CHAPTER 13

Psychotropic Drugs and Experimental Psychiatry

ACADEMIC ADDRESS

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Progress in psychopharmacology has made available to clinicians a whole series of psychotropic drugs capable of influencing behavior in different directions. The word "psychotropic" is useful since it identifies in a general fashion a whole group of natural or artificially occurring substances that modify behavior. Whether they depress, stimulate, or deviate the mental energies or produce a state of stimulation, relaxation, or delusion, it is possible to classify them clinically in a rather simple fashion, at least until a more scientific classification becomes possible which will allow one to correlate psychological changes with chemical formulas and to selectively localize their site of action in the brain and their intracerebral metabolism.

Psychopharmacology has opened up new areas which hold promise for investigation of problems in human psychology and experimental psychiatry. I will limit my presentation to three aspects: (1) variations of psychological "tonus," (2) induction of the neuroleptic syndrome, and (3) experimentally induced states of abnormal behavior.

EXPERIMENTAL VARIATIONS OF PSYCHOLOGICAL "TONUS"

Just as muscle tonus depends on whether there is a state of contraction, semicontraction, or rest, there exists a state of mental "tonus" which varies according to the intellectual effort expended and is thereby a function of the level of cerebral activity. In the psychological as in the muscle systems there are oscillations between the states of contraction that can be called concentration and relaxation whether we use physiological or psychological terms.

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Pierre Janet was the first to conceptualize the mind's function in a dynamic sense based on the "psychological tension" and its oscillations. The hierarchy of activity that he described rested on the opposition of "involuntary and synthetic activity," the former referring to low-tension states which allow fantasies to take place and the latter referring to states of heightened tension and implying a voluntary act of concentration. Each human being experiences both of these states. We all feel the effects of our psychological tension, depending upon whether we are awake or drowsy, attentive or distracted, tense or relaxed, stimulated or depressed. The organism's needs for dynamic adaptability to the complexities of daily life are far more exhausting than when the activities are involuntary. Involuntary activities require no conscious attentive effort, no matter whether we are dealing with an act learned by rote or with free association as in daydreams. What we call "fantasies" today were described years ago by Maine de Biran when he drew the analogy to dreamy meditation, which referred to the decrease in the synthetic and adaptive functions of the mind leaving the inner self submerged by a succession of images, like waves beating against the shore. Moreau de Tours felt that ego flexibility permitted the individual's reality adaptation. Janet developed his dynamic concept of the levels of psychological tension based, among others, on these lines of thinking.

For Pierre Janet, psychological readiness depended on the state of nervous tension which was comparable to an electric potential. This assumes more than metaphoric importance if we think of comparing the brain to an electronic unit functioning according to the laws of cybernetics.

In describing psychasthenia Janet wrote, "We are unaware of the causes that inhibit the brain's reactivity; if there is a special center that produces or regulates this tension; if this center is cortical, subcortical, or located in an endocrine gland." One of the principal contributions of modern neurophysiology has been to recognize the regulation of psychological activity by the brain through the cortical and subcortical circuits. It would be foolhardy to attempt to localize the center regulating the state of psychological tension. The problem is worthy of discussion, nevertheless, in view of the center's dependence on the set and mood of the organism and their regulation by cerebral mechanisms.

There is a gross analogy between oscillations of the psychological tonus and the state of "vigilance." Janet considered the highest

degree of psychological tension to be the state of awareness (of past, present, and future), an intellectualized function. On the other hand, he felt that fantasy resulted from liberation of the subconscious, as tensions decreased and consciousness was less sharp. If one goes a step further, it could be said that the opposite of psychological tension could be considered as sleep, a periodic loss of consciousness in which the mental faculties are inoperative and the dream becomes master.

Most physiologists today define "sleep" as a cortical inhibition originating in the diencephalon. The oscillations between the waking and sleeping states appear closely linked to the sympathetic nucleus of the diencephalic portion of the reticular activating system. Sympathomimetic substances stimulate this formation, leading to insomnia, while sedatives are depressant agents leading to sleep. The state of psychological tonus depends on the cerebral centers regulating the states of consciousness or sleep. To a degree, this state of tension is related to the oscillations of the state of alertness.

The basic emotional disposition of the individual is intimately linked to the state of psychological tension. The former is a function of oscillations in emotional tonus between vigilance and apathy. These mood swings, which exist in all people, show characteristic periodic exaggerations in the affective disorders. In 1946, I attempted in my book, "Disorders of the Affect" [1], to unify neurophysiological, neurosurgical, and neuropsychiatric observations, indicating that mood is regulated by the central nervous system. Since then, many similar observations have been made. The cortico-subcortical circuits are related to this complex in a fashion similar to the state of vigilance. However, some of the key areas are localized in the hippocampus and diencephalon. The variations in psychological tonus and mood changes are related to the same cerebral centers insofar as the former is dependent upon the latter.

Psychopharmacology has shed new light on the neurophysiological concepts of psychological tonus. Through the experimental use of psychotropic drugs, which act directly on the central cerebral regulating mechanisms, it has been possible to experimentally lower or heighten the psychological tonus by decreasing or increasing either the state of alertness or mood or both.

