American Handbook of Psychiatry

PHYSICAL THERAPIES OF SCHIZOPHRENIA

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Historical Introduction

Once dementia praecox had been established as a nosological entity by Kraepelin, an entity which was later extended by Bleuler to encompass the whole concept of the schizophrenias, the search for some physical treatment of this condition began in earnest. Since no single cause of schizophrenia has ever been found, no systematic, rationally focused research in this field could be mounted, except for some isolated attempts to test certain hypotheses. As a result, empirical experiments with a very large number of treatments were conducted by many clinicians all over the world, involving such varied approaches as the administration of manganese[1], or the production of sterile abscesses, and such heroic procedures as the artificial induction of aseptic meningitis.

Six physical treatment methods of schizophrenia proved eventually to be at least partially effective, and all were, in fact, developed on a trial-and-error basis, sometimes supported by theoretical speculations or generalizations and sometimes only by chance observations. These six treatment methods were, in chronological order:

1. *Fever*, induced either by typhoid vaccine, foreign protein (milk), or Sulphur injections. It was tried, with varied temporary success, by many investigators who were encouraged to attempt this approach following Wagner-Jauregg's successful malaria treatment of dementia paralytica.

2. *Continuous sleep*, induced and sustained by a variety of hypnotic and sedative substances, and introduced as a somewhat risky, but nevertheless sometimes successful, treatment by Klaesi, at a time when no other equally effective treatment of schizophrenia was known.

3. *Hypoglycemic coma*, induced by insulin, and introduced as the first dramatically effective treatment of schizophrenia by Sakel, after he had observed that the accidental occurrence of hypoglycemic coma in drug addicts was sometimes followed by improvement of their mental state.

4. *Convulsions*, induced first by camphor and later metrazol, and introduced as an effective treatment into psychiatry by Meduna who—incorrectly—speculated that there was biological antagonism between epilepsy and schizophrenia. Convulsive therapy was later improved in its clinical application by Cerletti and Bini, who developed an electrical method of producing convulsions (ECT).

5. *Psychiatric surgery*, first consisting in the surgical severance of the cerebral tracts between frontal lobes and thalamus (prefrontal lobotomy), after Moniz had learned of certain behavioral observations following experimental

neurosurgical interventions in monkeys. Since then, many varieties of the neurosurgical procedures which characterize this treatment modality have been developed.

6. *Systematic pharmacotherapy*, the most successful single treatment of schizophrenia to date, which was introduced into psychiatry by Delay and Deniker in 1952, after they had observed the pharmacological action of a newly developed class of psychotropic drugs, i.e., the neuroleptics, on psychiatric patients.

Hyperpyrexia and continuous sleep therapy have now become obsolete as treatments for schizophrenia. Insulin coma therapy is only rarely used today, since electroconvulsive treatment is equally effective for the production of temporary remissions, but simpler, shorter, less hazardous, and less expensive in its application. ECT is still used widely in the treatment of schizophrenia, although mainly in special cases and in combination with pharmacotherapy; but psychosurgery is only very occasionally employed, when all other treatments have failed. The physical treatment of choice in acute and chronic schizophrenia today is pharmacotherapy. It is not equaled by any other treatment in effectiveness, reliability, simplicity, availability, and relative absence of major risks.

Some new physical therapies have been proposed in recent years, e.g., high-dose nicotinic acid and multiple megavitamin treatment, based on the so-called orthomolecular approach. Although controlled studies have not yet

produced convincing evidence that these treatments are specifically effective, they have been so widely publicized in the professional and lay press that a lively controversy has arisen around them; and for this reason, they will be discussed in some detail.

In this chapter, these physical treatment modalities of schizophrenia which are currently in general use—or, at least, are claimed to have some clinical validity—will be divided into four categories and dealt with under the headings: (1) Pharmacological treatment; (2) metabolic treatment; (3) hypoglycemic coma treatment; (4) neurophysiological treatment; and (5) psychiatric surgery.

Pharmacological Treatment

There are today ten different chemical groups of drugs that have been shown in clinical trials to effectively reduce schizophrenic symptomology. All of them belong to the pharmacological class of neuroleptics, also often referred to as major tranquilizers and, occasionally, as antipsychotics. These groups are: the phenothiazines, the thioxanthenes, the butyrophenones, the rauwolfia alkaloids, the benzoquinolines, the benzothiazines, the acridanes, the diphenylbutylpiperidines, the phenylpiperazines and the indolic derivatives.

Only compounds belonging to the first four of these chemical groups are

in clinical use today, but drugs belonging to some of the other known, or still undiscovered, chemical groups will probably be marketed and find clinical application in the near future. Some of the more promising candidates for future use will be referred to later in the text.

The first two drugs that were developed in this new pharmacological class were chlorpromazine and reserpine, and their most prominent action appeared to be sedation. This fact accounts for their designation as "tranquilizers," although some of the subsequently developed drugs of this type did not produce primary sedation and were, in fact, weak stimulants. To distinguish these substances from the old-type sedatives, which do not possess any specific antipsychotic potential, they are now usually referred to as "major tranquilizers," while the traditional sedatives are called "minor tranquilizers" or "anxiolytics."

All major tranquilizers are characterized by their neuroleptic effects and thus are also frequently classified as neuroleptics. Neuroleptic effects are of three types: (1) on the extra-pyramidal system (globus pallidus and corpus striatum), often resulting in a variety of extra-pyramidal symptoms, such as Parkinsonism, akathisia, or dystonia; (2) on hippocampus and amygdala, resulting in a lowering of the convulsive threshold; (3) on the reticular formation and the hypothalamus, resulting in a reduction of perceptual input, as well as psychomotor excitement and emotional tension, and in the

occurrence of varied changes in the functioning of the autonomic nervous system.

