon may be involved, as suggested by experiment with animals. Rats rendered savage by

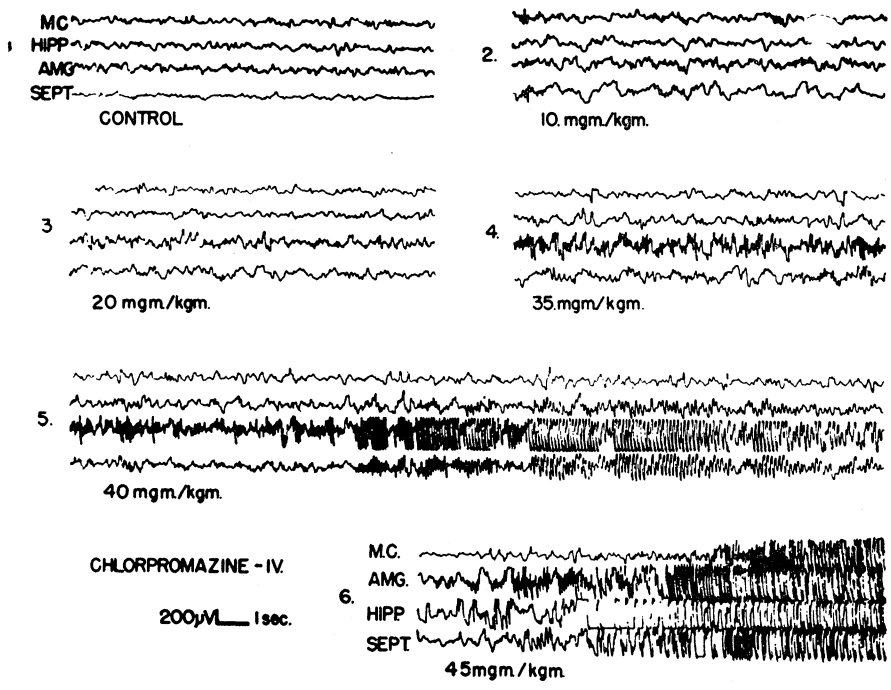


Fig. 9. Effects of gradual increases of chlorpromazine upon brain. Seizure spiking is initiated in amygdala and gradually spreads to other areas. [Preston, *J. Pharmacol. Exptl. Therap.* (*65*)]

the extirpation of their septal regions are restored to their preoperative behavior by that drug. Apparently meprobamate influenced a portion of the brain which is functionally associated with the septum. It is of more than passing interest that rats that have not been operated on show little or no change in their conduct when the same doses of meprobamate that calm the experimental animals (*72*) are administered.

Theory for Therapeutic Effects

To bridge the gap between our information of the pharmacologic actions of reserpine and chlorpromazine and their therapeutic results is a goal greatly to be desired. Unfortunately, we do not have sufficient data or even the basic neurophysiologic facts to do this. It is realized that such speculations on the mode of action of tranquilizers in man are largely based on observations of animals—a doubtful procedure. Moreover, there is a genuine logical difficulty, for it has not been proved that the behavioral improvements noted with use of these drugs are due to the pharmacologic effects. The two diverse groups of phenomena may be related to each other only by a common causative factor—namely, the drug. But it is useful to make the assumption that the medicines are causes of the clinical changes as a device to clarify our thinking in seeking indications for the direction of future research in the field of psychopharmacology.

In our analyses of the therapeutic results of reserpine and chlorpromazine, we found that they are of two different kinds: one is a calming of the individual and another is directed against schizophrenic manifestations. Can each of these two different clinical improvements be related to specific actions of the drugs? The decreased reactivity of tranquilized patients may be ascribed in part to the depletion of the catechol amines, the depletion depriving the organism of part of the mechanism of reactivity. Obviously, tension and anxiety, whether evoked by real or imaginary emergencies, will nevertheless mobilize the autonomic nervous system. Not only adrenaline and noradrenaline but also other hormones, including serotonin and acetylcholine, are probably released during threatening emergencies. Thus, in general, a pharmacologic action of these drugs is to remove part of the mobilization mechanism, and the beneficial results include tranquilization and decreases of anxiety and tension. Turning to the electrophysiological portion of this analysis, we find ourselves examining the parts of the brain which help to regulate the activity of the neurohormones. A neu-

ronal depression of the reticular formation and of the hypothalamus diminishes the actions of these portions of the brain. This depression can only render more profound the decrease in reactivity due to the emptying of the neurohormonal storehouses.