Lowering of the psychological tension was described by Pierre Janet as "psycholepsy," an interesting word derived from the Greek. It would be, perhaps, more appropriate to speak of "psychocatalepsy," the "cata" signifying "down." It would seem to me of more

than passing interest to conserve the meaning that Janet gave to the word "psycholepsy." Thus, "psycholeptics" would be drugs that diminish the psychological tonus, while those that produce the reverse effect would be called "psychoanaleptics" (the Greek "ana" meaning "up").

The compounds that depress psychological tension are called "psycholeptics," whether the result is a decrease in consciousness or of the intellectual forces or the sedation of psychic tension. One may subdivide this large group into two categories: (1) hypnotics—those drugs that decrease states of consciousness—and (2) tranquilizers or mood depressants. All hypnotics comprise those drugs capable of depressing consciousness, and when used correctly can achieve different levels between the waking and sleeping states. In the first (hypnoid) stage, there is a decrease of the cognitive functions undetectable by the electroencephalogram. The second stage shows slight alterations of the electroencephalogram, usually considered to be the desirable level for hypno- or narcoanalysis. The third (hypnotic) stage shows clinical and electroencephalographic signs of sleep; this is the state used for the sleep cure.

Tranquilizers are those drugs that depress the emotions, and their action is to substitute a state of torpor for agitation. They are sometimes called "ataractics," since ataraxia is by definition a state free of emotional problems in an individual unperturbed by external stimuli. The tranquilizers produce an experimental ataraxia, just as the barbiturates produce an experimental sleep.

In 1952, Deniker and I described the first results with chlorpromazine in the treatment of mental illness and noted its psychological action as follows: "The psychological syndrome resulting from treatment with chlorpromazine consists of an apparent indifference, increased reaction time, flattened affect, decrease of initiative and self-preoccupation, without alteration of consciousness or the intellectual faculties."

The experimental production of a state of ataraxia with psychotropic drugs is not new if we think of the fact that the Greeks used "nepenthes." May I cite in this regard a passage from Homer's "Odyssey":

> ...Telemachus has described the siege of Troy and the unhappiness in his country, as his compatriots began to cry. Helen, daughter of Zeus, poured some "nepenthes," a balm, into their glasses, making them forget their problems. He who drank this potion could not cry all day, even if his

parents or beloved son were killed before his very eyes. This excellent liqueur was given to Helen by Polydamna, wife of Phebus, born in Egypt whose fertile land produced many balms, some healthy and some deadly.

Nepenthes is in a way the ancestor of the ever-growing list of modern tranquilizers.

It is necessary to distinguish between the minor and major tranquilizers (neuroleptics). The latter differ from the former by virtue of a greater degree of psychologic activity and through the induction of a neurological syndrome. The reduction of emotional tonus by the neuroleptics lends itself to many applications in psychiatric and psychosomatic medicine. The continued barking of aggressive dogs will induce a Basedow disease in the rabbit. But, prior treatment with neuroleptics will block the thyroid reaction and there will be no signs of Schreck-Basedow disease.

All the psychoanaleptics stimulate the psychological tonus no matter if this be owing to a more intense state of wakefulness, which can lead to insomnia and an increase of the intellectual functions, or to a heightening of the psychic tension, which can lead to euphoria or anxiety. Compounds that make the individual more alert stimulate the thinking processes (psychotonic effect) and produce insomnia (antihypnotic). The amphetamines (methylamphetamine) best characterize this group, whose effects are antagonistic to the barbiturates. Other compounds in the amphetamine group are: methylphenidate (Ritalin), oxazimedin (Preludin), pipradol (Meratran). Centrophenoxine derived from the acid growth factors of vegetables has been found to be particularly effective in the treatment of alterations of consciousness resulting from organic cerebral damage on a traumatic, vascular, or neoplastic basis. It can be used in comas as well, where it tends to awaken the patient, although it is not actually a stimulant like the amphetamines.

Mood-elevating drugs affect psychological tonus, either by giving rise to euphoria by direct action, as cocaine would, or by influencing a depression, as the antidepressant drugs do. These compounds are effective chemotherapeutic agents in depression and can replace electroconvulsive treatment. The monamine oxidase inhibitors (iproniazid) are good examples of such activity but more important is imipramine, which is not an inhibitor of this enzyme. Imipramine has been described as a thymoleptic, but it is really a thymoanaleptic since it heightens the mood and increases emotional reactivity.

The classification of psychotropic drugs in relation to psycho-

logical tonus has value only to clinicians, in that it allows them to categorize each group according to its major effects. Although the division between psycholeptic and psychoanaleptic is generally clear, the subdivisions of these groups are not so sharp. Barbiturates depress the state of wakefulness and to a lesser degree the mood as well. The phenothiazines, on the other hand, are mood depressants and do the same to the state of wakefulness, although to a lesser degree. The amphetamines alert and to a lesser degree elevate the mood. Imipramine lifts the mood and to a lesser degree makes the individual more "vigilant." Although the hypnotic and antihypnotic drugs are antagonistic, the difference between tranquilizers and mood-elevating drugs is not clear. This can be shown in studying benactyzine or the potentiating effect of levomepromazine on the antidepressant effects of imipramine.

A classification based on the drug's psychological activity is essentially of clinical interest and must be compared to others being developed by psychopharmacologists. Bovet uses the electroencephalogram to distinguish between those substances that depress or activate the reticular activating substance, while Monnier distinguishes between trophotropic and ergotropic drugs.