Mechanisms of Action

No definitive account can be given of the way in which neuroleptic drugs bring about their antipsychotic effects, but several theories exist. Neurophysiologically, the drugs diminish activation (arousal) of the CNS without producing significant inhibition of cortical functioning and thus, in contrast to the minor (anxiolytic) tranquilizers, they do not induce disinhibition of behavior and affect, nor significant impairment of the higher functions of the CNS, e.g., impairment of the processes of rational abstraction and synthesis. The reduction of excessive perceptual input and psychomotor output serves as a therapeutic intervention in conditions where "jamming" of the CNS, through disproportionate input and arousal, has resulted in psychotic disintegration of functioning.

Most neuroleptic drugs possess a strong sympatholytic action which is probably mediated through a blocking of adrenergic and dopaminergic receptor sites in the neurons.

Mobilized by this blockade, compensatory feedback mechanisms call forth an accelerated production of catecholamines, with the result that dopamine levels in the brain are increased following the administration of

neuroleptic drugs, despite the fact that systemic adrenergic effects are diminished.

Metabolically, the major tranquilizers seem to exert a sparing action, which manifests itself in increased cerebral levels of the high-energy phosphate ATP.

Finally, there is considerable evidence that neuroleptic drugs interfere with the functioning of cellular membranes and thus with the exchange of electrolytes at the neuronal level.

Clinical Application

The use of neuroleptic drugs in the treatment of schizophrenia may be considered under four headings:

1. As symptomatic treatment of acute psychomotor agitation, aggression, or chronic tension.

2. As the principal therapeutic agent in the management of acute schizophrenic breakdowns.

3. As a major single treatment factor in the management of chronic schizophrenic conditions.

4. As maintenance therapy for patients in remission, in whom the recurrence of schizophrenic symptoms must be prevented.

Prior to 1952, no drugs were known which could deal effectively with psychotic symptoms indicating a severe disturbance of a patient's contact with reality, such as hallucinations, delusions, and autistic thought disorders; nor was there any effective way of preventing psychotic relapses of a patient in remission. Now, there is a wide choice of pharmacological agents which can help the psychiatrist to control both of these special problems.

Table 28-1. Different Neuroleptic Drugs Available in the United States and/or Canada and Their Estimated Equivalence in Milligrams When Compared to Chlorpromazine

	TRADE NAMES		ESTIMATED EQUIVALENT
GENERIC NAMES	*United States*	*Canada*	POTENCY
PHENOTHIAZINES			
Aliphatic Derivatives			
Chlorpromazine	Thorazine	Largactil	1
Methotrimeprazine	Levoprome	Nozinan	1.5
Promazine	Sparine	Sparine	0.5
Triflupromazine	Vesprin	Vesprin	4
Piperazine Derivatives			
Acetophenazine	Tindal	Notensil	6
Butaperazine	Repoise	Randolectil	10
Carphenazine	Proketazine	N.A.	4
Fluphenazine	Prolixin	Moditen	50
Perphenazine	Trilafon	Trilafon	10

Prochlorperazine	Compazine	Stemetil	6
Thiopropazate	Dartal	Dartal	10
Thioproperazine	N.A.	Majeptil	40
Trifluoperazine	Stelazine	Stelazine	20
Piperidine Derivatives			
Mesoridazine	Serentil	Serentil	1.5
Piperacetazine	Quide	Quide	10
Propericiazine	N.A.	Neuleptil	3
Thioridazine	Mellaril	Mellaril	1
THIOXANTHENES			
Chlorprothixene	Taractan	Tarasan	1
Thiothixene	Navane	Navane	50
BUTYROPHENONE			
Haloperidol	Haldol	Haldol	70
RAUWOLFIA ALKALOID			
Reserpine	Serpasil	Serpasil	60

Table 28-1 lists the neuroleptic drugs that are currently available in the United States and Canada. Figures 28-1 to 28-4 show the chemical structure of some representative compounds of the four groups of the neuroleptics which are now in clinical use, i.e., the rauwolfia alkaloids, the phenothiazines, the thioxanthenes, and butyrophenones.

The active principle of the rauwolfia plant, which had been used for centuries in India as a treatment for various mental and emotional ills, was isolated in the form of reserpine.

The first derivative of the phenothiazine group which proved to be effective in the treatment of psychotic symptoms was chlorpromazine; it was the synthetic product of a pharmacological search for a tranquilizing substance to be used in anesthesia.

The thioxanthenes were the result of a systematic modification of the phenothiazine nucleus, once its therapeutic potential had been discovered.

The first butyrophenone derivative with good therapeutic action in psychotic conditions was haloperidol. This drug was the result of a deliberate search for new chemical compounds with antipsychotic properties, such as had been discovered in the rauwolfia and phenothiazine derivatives.

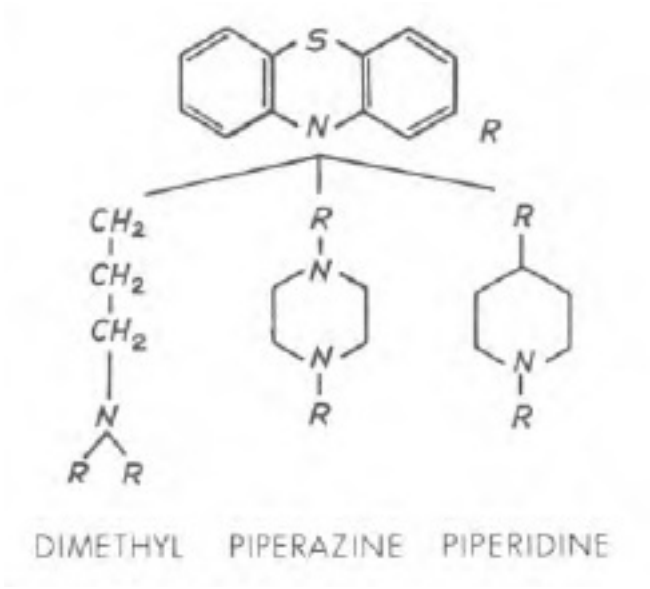

Figure 28-1.
Phenothiazine structure.