Animal experiments indicate a close relationship between rhinencephalic structure and the emotions, while drug studies have disclosed the sensitivity of the amygdala to chlorpromazine and reserpine. But here we see that a similar final effect of tranquilization is associated with an action which is quite the reverse of that seen in the hypothalamus. Inhibition of nerve function is not observed. On the contrary, the affected areas reveal abnormal hyperactivity. Does the drug-induced aberrant operation of the amygdala interfere with the functions of the rhinencephalon, and, if so, does such an interference afford a basis for the second action of these drugs against schizophrenic symptoms? It would seem that the normal contribution of the amygdala to the economy of the brain cannot continue when that structure is being subjected to seizures (*73*). Perhaps the rhinencephalic chain ceases to act physiologically because of the functional failure of the amygdaloid link—a failure which makes for a loss in a connection between the most primitive brain area (concerned with emotion), the midbrain reticular formation, and the later developed rhinencephalon.

The diminution in reactivity of the organism probably influences the quantity or intensity of the emotional impact on the cortex. But it is difficult to see how such an amelioration can change the quality of thought so that the dissociated "word salad" of the hebephrenic patient can become less incoherent, more logical and comprehensible. One can appreciate that a decrease in emotional intensity might mitigate the violence in the expression of hallucinatory and delusional material, but again it is more difficult to understand how such a mitigation can cause the correction of schizophrenic mentation. For that change, thinking must be altered in quality.

Though the various parts of the brain work together as a unit in a coordinated manner, we have seen that certain structures, both cortical and subcortical, are more involved than others in our emotional life. Similarly, as is pointed out by Bailey (*74*), some subcortical regions add a crude awareness, but for the discriminative contribution to that complex function, the cortex must be included in a prominent position. The cingulate gyrus, which is a part not only of the rhinencephalon but also of the cortex, may be the area where the abnormal elements concerned with awareness and thinking enter into discriminative conscious activity. It is not said that rhinencephalic structures do not affect emotional reactions, but it is suggested, as a working hypothesis, that the cessation of rhinencephalic function is a possible factor in the prevention of the morbid thinking of schizophrenia. This would indicate that the disease process of schizophrenia is tied up with the malfunction of certain brain areas and that the rhinencephalic circle carries impulses which are sources of the pathologic psychophysiology of schizophrenia. It is realized that a change of behavior produced by a loss of the contribution from a specific brain area, whether due to a physical extirpation or to functional incapacitation, does not prove that pathology in that area is the source of the disease. The removal of a part of the brain may interfere with the function of another region more directly concerned with the disease process. For example, an origin of the pathologic course may lie within the septal region, as is indicated by the work of Heath and his colleagues (*75*), or the warped emotional reactions may find their earlier expression in the midbrain reticular formation. But at least it can be said that the anatomic site sensitive to drug action bears a relationship to schizophrenia, because the functional diversion of that area may correct the symptomatology of the disorder.

Paths of Research

A review of the present pharmacologic data can serve to throw light on paths for future exploration. One series of observations has emphasized quantitative changes causing shifts in the neurohormonal balance, involving excesses or deficits of acetylcholine, adrenaline, noradrenaline, serotonin, or serotoninlike substances. Concentrations of serotonin in the brain can be increased by the administration of its precursor, 5-hydroxytryptophan, which provokes disturbances in the electroencephalogram and in the behavior of the rabbit (*76*) (Fig. 1). Apparently, 5-hydroxytryptophan enters the brain rapidly and, presumably, is transformed into serotonin. But that does not demonstrate that serotonin is excessive in hyperactive psychotic patients (*77*) or that their improvement is necessarily due to the decrease of serotonin in the brain. On the other hand, there is a recent suggestion that Marsilid, which increases the serotonin content of the brain, benefits depressed patients (*78*). Again, that does not prove that patients are depressed because of abnormally low levels of serotonin in the brain. But it must be admitted that this circumstantial evidence is of such interest that it calls for further investigation of these possibilities.

An experiment to throw light on this subject would be to determine the cerebral serotonin contents in the brains of psychotic patients and compare them with those of nonpsychotics. A start has been made. Costa and Aprison have demonstrated that serotonin is a normal constituent of the human brain just as it is of the brain of lower animals (*32*). However, it can be said conservatively that the suggestion of Woolley and Shaw (*18*) on the role of serotonin is an attractive one and that it has been useful in turning up new material (*79*). For example, Shaw and Woolley (*80*) have synthesized compounds which block serotonin, including BAB, the benzyl analog of bufotenin, and BAS, the benzyl analog of serotonin (Fig. 1). We have employed BAS in the treatment of schizophrenics on the possibility that it may exert a reserpinelike action (*79*). The salutary results on these psychotic patients were very encouraging, but the side reactions contraindicate the clinical use of BAS.

It is not justifiable, however, to separate the role of serotonin from that of the catechol amines, for both are affected simultaneously by reserpine and probably by other tranquilizing drugs. A strong point in favor of the catechol amines is that one of them, deoxyephedrine, is able to substitute for depleted catechol amines in the brain (*81*). Mice and monkeys, under the influence of reserpine and showing the depression, reduced mobility, and the hunched posture typically produced by that drug, are dramatically restored to apparently normal activity by deoxyephedrine. Another line of investigation is concerned more with qualitative changes in the neurohormones than with quantitative ones, and it implicates a metabolic factor in schizophrenia. This work cannot be reviewed here, but it involves the more rapid oxidation of adrenaline (*82*) or the production of abnormal oxidation products of that neurohormone (*83*). As a result of an abnormal enzyme system, the metab-

olism of adrenaline is perverted, and an aberrant metabolic product, which may be a pathogenic factor in schizophrenia, is formed (*84*).