Experimental study of psychological tonus and psychological tension (in Janet's sense of the terms) has been made possible by the use of psychopharmacological agents through an analysis of the variations in these states under the effects of drugs that either stimulate or depress the emotions or the state of consciousness. Since it has been shown that the psychotropic drugs tend to localize in various subcortical centers, particularly the reticular-activating system and its cerebral projections, the suggestion is made that consciousness and mood are regulated by central cerebral mechanisms. The use of sulfur-tagged chlorpromazine can give useful evidence in this area. Variations in different neurohumors (adrenalin, noradrenalin, serotonin, etc.) and other chemical mediators of central nervous system activity have brought forth evidence of the biochemical mechanisms underlying depression and agitation. The discovery of these chemical mediators and their psychophysiological implications cannot help but recall the old Cartesian doctrine of "the animal spirits."

THE NEUROLEPTIC SYNDROMES

Since 1954, we have used the term "neuroleptic" when referring to that subgroup of psycholeptic drugs which are highly effective

in the treatment of acute and chronic psychoses. Chlorpromazine and other phenothiazines were the major compounds in use with reserpine. To these have been added a whole new series of non-phenothiazine and nonreserpine drugs, of which haloperidol is a good example. What criteria justify the separation of neuroleptics as a group, as opposed to the hypnotic agents and other tranquilizers?

In humans, as well as in animals, the syndrome produced by drug saturation of the tissues* can be accompanied by somnolence, but drug-induced sleep is not seen at the therapeutic doses used. It is always possible with these doses to awaken the animal by simple stimulation if the drug produces a hypnotic effect. It would appear as if the indifference and inertia produced by neuroleptics facilitates sleep without a real hypnotic effect. As Bergson said, "Sleep is a form of indifference." Neuroleptics cannot be considered as a variant of sleep treatment, since at equal doses the patients treated with neuroleptics do not fall asleep.

The neuroleptics, like the other tranquilizing drugs, reduce the mood tone until a state of emotional indifference and flatness is achieved. The neuroleptics to a greater degree than the others have diminished agitation and aggression, as a result of which special services for the disturbed and the need for restraints have been eliminated in psychiatric wards. This has led to a transformation of the atmosphere in psychiatric hospitals, so that in the future they will not be much different from general hospitals.

The unusual sedative action of tranquilizers has been demonstrated in laboratory experiments on naturally aggressive animals (*Macaca rhesus* and the fighting fish). Other work has been done with the sham rage of decorticated preparations, and animals in whom agitation is experimentally induced (Thuillier worked with 3-amino-diproprionitrile, which causes rats to move in circles endlessly). The neuroleptics not only are effective against various acute and chronic psychiatric syndromes, but they can abruptly stop an artificially induced state ("model psychosis") or even present it through prior administration. The principal criteria which allow their differentiation from other tranquilizers is the production of a neurological syndrome (from which the word is derived).

There are several varieties of this syndrome or group of syndromes which have in common an extrapyramidal reaction, and they depend to a degree on the particular compound. Their characteristics are different with prochlorperazine, as opposed to the sulfonamide

*"imprégnation médicamenteuse."

phenothiazine-thioproperazine. But the clinical syndrome also depends on the individual's sensitivity, for catalepsy and the experimentally induced hysteroid states are seen much more frequently in subjects with a hysterical personality and in those prone to cataleptic phenomena. Even though the symptoms are polymorphous in type, they can be separated into three general groups: (1) the hypokinetic or akinetic syndrome, characterized by a reduction in motor activity and initiative, (2) hypertonic syndromes, characterized by muscle hypertonus, and (3) the hyperkinetic or dyskinetic syndrome, characterized by abnormal movements.

Frequently, if a minimal neurological syndrome due to neuroleptic medication develops, it can pass by unnoticed if one is unaware of what treatment the patient is receiving. Actually, there is a whole series of gradations from the most minor neurological symptoms to the major clinical syndromes. We have approached the problem through a minute study of the sequential changes in the facial features of patients being treated with neuroleptics. A slight change in facial expression resulting from hypertonia of the facial muscles can always be demonstrated. This often precedes the hypertonia of the body musculature and appears in a determined order: palpebral and lateral nasal muscles, then frontal and periorbital muscles, and finally the peribuccal and mandibular musculature. It is thus possible to follow the tissue drug saturation as well as the regression of anatomical changes, which take place in reverse order. In correlating these tonic changes of the facial musculature and expression with modern neurophysiology, one can ask what role the temporal amygdaloid nucleus plays. This formation has projections to most of the cerebral centers that have been implicated as sites of action for the neuroleptics.

The signs and symptoms of the akinetic syndrome are relatively constant and some cases can exhibit the picture of catalepsy, while the hypertonic syndrome resembles parkinsonian rigidity. On the other hand, the hyperkinetic or dyskinetic syndromes are polymorphous in appearance and a whole series of abnormal movements can be produced by the neuroleptics: parkinsonian tremor, which with akinesia and hypertonia produce an experimental parkinsonian state; paradoxical kinetic movements with latero- and retropulsion; choreiform bradykinesias; tasikinesia and akathisia; cervical, facial, and buccal-laryngeal dystonic seizures; and finally the major hysteroid crises.