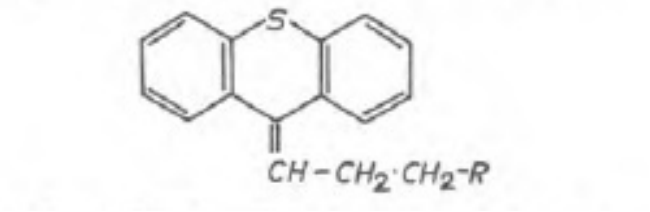

Figure 28-2.
Thioxanthene structure.

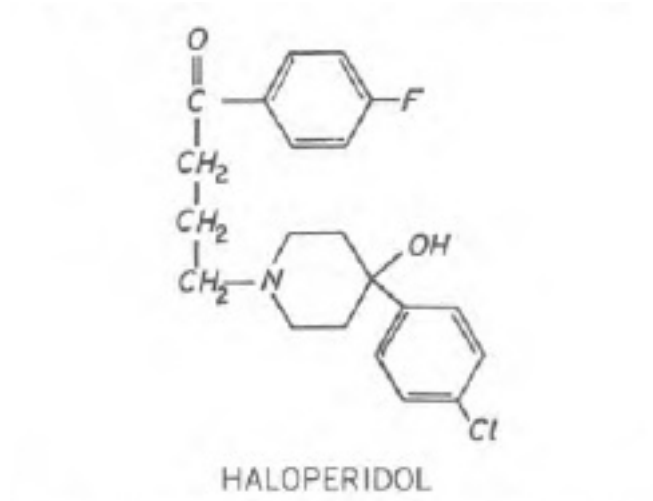

Figure 28-3.
Butyrophenone derivative.

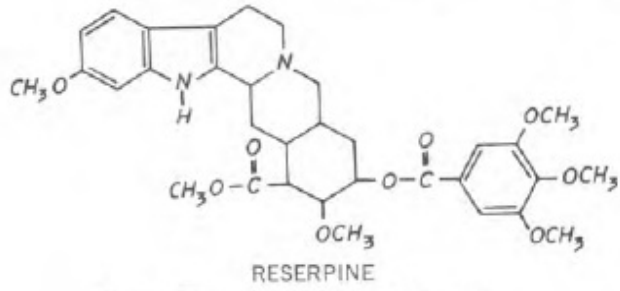

Figure 28-4.
Rauwolfia derivative

Rauwolfia Alkaloids

Reserpine and other rauwolfia preparations are prescribed today only

infrequently in the treatment of schizophrenia. They act more slowly than phenothiazines and butyrophenones, and their side-effects are often more disturbing. However, in a small number of cases which have been relatively refractory to treatment with other antipsychotic agents, the rauwolfia derivatives are still prescribed occasionally.

A specific effect of reserpine is the release of stored neurohormones, e.g., serotonin and norepinephrine, from brain cells. Related to this effect is probably the observation that a certain proportion of patients receiving reserpine may develop depressive conditions. Rauwolfia derivatives are incompatible with monoamine-oxidase inhibitors and should not be prescribed simultaneously with them. It has also been shown that electroconvulsive therapy must not be administered while patients are on reserpine medication. At least a week should elapse between discontinuation of reserpine therapy and the first electroconvulsive treatment.

Phenothiazines

The most widely employed drugs in the management of schizophrenia are the phenothiazines. Common to all of them is the phenothiazine nucleus. However, the various phenothiazine derivatives differ in the structure of their side chains. Almost all of the currently used preparations with good antipsychotic action present a straight chain of three carbon atoms attached

to the nitrogen of the phenothiazine nucleus, but in other respects the side chains may differ considerably (Figure 28-1).

Phenothiazine compounds with a *dimethyl or aliphatic* side chain tend to evoke drowsiness and various autonomic symptoms.

The *piperazine derivatives* do not produce drowsiness as a rule, and might, in fact, be mildly stimulating in their pharmacological action. However, since many schizophrenic patients are agitated, owing to their particular psychopathology, the secondary and global effect of these drugs might, nevertheless, be tranquilization, because the drugs reduce psychotic tension or other psychopathological manifestations, such as hallucinations and delusions. While less likely than the aliphatic derivatives to produce sedation and autonomic effects, phenothiazine derivatives with a piperazine structure are characterized by a much greater likelihood to evoke extra-pyramidal symptoms than the phenothiazines with an aliphatic side chain, and milligram for milligram, they possess greater pharmacological potency than the latter.

The *piperidine derivatives* currently in clinical use are characterized by the lowest incidence of extrapyramidal symptoms and also, like the group with an aliphatic side chain, by a tendency to produce somnolence and more autonomic symptoms.

Thioxanthenes

The thioxanthene derivatives are tricyclic neuroleptics with a modified phenothiazine nucleus: The nitrogen in the middle ring is missing. Only two drugs of this category are on the market now, and most of what has been stated about the structure-response relationships in phenothiazines, depending on the nature of the side chains, applies also to the thioxanthenes.