At this time, when theories of schizophrenia are actively multiplying, it would seem that the two different aspects of quantitative and qualitative changes in the hormones are not mutually exclusive. One example is afforded by Hoffer, who suggests that there are two basic conditions for the production of schizophrenia—an increase in the concentration and activity of acetylcholine within the brain and an abnormal metabolic diversion of adrenaline to some aberrant indole compound (*85*).

The inclusion of electrical changes of brain areas in our field of research diversifies the problem still more. At the present state of development of psychopharmacology it is difficult to apply William of Occam's razor, for each successful drug seems to differ from the others. Perhaps when we know more, the attack will be simplified by a unitary hypothesis on the pharmacologic actions of these drugs. We are therefore left with a number of tempting speculations, and the judgment of the investigator will largely determine which one will be emphasized in his researches.

The fact that we have effective drugs will not stop the production of better ones. In that process, a guiding principle is concerned with a characteristic of the brain—the fact that it, more than any other organ, is sensitive to changes in the chemical structure of a drug (*86*). Illustrations may be drawn from the phenothiazine derivatives. Profound differences in the intensity of the therapeutic effects and the distribution of the side reactions (*35*) may be produced either by the replacement of the chlorine (Cl) atom of the nucleus with another chemical or by an alteration in the number of carbon atoms between the two nitrogen atoms (N) of the side chain. We are looking forward to the discovery of compounds of new chemical structures, to be used for types of patients who require not tranquilization but other kinds of therapeutic aid—for example, for the blocked and retarded individual who must be stimulated without an increase of hostility or an activation of hallucinations and delusions.

We have seen, however, that thus far in the field of psychopharmacology, practice has outstripped theory. Though we recognize that tranquilizers correct certain schizophrenic symptoms, there is less agreement on the mechanism by which the improvements are achieved. Whether or not drugs effect cures is a problem for the future. But the practical value of the advance should not be underestimated. It may be compared with the advent of insulin, which counteracts symptoms of diabetes without removing their cause.

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University of Arizona Radiocarbon Dates

Edward N. Wise and Dick Shutler, Jr.

The Carbon-14 Age Determination Laboratory of the University of Arizona is operated by the anthropology department under the direction of Emil W. Haury, with the technical supervision of one of us (E. N. W.). A steering committee of the university (*1*) was appointed to approve the acceptance of submitted samples, to assign them a relative priority, and to examine critically and approve for publication the dates obtained by the laboratory.

The work of the Carbon-14 Age Determination Laboratory is an integral part of the geochronology-dendrochronology program of the university. Students in this program obtain laboratory experience by observing all the chemical and physical operations performed during the dating of a sample.

The laboratory was constructed in 1953 with the aid of a grant from the Research Corporation. The solid-carbon method developed by Willard F. Libby and his co-workers (*2*) is used for dating samples. Trial runs were made in the spring of 1954, and the laboratory was ready for calibration and dating runs in 1955. The solid-carbon method has been retained, for the majority of our samples are not more than 20,000 years old, and we have not experienced the radioactive contamination reported by other radiocarbon-dating laboratories. Fallout from the Nevada atomic-weapon test site apparently passes to the north of our laboratory.

The elemental carbon is prepared in essentially the same manner as that described by Libby, except for a modification suggested by Ballario and his coworkers (*3*). The modification concerns the omission of the steps in which carbon dioxide is condensed with liquid nitrogen. In the combustion train, the traps cooled with liquid nitrogen are replaced by a two-stage absorption train containing ammonium hydroxide, which absorbs the carbon dioxide directly. A water aspirator is attached to the end of the train to remove unabsorbed gases, such as excess oxygen. After precipitation and purification of the sample as calcium carbonate, carbon dioxide is evolved by the addition of hydrochloric acid. The carbon dioxide is thoroughly dried and directly reduced to elemental carbon with magnesium turnings. The elimination of the steps in which liquid nitrogen is used speeds up the preparation of samples and simplifies the control of the chemical processes involved in absorption and reduction. No deleterious effect on samples due to the omission of the use of liquid nitrogen was noted.

The problem of smooth and continuous chemical reaction during the reduction step, which gave trouble during our trial runs, was solved by heating the magnesium turnings in the steel reduction tube under high vacuum for several

Dr. Wise is associate professor of chemistry at the University of Arizona, Tucson. Mr. Shutler is a research assistant in the department of anthropology and operating technician of the Carbon-14 Age Determination Laboratory at the University of Arizona.