There are a number of problems inherent in the consideration

of the neurologic syndromes produced by neuroleptics: (1) their analogy to the epidemic encephalitic syndrome, (2) the meaning of the hyperkinetic syndrome, (3) the relationship of hysteroid states to hysteria, (4) the linkage of psychological and motor changes, (5) the effectiveness of chemotherapy in the psychoses as related to the intensity of the neurologic manifestations, and finally (6) the prevention or blocking of the neurologic changes by other psychotropic drugs, which are antagonistic in nature. Even though we cannot pretend to offer a solution to these difficult problems, there is a certain usefulness in considering them.

Deniker and I have compared the transitory and reversible neurological syndromes due to drugs with those observed during or after the von Economo encephalitis: the akinetic syndrome of Lhermitte, the hypertonic Parkinson syndrome (Steck), and the excitomotor syndrome of Marie and Levy. These entities are not only analogous but identical. It would seem as if the neuroleptics have the same neurotropism as the virus of von Economo's encephalitis, leading to a sort of therapeutic encephalitis by the saturation of the meso-diencephalic centers with drugs in a selective but transitory fashion. This concept is corroborated by an analysis of the autonomic, endocrine, and metabolic changes resulting from neuroleptic treatment.

Pierre Marie made very clear that his description of the abnormal movements seen after epidemic encephalitis (excitomotor syndrome) was purely clinical and unrelated to pathogenesis. It was not indicated if there was focal excitation of the central nervous system or only a liberation of these centers with respect to the normal inhibition exerted by subcortical centers according to the Jacksonian concept of "escape from control." We believe that the hyperkinetic or, more correctly, the dyskinetic syndrome produced by the neuroleptics should be considered in the light of the latter hypothesis.

The neuroleptics depress without stimulating nervous activity, and the inhibition of the superior centers is the prime condition for the escape of activity from the lower involuntary centers giving rise to the different abnormal movements. These apparently new ("positive") reintegrative aspects of the latter symptoms are conditioned by the negative* aspects which in Jacksonian terms would be equated to a return to a less complex function.

Early investigators classified some of the symptoms of the

*A direct effect of the pathological process.

hyperkinetic syndrome (particularly severe with prochlorperazine and thioperazine) as hysteria or a hysteroid state. The same problem arose earlier with epidemic encephalitis when a whole sequence of symptoms of obviously organic nature appeared—choreiform movements, torsion spasms, cervicofacial and buccal-laryngeal dystonias, opisthotonos, and the entire Charcot's syndrome. As a result of these observations, Marinesco and van Bogaert developed their diencephalic theory of hysterical symptoms.

The neuroleptic-induced hysteroid states are particularly important because the acute neurological manifestations are paired with psychological changes: suggestibility, psychomotor variations, and the narrowing of the field of consciousness. These symptoms can be eliminated by suggestion without a loss of any of the drug's activity. As noted previously, these reactions appear, above all, in those patients who seem predisposed to them, particularly those patients in the paranoid and paraphrenic states.

Even though this tendency to suggestibility exists in the hyperkinetic syndrome, indifference is the rule in the akinetic group and a tendency to depression is relatively frequent in the parkinsonian hypertonia. While one may discuss at length the relationship between psychological changes and motor phenomena, the essential problem still remains to determine whether or not a relationship exists between the neurological syndrome and the therapeutic effects. There is much evidence to show that the results have often been directly related to the intensity of the neurological effect, but this remains to be demonstrated conclusively. Briefly stated, our view is that there is no such relationship but rather that the neurological syndrome offers evidence of a generalized drug diffusion and penetration to the subcortical centers, where those centers regulating mood and consciousness are found. According to this concept, the centers related to the mental syndrome are anatomically contiguous to those producing the neurological syndromes. Thus, the induction of the latter has a "spill-over" effect and favorably influences the former.

One could eventually consider the possibility that a selective localization of the drugs might be dissociated from any therapeutic activity. As noted before, the whole problem is still unclear, and it would seem reasonable to analyze the effects of the neurological syndrome on the mental symptoms by studying the influence of the compounds capable of blocking the former syndrome. The akinetic syndrome is blocked by antidepressants and other drugs that increase alertness; the hypertonic syndrome is affected by the various

anti-Parkinson drugs; and the autonomic syndrome is affected by sedatives. At present there does not exist any drug capable of annulling all three syndromes at one time.

My collaborators and I have studied the effects of adenosine triphosphate (ATP), since it appears to protect laboratory animals against experimental diencephalic lesions produced by reserpine. When given by intravenous drip in man, adenosine triphosphate can annul the hyperkinesia, hypertonia, and autonomic nervous symptoms produced by neuroleptics but akinesia and somnolence are accentuated. This would seem to demonstrate how difficult it is to eliminate all symptoms of the drug-induced neurological syndrome simultaneously and thus be able to determine if the elimination had any effect on the therapeutic process. On the other hand, it is possible to correlate the action of adenosine triphosphate on the neuroleptic-induced syndrome with the very important role it plays in neuromuscular metabolism. This has served as a point of departure for some of our current investigations.