Butyrophenones

Butyrophenones differ in their chemical structure from reserpine, the phenothiazines, and thioxanthenes. Pharmacologically, they resemble the piperazine group of phenothiazines, in that they are effective in small doses and provoke extrapyramidal symptoms in a high proportion of cases.

Differential Action of Drugs

Which of the many neuroleptic drugs should one prescribe in a given case? If the use of reserpine today is limited because of the reasons given above, what about the choice between the different phenothiazines, thioxanthenes, and butyrophenones? For some time, it was thought that phenothiazines with predominantly sedative properties—for instance, chlorpromazine and Thioridazine— would be indicated in the excited schizophrenic, but would be contraindicated in the withdrawn or stuporous one. It has been shown, however, that a stuporous catatonic patient might respond with an increase of spontaneity and activity to chlorpromazine just

as rapidly as he might respond to one of the more stimulating phenothiazines, for instance, perphenazine or trifluoperazine. Most clinicians prefer, nevertheless, to prescribe one of the more sedating phenothiazines for the excited schizophrenic, and one of the piperazine derivatives, which have a mildly stimulating effect, for the chronically inert patients. While this is the general practice, the fact remains that there is no persuasive evidence that the reasoning behind this choice is valid.

Some authors were able to reveal certain differential effects of one phenothiazine or another, and the findings—while significant more in the statistical than in the clinical sense—were based on carefully designed and well-controlled multihospital studies and on relatively large samples of patients.[2] However, when trying to replicate their findings in follow-up studies, two investigators could not cross-validate their original results. Others have been unable to detect any differential pattern of response to haloperidol, a butyrophenone, or perphenazine, a phenothiazine.

For clinical purposes, it may thus be concluded that all neuroleptic drugs are of approximately equal therapeutic efficacy in the treatment of schizophrenia. Their chief differences are to be found in the dosages they require and in the side-effects they produce. Of course, another difference to be considered, particularly with drugs which may have to be used for a long time, is the economic differential—the price of each drug.

Dosage

Dose requirements for neuroleptic drugs vary according to the following factors: (1) Type of drug; (2) stage of the illness; (3) therapeutic goals, e.g., suppression of symptoms or preventive maintenance treatment; (4) individual differences.

In discussing dosage, it is convenient to reduce the dose requirements for different drugs to standard "chlorpromazine units," or the milligram for milligram potency of other neuroleptics relative to chlorpromazine. Table 28-1 gives this ratio by showing the approximate potency (in milligrams) of various neuroleptic drugs in comparison to chlorpromazine. For example, perphenazine being ten times as potent as chlorpromazine, one milligram of perphenazine is roughly equivalent to 10 mg. of chlorpromazine. As a rule of thumb, it may be assumed that neuroleptic drugs which are administered intramuscularly—they should never be given intravenously—are about three times as effective as orally administered drugs.

An informative review by Klein and Davis has shown that in a large number of placebo-controlled studies, the cutting point for effective doses of neuroleptics in the treatment of acute schizophrenic conditions was at a daily dose of about 300-500 mg. of chlorpromazine. We consider a daily dose range of *300-1000 mg.* as indicated for the treatment of *acute schizophrenic conditions.* In certain patients, these daily doses may have to be increased to

2000-3000 mg. of chlorpromazine, or the equivalent dose of another neuroleptic. When the acute symptoms have been brought under control, a gradual reduction of dose should be attempted to prepare the patient for *maintenance therapy,* which usually employs daily doses of 100-500 *mg.* of chlorpromazine, or its equivalent.

While it is a good general rule to gradually increase the dose of drugs which may cause systemic effects, one will often have to proceed more rapidly in the case of an acutely disturbed schizophrenic patient. It is advisable to initiate treatment in an agitated patient with a 50 mg. dose of chlorpromazine, or its equivalent, given intramuscularly (or 100 to 150 mg. by mouth), and then give subsequent doses at thirty-minute intervals—if necessary, doubling the initial dose—until the patient's most disturbing symptoms are controlled. It may thus be necessary to reach a dose of 500-600 mg. in staggered increments during the first day.

Once the optimal daily dose has been established, it may be divided into three or four daily doses during the acute stage, but when the subacute or chronic stage of the illness prevails, there will be no need to exceed twice-a-day medication, as has been demonstrated in recent studies. During maintenance treatment, it is advisable to restrict the patient's drug-taking to once—certainly not more than twice—a day.

Neuroleptic drugs have relatively low toxicity, which allows for a large therapeutic margin. It is not well understood why dose requirements of neuroleptic drugs often vary widely in different individuals, but some recent work indicates that different ways of metabolizing drugs characterize different individuals, and genetic-constitutional differences of enzymatic breakdown mechanisms and protein binding are probably responsible for the fact that identical doses of neuroleptics may produce greatly different plasma levels in different subjects. Although no clear correlation between plasma levels and therapeutic outcome has been established so far, plasma levels do correlate with the occurrence of side-effects.

What is an adequate dose? There is a clinical relation between the time of disappearance of certain symptoms and dosage, which can be helpful in determining whether a particular dosage schedule is effective. It has been observed that symptoms belonging to the parameter of arousal, e.g., excitement, restlessness, irritability, and insomnia, tend to be the first ones to be controlled by effective doses of neuroleptic drugs, i.e., after two to four weeks of pharmacotherapy. Symptoms related to perceptual and cognitive functions, e.g., hallucinations, delusions, and thought disorder, disappear last, i.e., in many cases, only after a treatment period of four to eight weeks.