It can be said in a general way that the major biological treatments used in psychiatry have a common point of reference with regard to the drug-induced neurological reactions in that the neurological syndrome they induce suggests involvement of the subcortical centers and the cortico-subcortical pathways. This is obvious with electroconvulsive treatment and cardiazol shock. Both act on the diencephalon and implicate the cortico-subcortical pathways as well. Some antidepressant drugs lower the convulsive threshold and may trigger a dormant epilepsy. The sleep cure and insulin coma are similar, for both sleep and coma imply participation of the basilar portions of the brain; the same can be said for cerebral pneumotherapy and prefrontal lobotomy. Chemotherapy and the shock therapies, insulin coma, and psychosurgery indicate that the biological treatments in psychiatry are essentially acting on and modifying the brain function. These different findings offer strong evidence that mental illness represents an organic brain change, more often functional, with changes in the dynamic equilibrium between the different cerebral centers. Those who espouse a purely psychogenetic view of the neuroses and psychoses have frequently lost sight of these facts.

EXPERIMENTALLY INDUCED STATES OF ABNORMAL BEHAVIOR

Up to this point we have been considering only those drugs that elevate or lower the psychological tonus and that exercise a stimu-

lating or depressing action. The psychodysleptic* compounds are the most interesting for experimental psychiatry since they produce an artificial or "model" psychosis. The substances that can be considered in this group are those that disturb the functioning of the mental apparatus, confuse thinking processes, and distort the individual's perception of reality. They produce dreamlike and confusional states, hallucinations, depersonalization, and in a general way a complete mental disorganization.† Lewin has called these drugs "phantastica," since they give rise to dreamy states with visual and mental disturbances. Hashish, cocaine, mescaline, LSD-25, and psilocybin are some of the more important drugs in this group.

The psychodysleptic drugs are antagonized by the psycholeptic agents, which diminish the intensity of or inhibit the drug-induced states of abnormal behavior. Yet, comparison with the psychoanaleptics is more difficult. Cocaine, which stimulates at high doses, will, if the dose is pushed high enough, produce a delusional-hallucinatory syndrome. The psychodysleptic drugs unquestionably stimulate the mood and appear at times to stimulate the intellectual activity as well. However, these newly apparent "positive"‡ effects are in reality the result of negative factors. In other words, the drug's psychological effects must be considered in the Jacksonian frame of reference as an "escape from control," a regression and liberation of the mental functions.

The relationship of drug-induced states to toxic deliria, stuporous conditions, and apparently spontaneous mental disturbances was noted in antiquity, but the first real experimental study dates to the nineteenth century with the report by Moreau de Tours. His publication on "Hashish and Mental Illness" appeared in 1845 and was based on self-observations with the drug and on studies with normal subjects and highly gifted individuals. He concluded that by using hashish it is possible to reproduce the primary aspects of mental illness: splitting apart of the different components of the mind and a hallucinatory syndrome which he compared to the structure of a dream. Today one speaks of the psychotic-like characteristics of a dream.§ In following Kant's definition ("the insane person is like the dreamer in a waking state"), Moreau de

*The "dys" means "distortion of."
†"Dêlire" in the etymological sense (de lira) means "out of line."
‡ As used in the Jacksonian sense.
§"structure onirique."

Tours not only felt that psychoses and dreams are analogous but that they are one and the same. While this concept can be criticized, it is correct when applied to the visual hallucinations resembling a dream state ("onirisme").

Hashish is a hallucinogen, as are most of the drugs used to produce artificial psychoses where the delusional state seems to depend both on a localized irritation of the sensorial analyzers (particularly those concerned with visual perception) and on a general reduction in the level of consciousness. I would like to insist on the fact that visual hallucinations are often absent and may only represent an illusory phenomenon even with mescaline and psilocybin. They are but one element of an extremely complicated clinical state which corresponds to the dream life of the mental apparatus. These drugs are not only hallucinogenic but can produce delusions, fantasies, dream states, etc.* They give rise to a state best defined as one in which the synthetic powers of the mind no longer function, in addition to which there is a release of the unconscious.**

In a Jacksonian frame of reference, we can speak of regression as suggested by the loss of the frames of reference for perception and memory, distortions in time and space, disturbances in body image and personality (ego), as well as a disruption of the philosophical unity and direction of the individual. These processes lead to a disruption of the normal mental stream. There is, running parallel to this, a loss of control, a liberation of the fantasy life, a projection of the esthetic aspects of the subconscious, and a reorganization of the apparently anarchic quality of the thought processes according to the needs of the instinctual life rather than to the demands of reality.

In the light of these facts, the experimental endogenous states of abnormal behavior can bring to light latent personality traits, since we dream or hallucinate in accordance with what we have and what we are. Long before psychoanalysis emphasized the meaning of the unconscious projections, of symbolism in dreams and hallucinations, Moreau de Tours had noted with interest the importance of a psychodynamic analysis of the hashish-induced state. One of our patients dreamed of killing his mother while under the effects of this drug; this feeling reflected a severe reality conflict. The drug-induced experience was so overpowering that, feeling it to

*"onirogène."
**"régime onirique."

be true, he surrendered to the police for the ostensible crime he imagined he had committed. Nevertheless, in general the projection of underlying conflicts during the artificial drug-induced state is not frequent, at least as seen in our studies with 40 patients who received mescaline, 75 who received LSD, and 100 who received psilocybin. The general tenor of the projections during the experimental psychosis was nonspecific, varying with many factors and ofttimes was purely fortuitous. In our experience, psilocybin is one of the most interesting drugs used to induce an experimental abnormal state of behavior.

I would now like to discuss some self-observations with psilocybin, carried out in the presence of two of my collaborators, one of whom noted the somatic and the other the psychological reactions. The sequences of this personal experiment could be divided into three phases: (1) hallucinations with colors predominating, (2) a resurgence of highly charged emotions, and (3) a veritable cascade of various psychomotor phenomena. I will now describe some of these findings.