Observing this “timetable” of therapeutic responses to neuroleptic therapy will enable the physician to determine whether the dose of the drug

he is prescribing is adequate for a given patient. There may be need to increase the dose if the patient is still restless, irritable sleepless, anxious, and withdrawn four weeks after drug treatment was started; on the other hand, dosage may be adequate if after six weeks of therapy the patient is quiet, friendly and co-operative, although in a psychiatric examination he may still show evidence of hallucinations, delusions, and thought disorder, which may not disappear for another few weeks.

Maintenance Treatment

It is now well established that medication must be continued for some time after the schizophrenic patient has become symptom-free, or an optimal level of symptom control has been reached. Since pharmacotherapy cannot cure schizophrenia—not any more than insulin can cure diabetes or digitalis congestive failure—but only suppresses its symptomatic manifestations, maintenance medication must be continued indefinitely, if no spontaneous remission of the basic pathology occurs. Unfortunately, there is as yet no way to select those patients in whom spontaneous remission in the natural course of schizophrenia would make it unnecessary to continue with maintenance medication. This means that one either has to accept the risk of a psychotic relapse, or the patient must continue, perhaps unnecessarily, on maintenance medication for an undetermined period of time.

Just how great is the risk of relapse? There are many studies, some controlled, some uncontrolled, all of which tend to indicate that the risk of recurrence of a schizophrenic attack is at least twice as great for patients on no maintenance drug or on placebo, as it is for those on active maintenance drug therapy.

Relapse rates reported in these studies vary widely, from 7 percent (in a one-year follow-up) of patients on maintenance drug in uncontrolled studies, to 33 percent in controlled trials; and from about 20 percent to more than 70 percent for patients not taking neuroleptics. In one of the best recent controlled studies, which was carried out simultaneously in three different clinics, Hogarty and his co-workers found a 72.5 percent relapse rate of schizophrenic patients at the end of twelve months in patients receiving only placebo, and a 32.6 percent relapse rate of schizophrenic patients receiving an active drug (chlorpromazine). These results were somewhat improved when social therapy was combined with placebo or drug; the relapse rates were then 62.65 percent with placebo and 25.74 percent with drugs. The investigators point out that 30 percent of their patients did well on placebo for a period of ten months, and then rather suddenly relapsed without having given warning. It was not possible to determine any criteria by which these late relapsers could have been identified earlier. The research team also felt that the relapse rate of the patients on drug would have been lower, 20 percent or less, if all patients would have taken their drug regularly.

It is, however, well known that many patients are very unreliable about following a maintenance drug regime. One study in Britain reports that almost 40 percent of patients on maintenance treatment were irregular drug-takers or stopped taking their medication altogether. How to induce patients —and their families, who are often opposed to the "doping" of a relative in remission—to take their maintenance treatment seriously, is a difficult problem in motivation, a problem which is frequently much more difficult to resolve than the one presented by the treatment of an acute schizophrenic breakdown.

Long-acting neuroleptics are now available, for instance, fluphenazine enanthate or fluphenazine decanoate, which can be injected intramuscularly every two weeks (in doses from 25 to 50 mg.) and remain effective for that fifteen-day period. A new butyrophenone derivative—penfluridol—is now being studied and may soon be available for clinical purposes; this drug may be given orally and retains its effectiveness for five to seven days. The potential impact of long-acting drug therapy on the management of the unreliable or possibly dangerous patient in remission is being widely discussed.

Adverse Reactions

Although the neuroleptics have a remarkably low toxicity and unusually

wide therapeutic margin, they also have a broad range of unpleasant side-effects. Most of these do not constitute serious complications, and many can be effectively counteracted with other drugs or through simple reduction of dosage.

However, the inconveniences they cause for the patient may become important obstacles to the proper and consistent application of pharmacotherapy in some schizophrenics. Itis, therefore, important to anticipate the occurrence of such side-effects, so that the patient may be reassured if they make their appearance.

Table 28-2 (adapted and extended from *Medical Letter)* lists some of the most important adverse reactions and their frequency of occurrence.

Over-sedation, particularly frequent with the aliphatic and piperidine phenothiazines and thioxanthenes, usually disappears after about two weeks, when tolerance to this reaction develops.

Extrapyramidal symptoms occur in about 30 percent of patients receiving aliphatic or piperidine phenothiazines or thioxanthenes, and in more than 50 percent of those receiving other neuroleptics. Anti-parkinsonism drugs counteract these reactions effectively. However, it has recently been shown that in many patients anti-parkinsonism drugs have to be administered only for a few weeks; they may then be withdrawn without a

recurrence of extrapyramidal symptoms. Because most anti-parkinsonism drugs have a powerful anticholinergic action and thus often produce complications of their own, it has been recommended that these drugs should not be prescribed routinely for prophylactic purposes, but used mainly to counteract extrapyramidal symptoms after they have appeared, and withdrawal should be tried after a few weeks.

Table 28-2. Nature and Frequency of Adverse Reactions to Various Types of Neuroleptic Drugs

	Phenothiazines				
	Aliphatic Derivatives	*Piperazine Derivatives*	*Piperidine Derivatives*	Thioxan-Thenes	Butyro-Phenones
Behavioral					
Over-sedation	+ + +	—	+ + +	+ + +	—
Extrapyramidal					
Parkinson's Syndrome	+ +	+ + +	+	+ +	+ + +
Akathisia	+ +	+ + +	+ +	+ +	+ + +
Dystonic reactions	+ +	+ + +	+ +	+ +	+ + +
Autonomic					
Postural hypotension	+ + +	+	+ + +	+ +	+ +
Anticholinergic effects	+ + +	+ +	+ + +	+ +	+
Genitourinary					
Inhibition of	+ +	+ +	+ + +	—	—

Ejaculation					
Cardio-vascular					
ECG abnormalities	+	+	+ +	—	—
Hepatic					
Cholestatic Jaundice	+ +	+	+	+	+
Hematological					
Blood dyscrasias	+ +	+	+	+	+ +
Ophthalmological					
Lenticular pigmentation	+ +	+	—	—	—
Pigmentary retinopathy	—	—	+ +	—	—
Dermatological					
Allergic skin reaction	+ +	+	+	+	+
Photosensitivity reaction	+ +	+	+ +	+	+
Skin Pigmentation	+ +	—	—	—	—

Key: +++, Common ++, Uncommon +, Rare

Tardive dyskinesia is an extrapyramidal syndrome that occurs in about 7-15 percent of patients who have been exposed to long-term treatment with neuroleptics. So far, the syndrome has been most frequently observed in patients on piperazine phenothiazines; but this may be because not sufficient

observations on cases who are treated with newer neuroleptics have been accumulated as yet. This syndrome, which is most likely to appear in elderly patients, is characterized by involuntary movements of the oral region of the face, mostly of the lips and tongue, and sometimes also by chorea-like movements of other muscle groups. What makes this drug-induced condition more serious is the fact that these late-occurring involuntary movements, unlike the earlier-appearing drug-induced extrapyramidal symptoms, are seldom reversible. However, they often appear only after the neuroleptic medication has been reduced or discontinued, since the same drugs that are causing the extrapyramidal damage underlying tardive dyskinesia are also capable of inhibiting its symptomatic manifestations. Until now, these complications have mostly been observed in aged, chronic, often institutionalized patients who seem to be little distressed by it. However, there is now some evidence that children who have been treated for a long time with neuroleptic drugs may develop a similar condition.

It may be possible eventually to develop antipsychotic drugs that do not produce extrapyramidal symptoms, which are the most troublesome of all neuroleptic side-effects. As an example, a recently developed drug (clozapine), which has not yet been released for general use, has shown good antipsychotic properties in clinical trials and appears to be free from extrapyramidal reactions.

Anticholinergic effects are usually restricted to constipation, dryness of the mouth, and, in some cases, to difficulties with visual accommodation. More severe reactions of this type, e.g., toxic psychotic states or adynamic ileus, are, as a rule, the result of a combination of neuroleptics, particularly phenothiazines, with anti-parkinsonism drugs and/or tricyclic antidepressants.

Inhibition of ejaculation may cause the patient some anxiety if he has not been warned of the possible occurrence of this symptom; reduction of dosage is usually all that is necessary to control this side-effect.

ECG abnormalities, consisting of a prolongation of the QRS complex and changes in the T-wave, are due to faulty repolarization in the myocard; they resemble the abnormalities seen in potassium deficiency and are fully reversible. They occur most frequently with Thioridazine and are probably of little clinical significance, except in patients who have some pre-existing cardiac impairment or are in electrolyte imbalance.

Cholestatic jaundice used to occur much more frequently when chlorpromazine was first introduced, but, for reasons not fully understood, is a comparatively rare occurrence today. When it occurs, it ends almost invariably in spontaneous recovery after a few days or weeks.

Of the *blood dyscrasias,* temporary leucopenia may occur rather

frequently, but agranulocytosis only once in every 1500 to 5000 cases. It has been observed most frequently with the aliphatic phenothiazines. Routine blood counts are of little help in predicting agranulocytosis; only continuous clinical vigilance can discover the appearance of this complication early enough to control it successfully with immediate, energetic, therapeutic measures.

Lenticular pigmentation, in the form of stellate cataracts and pigment deposits in the posterior wall of the cornea, is seen almost exclusively after long-term treatment with chlorpromazine. They can be detected by slit-lamp examination. Fortunately, they usually do not interfere significantly with visual acuity, even when they are present to considerable degree. *Pigmentary retinopathy* has only been observed with large doses (over 900 mg./day) of Thioridazine. It is a serious complication, because it impairs visual function and is often irreversible.

Allergic skin reactions usually respond promptly to antihistaminics, a reduction of dosage, or a change to another neuroleptic. *Photosensitivity* is most pronounced with chlorpromazine; but every person taking a neuroleptic drug should guard against exposing unprotected skin to sunlight. Persistent purple *pigmentation of the face* has been observed in a small proportion of patients who had been exposed to large doses (over 500 mg./day) of chlorpromazine for extended periods of time (longer than twelve months).

A number of *sudden, often unexplained and autopsy-negative deaths* occurring in patients receiving neuroleptics, more particularly phenothiazines, have been attributed by several authors to certain adverse effects of these drugs on the cardiovascular or respiratory system, or on autonomic regulation mechanisms. This conjecture has recently been challenged by two investigators who surveyed the literature on such cases in several countries and concluded that many of the "sudden phenothiazine deaths" may have been cases of "lethal catatonia," or the result of some other unexplained factors which are also operating in drug-free subjects in the general population.

A survey of 4,625 patients, half of them on neuroleptics, showed that the mortality of patients on neuroleptic drugs was not higher than of hospitalized schizophrenic patients who were not on drugs.

A study in a Canadian mental hospital compared the death rates in several patient groups prior to and after the introduction of neuroleptic drugs and concluded that mortality in hospitalized patients under sixty-five years of age was actually significantly decreased in the years following the introduction and general use of these drugs.

Neuroleptic drugs have been administered to thousands of *pregnant women,* and except for a few isolated, and unconfirmed, reports of malformed

children born to those mothers, one is probably safe to assume that neuroleptic drugs are not teratogenic, although the usual precautions during the first trimester of pregnancy should be observed as with any other medication. It has been reported that a newborn infant whose mother had been on a neuroleptic regimen right up to delivery showed signs of extrapyramidal dysfunction, which disappeared rapidly and completely with conservative management.