The first phase was marked by visions of a kaleidoscopic nature with many colors, giving rise to much feeling, particularly the reds and violets. A sentence was noted in the protocol which under ordinary circumstances I could never have said, "If I were a painter, I would like to color this violet, which would make the whole world happy." The colors were very bright, present with eyes closed, and disappearing with eyes opened.

The phase in which previous memories returned began with an auditory illusion. I confused the noise of an airplane passing over the hospital for the noise of a train. This produced a memory recall, in which I found myself back in 1917. At that time I lived with my family in the country in a house whose property was traversed by a railroad. This house surged forth before my eyes in an unmistakable fashion, but, curiously enough, it had neither doors nor windows. Certain of the details suddenly stood out with extraordinary clarity: a magnolia leaf in front of the door, a shawl left on one of the pieces of garden furniture, the empty bird cage whose door had been torn off. Although no human figures appeared in these visions, I was wracked with tense emotion and, losing all self-control, began to cry, not paying any attention to the presence of my two assistants. One of them took my blood pressure, which had risen from 150/90 mm Hg to 210/100 mm Hg, probably a result of the strong emotional reaction rather than a direct effect of psilocybin. I wondered why

the hallucination of this old house, whose name was Saint Bernard,* provoked such strong emotions in me. This was linked both to significant memories of my childhood and to fortuitous circumstances. Actually, I had learned several days before the experiment that the house, which had been rented for the past thirty years, was to be sold. I had learned this with no apparent conscious reaction, but subconsciously there must have been some telling effect. I must at this point note another memory triggered by a kinesthetic stimulus. As my knees were pressed against my desk, I had the same feeling as years ago when I was a child and leaned against the window sill of our house in Bayonne; here in the Basque country I could look at the wharfs along the Nive River which meandered below the window. And again, the eerie magic lantern of my childhood lit up the apartment in a sort of halo, yet in a very exacting manner showing different pieces of furniture whose existence I had forgotten about long ago.

Next, there was a relative logorrhea which gave the observers an impression of confusion and incoherence. Body image defects appeared which I recalled afterwards, as well as a tendency to perseveration. At the end of three hours, the experiment was ended. I was able to go about my regular work that afternoon without any trouble but nevertheless noted that my mood was somewhat quickened and that colors appeared brighter than usual; this disappeared several days later. It is of interest to report Volmat's studies in our department of psychopathological art at Saint Anne. He observed that some painters not only had a modification in their color sense after psilocybin but in their technique as well.

In London this past March, Pichot, Lemperiere, and I presented our results concerning the somatic and psychological effects of psilocybin in 101 abnormal and 52 normal patients. We observed changes in (1) emotional, volitional, and intellectual spheres, (2) perception of the body image, (3) contact with the surroundings, (4) mood, and (5) time and space. Analysis of these parameters with psilocybin offers an advantage over mescaline because of the time factor—the whole experiment lasts about four hours. Systematic analysis of these changes can be very useful for experimental psychiatry. Thus, data become available on the differences between hallucinations and hallucinosis, the changes in self, and the individual's relations in time and space. Outside these particular problems, the technique is of value for analysis of the individual's

*It had formerly been a monastery.

psychological state and psychopathological condition since each entity has its own particular way of reacting to psilocybin.

One may ask, what is the relation between the experimental psychoses and the endogenous psychoses? Do these relationships offer any argument in favor of the biochemical origin of the psychoses? Do they have any importance insofar as diagnosis and treatment of mental illness is concerned?

The artificially induced psychoses produced by the psychodysleptic drugs are acute exogenous states whose symptomatology is variable, depending upon the drug and the patient as well as on the interaction between both, oscillating between a depersonalized state and one in which there is a complete loss of the associative processes with confusion, delusions, hallucinations, temporal-spatial disorientation, etc. The acute experimental exogenous psychoses are the same as the hallucinatory psychotic states seen in the wards whether the latter are endogenous or exogenous in origin. These drugs can produce a whole gamut of syndromes which can be suggestive of different diagnoses. Even a psychiatrist with considerable experience, when asked to examine blindly patients under the effects of LSD or psilocybin, will not fail in some cases to question the possibility that these may be cases of early schizophrenia.

The psychodysleptic drugs can produce a hallucinatory psychosis but cannot reproduce the characteristics of schizophrenic process. However, if one takes into account the polymorphic characteristics of the artificial psychoses and the early schizophrenic syndromes and if one compares one acute state with another (not an acute with a chronic condition), certain similarities become apparent. Depersonalization and confusion with loosening of the associative processes can resemble the schizophrenic dissociation. Régis certainly had this in mind when he separated the condition called "chronic mental confusion" or "postconfusional schizophrenia." The experimentally induced drug states are, of necessity, short lasting, but chronic states are known, as with hashish. Uzman described the latter clinical condition as analogous to a schizophrenic dissociation. The drug-induced state differs from the paranoid syndrome because of the preponderance of visual hallucinations and the confusional state. But, between the hallucinatory dreamy states* and autistic thought, there is a strong structural similarity, as suggested by an analysis of the symptoms, the psychodynamics, and the Rorschach material.

*"pensée onirique."

In addition, certain schizophrenic conditions begin with an acute delusional state, periodic attacks of visual hallucinations, or a dream state with clouded consciousness and frequently lead to chronic schizophrenia. It would not seem necessary to give these a special name ("oneirophrenia," according to Meduna), since they are probably all varieties of the same fundamental schizophrenic process. The symptoms of paranoid schizophrenia respond very well to chemotherapy, just as the drug-induced states, provided that in the former sufficiently high doses are given for a considerable period of time, as one would do in the chronic psychoses. Is it not possible, then, that there might be some pathogenetic similarity between both conditions? Hippocrates said, "Treatment will reveal the nature of the illness."

Inappropriate affect and laughter (noted previously by Moreau de Tours with hashish), dysphoria, ecstatic states, bizarre behavior, feelings of being "far away," strangeness in the immediate environment, and inexplicable changes in relationship of self to the world have been noted in some of the experimental psychoses. All of these symptoms are observable in early schizophrenia, as Morcelli indicated with regard to mescaline. Some of the chronic schizophrenic patients can relive their earlier acute psychotic symptoms under the effects of these drugs, particularly psilocybin. The relationship of the catatonic syndrome observed during an early acute exogenous psychosis with catatonic schizophrenia has already been discussed by Baruk and de Jong, as well as Buscaino, and more recently by Gjessing in his studies of periodic catatonia. Taking into strict account the problem of nosology in the group of schizophrenias as well as our limited experiences with the psychotropic drugs (which, nevertheless, increases and even changes directions with time), it can be said that there are some similarities between certain forms of the artificially induced psychoses and certain schizophrenic syndromes; to be analogous does not, of course, mean being identical to. This analogy has given new impetus to the biochemical theories of psychoses.

The organic concept of mental illness is strongly opposed by those favoring the psychodynamic etiological approach. Yet, the apparent dissimilarity between the opposing view is more apparent than real. In any case, the psychopharmacologic studies are aimed at the pathogenetic mechanisms of the mental syndromes so that there really is no conflict with the psychodynamic hypotheses.

Is it not possible that emotional tension of either an acute or

chronic variety can give rise to metabolic disorders via the mechanisms of the alarm and exhaustion syndromes? Thus, the psychodynamic pathogenesis could still be considered even though their effects theoretically were produced by biochemical mechanisms. There is even more. The human emotions are capable of inducing symptoms that are as intense and variable as those induced by psychotropic drugs (whose action can be depressing, stimulating, or disorganizing) with disorders in the intellectual, emotional, visceral, and motor spheres. In addition, it has been known for a long time that an emotional shock is not only symptom producing but symptom removing as well, perhaps by the alarm-reaction mechanism acting through the diencephalic-pituitary axis. In all probability, there is reason to believe that symptoms of the various psychoses are organic in nature, resulting from the organization and integration of different central cerebral pathways. The psychophysiological mechanisms described can also be precipitated by somatic and psychological factors as well as by psychotropic drugs. Their effects are felt via the intermediary of the central physicochemical changes in the brain; this can be considered one of the bases of mental life but not necessarily the only one.

Experimental studies with psychotropic drugs in the light of their selective central action have elicited a wealth of information on the topographic etiological localization of the different mental syndromes. One of the central problems of psychopharmacological research today is the relationship between the cortical and subcortical structures: consideration could be given to the diencephalon and reticular-activating substance in relation to the regulation of sleep and waking states, the influence of hypothalamic and limbic structures in the regulation of mood and emotional tone, the relation of the mammillary bodies and their projection tracts to the psychopathology of time relation and memory, and the cortico-infracortical pathways in respect to psychomotor activity. Everything that we can learn about the localization of action of psychotropic drugs will help in understanding the specific central pathological component of mental illness.

The importance of pinpointing the topographic localization of these syndromes is self-evident, but yet more important is a knowledge of the biochemical mechanisms. Much has been written about the many contributions of neuropathology to neurology and the sterility of such findings in the psychoses. It would, indeed, be tempting to conclude that with no neuropathologic changes in the

psychoses, consideration of an organic cause would be fruitless. However, the problem is of such importance that it could be considered from another angle—the functional biochemical disturbance. This would not be a matter of an anatomical lesion but of physiological changes revealed through the use of biochemical techniques.

The concept of the functional biochemical disturbance, conceived from neurochemical evidence suggesting metabolic changes of central neurohumoral substances and their enzymes, represents one of the most heuristic orientations in biological psychiatric research. This is particularly true in so far as the problems of enzymatic inhibition are concerned. Certain drugs, for example, act by inhibiting the enzyme that normally destroys a mediator (monamine oxidase and iproniazid). Other drugs do the contrary—inhibit an enzyme whose role is in synthesis. Enzymatic control, thus, can act in two ways: inhibition or activation of a mediator. It is only recently that the biochemical mechanisms of action of mediators has been elucidated. Thus, some of the pharmacological activity of catechol amines (e.g., hyperglycemia) can be explained by the activation of a phosphorylytic enzyme necessary to break glycogen down to glucose. In this regard, may I point out that psilocybin is not only the first naturally occurring phosphorylated indole but that the phosphorylation of this nucleus is probably unrelated to the drug's action, since psilocin (a dephosphorylated psilocybin) has the same properties as psilocybin.