Efficacy

How effective are neuroleptic drugs in the treatment of schizophrenia? Extensive and carefully controlled multihospital studies, carried out by the Veterans Administration and later by the National Institute of Mental Health, have established, beyond any doubt, the superiority of all phenothiazines tested over phenobarbital and placebo in chronic and acute schizophrenics. Klein and Davis reviewed 118 placebo-controlled studies and found that in 101 the neuroleptic drugs were definitely superior to placebo. Whenever chlorpromazine or another neuroleptic was not found to be superior to placebo, it was almost always due to inadequate doses (less than 500 mg./day) or insufficient time of treatment (less than two months).

An informative study by Prien and Cole showed that higher than usual doses, i.e., 1000-2000 mg./day of chlorpromazine or the equivalent, were

effective in a proportion of patients who had remained refractory to lower doses, if the patients were under forty years of age and had been hospitalized for less than ten years.

Neuroleptic drugs can be safely combined with each other, as well as with anxiolytic sedatives, tricyclic antidepressants, and MAO inhibitors. However, except for the practice of combining neuroleptics with antidepressants for schizophrenic patients who are also clearly depressed, there is no good evidence that such combinations are more effective than a single neuroleptic drug by itself.

In comparison with insulin coma therapy, neuroleptic treatment has consistently been shown to be at least equally effective—and, of course, simpler, less expensive, and less hazardous—but Kelly and Sargant demonstrated convincingly the superiority of neuroleptic pharmacotherapy over insulin coma treatment.

Similarly, ECT was shown to be as effective as pharmacotherapy or somewhat less effective than neuroleptic drugs.

In a frequently quoted paper, Brill and Patton reported a decrease of 500 hospital patients in the State of New York—instead of an increase of 2,000-2,500 patients, anticipated on the basis of previous yearly increases—following the first year of large-scale neuroleptic treatment. Battegay and

Gehring, in Switzerland, compared the average duration of hospitalization before and after the introduction of neuroleptic drugs, and found a marked shortening of hospital stay for patients in the post-neuroleptic era. Even if new social attitudes and practices, not directly related to drug therapy, might have been responsible for some of these changes, as British and Scandinavian authors point out, there is no doubt that pharmacotherapy has played an important role in reducing the duration of hospitalization of many schizophrenics.

Forty years ago, 60 percent of schizophrenic admissions were expected to remain in hospital indefinitely, only 20 percent made a good remission, and another 20 percent, still symptomatic, nevertheless also had a chance to get out of the hospital. Following insulin therapy, between 1945 and 1950, only 34 percent of a group of schizophrenic patients in Britain were still hospitalized after five years, while 45 percent had made a good social remission, and 21 percent were still showing symptoms, but lived in the community. Finally, after the introduction of neuroleptic pharmacotherapy, a five-year follow-up study of another group of schizophrenic patients in Britain revealed only 11 percent to be still hospitalized, 56 percent as socially recovered, and 34 percent as showing symptoms, but living in the community. These figures also reflect the general clinical impression that modern pharmacotherapy has been instrumental in increasing the proportion of schizophrenic patients who, although still showing residual symptoms of

their disease, can be managed in the community; but, at the same time, drug treatment seems to have substantially increased the number of schizophrenics who make a good social remission.

Well-designed studies, comparing neuroleptic pharmacotherapy with milieu therapy, group therapy, or individual psychotherapy, in schizophrenic patients, report the greatest improvement with pharmacotherapy. That drug treatment did not impede progress of individual psychotherapy in schizophrenics was demonstrated in a placebo-controlled two-year study by Grinspoon and Ewalt; on the contrary, the neuroleptic (Thioridazine) seemed to increase the effectiveness of psychotherapeutic communication.

Several studies have suggested that the combination of psychotherapy, milieu therapy, or other social therapies with pharmacotherapy may increase the effectiveness of the latter.'' Similarly, Hogarty et al. observed that patients in remission who receive drug maintenance treatment combined with social therapy tend to do better after six months than patients on drugs alone.

Conclusion

Pharmacotherapy has clearly emerged today as the most important and most widely used single treatment of schizophrenia. It is simpler, much more available, more effective, less hazardous, and less expensive than insulin therapy. It is simpler and more effective than ECT, at least over extended

periods of time. It is simpler, much more reliable, briefer, and, as May has shown in an interesting analysis, considerably less expensive than psychotherapy or milieu therapy. The effectiveness of megavitamin therapy has by no means been convincingly demonstrated, and psychosurgery is no longer considered a serious therapeutic choice for any but the most exceptional schizophrenic patient.

Perhaps the most significant achievement of pharmacotherapy has been its impact on the uncertainty that used to surround the schizophrenic patient in remission; whether he recovered spontaneously or in response to treatment, he always carried a relapse risk of at least 50 percent within the next twelve months. Twenty years ago, there was still nothing anyone could do to effectively reduce this threat. Today, neuroleptic drugs allow the psychiatrist to control and decrease this risk to a considerable extent, if his clinical judgment tells him that constitutional, social, or psychological factors —or the natural history of schizophrenia—seems to make such pharmacological control desirable.

Metabolic Treatment

In 1954, Hoffer et al. proposed large doses of nicotinic acid (niacin or Vitamin B3), and later of nicotinamide, as a new treatment for schizophrenia. At that time, he gave 3000 mg. of niacin per day; lately, he has been

recommending doses of up to 30,000 mg. of niacin per day in unresponsive cases. Ascorbic acid (Vitamin C) in doses of 3000 mg. per day, and pyridoxine in doses of 150 mg. might be added to this regimen.