A study of the antagonism between psychotropic drugs can yield much interesting information. Thus, psychoanaleptic states induced by amphetamines are neutralized by psycholeptic states induced by barbiturates and vice versa. The psychodysleptic states can be terminated or even blocked by the neuroleptics. One can even go further. Studies of the antagonism between LSD-25 and serotonin have opened new horizons as well as stimulated research concerning central variations in serotonin and noradrenalin content resulting from reserpine and neutralized by antireserpine compounds. The indole nucleus, present in some substances capable of inducing an abnormal state of behavior, has stimulated other studies. The structural analogy between LSD-25 and psilocybin is clear, since both possess a 4-substituted indole nucleus.

In spite of all these theoretical considerations of experimental psychoses, the clinical use of psychodysleptic drugs does not seem to be justified as a general procedure. They should not be used clinically without specific indications, either diagnostic or thera-

peutic. This, of course, does not relate to experimental studies by volunteers or physicians.

PSYCHODYSLEPTIC DRUGS AS AIDS IN DIAGNOSIS AND TREATMENT

Psilocybin offers diagnostic possibilities. A psychodynamic analysis of the material revealed during the drug study period permitted one to understand the unconscious material much better; it could almost be called a chemical psychoanalysis. I will come back to the possible therapeutic aspects later.

Since psilocybin exaggerates the underlying neurotic or psychotic trends, it can clarify many problems and help in the diagnoses of clinical problems that are unclear. For example, an atypical anorexia nervosa showed a frank hebephrenic reaction, which was then treated with neuroleptic medication. There was, on the other hand, an atypical depression treated unsuccessfully for one year with psychotherapy. Psilocybin produced a frank melancholic reaction. Subsequent electroconvulsive treatment eliminated all the symptoms of depression, and the patient was well. Hebephrenic patients show an atypical excitement or cataleptic state, with the only signs of emotional involvement being inappropriate laughter. The paranoid or chronic delusional psychotic individual shows a depersonalization and derealization resembling the earlier phases of the illness, a hallucinatory delusional state, the reappearance of significant psychotic symptoms, or an anxiety syndrome with agitation and combativeness. The psychoneurotic patients show a fairly constant picture with anxiety and dysphoria predominating. The type of reaction will differ according to the significant character traits—hysterical, phobic, obsessive, or others. The neurotic subject generally lives through the drug-induced experience much more intensely than normal subjects, focusing upon and abreacting the traumatic events and past significant conflicts.

The interest in using psilocybin, as well as other pharmacologic substances, in the traumatic neuroses is obvious, in view of the possibility of producing, almost at will, an abreaction of past events. Besides these rather infrequent cases, one can consider the drug's therapeutic action from two points of view.

There is first a direct biological mood-stimulating effect on the organism. This is very clear in neurasthenic conditions and some depressions. In depression there can at times be a mood

reversal under the effects of the drug. Second, there is the psychodynamic action I have already mentioned. The physician can use this material to great advantage in terms of the patient-physician relationship during the experimental period. The patient can play a dual role—the observer and the observed. He thus can be close to the symbolism inherent in the drug-induced state and yet observe it at a distance. Since this all takes place in clear consciousness, a detailed analysis is possible at a later time, since it is only in the hours and days that follow that the analytic work becomes more meaningful. The patient can bring together his past and drug-induced present, and with the therapist arrive at a synthesis—a "psychobiography."

One frequently observes changes in the patient-physician relationship as a result of the emotional changes in the patient. The transference which is often very strong during the experimental period continues afterwards as well. This can be used psychotherapeutically, since the analysis can now proceed without the transference resistance.

This leads me to state a concept of fundamental importance in psychiatry—the reciprocal relationship between chemotherapy and psychotherapy. The neuroleptic drugs have facilitated the psychotherapeutic process by removing those symptoms that have blocked the patient's efforts in relating to others. Actually, they have not decreased the need for social therapy, psychotherapy, and other modalities but have facilitated their application and extended their use to patients hitherto unreceptive to such treatments. In addition, it has been possible to introduce new techniques in psychotherapy through the use of leptic, analeptic, and dysleptic drugs. I refer here to narcoanalysis, amphetamine shock, and the drug-induced states of abnormal behavior produced with LSD and psilocybin; and, in all probability, new drugs and new techniques will appear in the years to come. In one of his last works, Freud wrote, "Only psychodynamically oriented treatment is of interest to us, since this is all we have at the present. In the future, we will probably learn to influence the libido directly and the mental life as well through the use of chemical compounds." This perspective, which to him seemed so distant, has in reality arrived, for in fact pharmacologic agents are capable of influencing psychological activity in a psychodynamic frame of reference.

Psychoanalysts and others have tended to identify psychiatry as a discipline based on philosophical, moral, and ethical values,

as well as the psychotherapy of mental illness. But, there has developed in a parallel fashion a biological approach based on neurophysiological research aided by the contributions of neurochemistry, endocrinology, and psychopharmacology. Yet, psychiatry cannot be reduced to a sort of pharmacologic medicine, no more than it can be reduced to the mere status of psychological medicine. The ancient opposition between psyche and soma has given rise to a holistic approach, a global concept. The physician can now view the personality as a totality in which biological, social, and psychological processes are only artificially separated for study. In this concept of the individual, psychiatry today is striving to remove its prejudices and its clashing doctrines so as to integrate the use of all techniques, physical or psychological, in its continued fight against the scourge of mental illness.

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