In 1968, Pauling—not a behavioral or biological scientist, but a Nobel laureate in chemistry—published his theory of orthomolecular psychiatry, which postulates that certain individuals, because of constitutional deficiencies, may need much larger quantities of vitamins than the average person.

In one of his latest publications, Hoffer recommends a therapeutic program approach to schizophrenia that makes use of all available treatment modalities in addition to high-dose vitamin (megavitamin) treatment. He claims that his therapeutic program gives results that are superior to other treatments—in particular to pharmacotherapy, if it is used as the principal treatment—in terms of general functioning and time out of hospital.

Mechanisms of Action

The original theory, proposed by Osmond and Smythies, assumed that in schizophrenic patients the physiological N-methylation of noradrenaline to adrenaline is replaced by pathological O-methylation. This metabolic fault would then result in the production of 3,4-dimethoxyphenylethylamine (DMPEA), which had been shown in animals to produce experimental

catatonia. Later, other psychotoxic metabolites of adrenaline (e.g., adrenochrome or adrenolutin) were postulated to be responsible for the pathological manifestations of schizophrenia, as a reaction to excessive stress.

Nicotinic acid was thought to act as a methyl-acceptor that would trap errant methyl-groups and thus prevent the formation of potentially toxic compounds. Nicotinamide—and later nicotinamide adenine nucleotide (NAD)—were also proposed by Hoffer for the correction of the assumed metabolic defect. Large doses of these substances would be necessary to counterbalance the daily normal intake of methionine, an amino-acid which serves as one of the chief methyl-donors in the human organism.

In support of the theory of disturbed transmethylation in schizophrenia has been the finding of a "pink spot" in the urine chromatogram of schizophrenic patients by Friedhoff and Van Winkle, who thought to have demonstrated that the substance responsible for the "pink spot" was DMPEA. This claim has since been challenged by a number of investigators, and the controversy about the identity of the spot and the association of DMPEA with schizophrenia has continued, almost unabated, for ten years.

Further support for the "transmethylation hypothesis" of schizophrenia has come from several clinical experiments which showed that the administration of methyl-donors, such as methionine and betaine,

consistently aggravated the psychotic manifestations of schizophrenic patients.'

Another hypothesis assumes that in schizophrenics there is a metabolic impairment in the pathway from tryptophan to nicotinic acid, leading to a deficiency of nicotinic acid and to a surplus of methylated indole-metabolites, which have psychotoxic effects. The administration of nicotinic acid might then correct this deficiency and also prevent the excessive production of noxious methylated substances.

While all these hypotheses are imaginative and intriguing, because they are based on interesting observations, it must be understood that none of them has been experimentally proven beyond a great deal of reasonable doubt.

Clinical Application

In a recent paper, Hoffer describes his two-phase approach to megavitamin B3 therapy in schizophrenia. In phase I, co-operative patients with acute symptoms are started on either nicotinamide or nicotinic acid, 3 grams per day. Sometimes ascorbic acid, 3 grams per day, is added, to reduce the danger of viral infections. Sucrose intake should be restricted. If improvement on this program is unsatisfactory after one month, the patients are then given any of the current drug therapies.

Phase II is entered when the patient is unable to follow this regimen and must be admitted to hospital, where he may be given ECT plus pharmacotherapy. The dose of nicotinic acid may be increased up to 30 grams per day, with a mode of 6 to 9 grams. The dose range of nicotinamide would lie between 3 and 9 grams.

After a patient has left the hospital, he is continued on outpatient therapy. If necessary, he may be brought back to the hospital at intervals of six to twelve months for another brief series of ECT. This entire program will be continued for at least five years.

Adverse Reactions

Nicotinic acid, particularly in high doses, is not as innocuous as had been thought for some time. Side-effects and complications with this substance include flushing, skin rashes, and lesions resembling acanthosis nigricans.

Nausea, vomiting, diarrhea, and activation of peptic ulcers have been observed, as well as increases in transaminase values, jaundice, and hypoalbuminemia. Other side-effects include hyperglycemia, hypotension, tachycardia, and headache.

Efficacy

Most of the positive reports on megavitamin therapy have been published by Hoffer and his co-workers. However, others, too, have reported good results, sometimes with great enthusiasm. Not many of these studies were designed and conducted according to the standards that might be expected in modern clinical trials.

Negative results with megavitamin therapy were also published by a number of authors, as well as inconclusive or negative results of treatment with NAD.

Lately, Hoffer has reported good results with nicotinamide, 3 to 6 grams, and ascorbic acid therapy, 3 grams per day, in mentally disturbed children. Favorable results have also been obtained with megavitamin treatment in children by Green and Rimland, while Greenbaum did not observe any significant improvement in the children he treated.

Conclusion

The conflicting reports on the efficacy of megavitamin therapy have been presented in some detail, because of the public controversy that has developed around this particular treatment modality in recent years. The underlying rationale has neither been proved nor disproved. Negative results of the clinical treatment have so far been reported more frequently than positive ones, when controlled clinical trials were designed so as to meet

current research standards. However, the possibility that certain schizophrenic patients may benefit from megavitamin therapy cannot be entirely excluded, in view of a great number of enthusiastic, though uncontrolled, clinical reports. Unfortunately, at this time we do not know any criterion that would reliably select those schizophrenic individuals who might possibly be helped by megavitamin treatment.

Although many conscientious clinicians might feel that under these circumstances the treatment should not be given until its efficacy has been proven, this author is taking the stand that the plausible theories behind the treatment, the existing reports of its positive results, even if largely unconfirmed, and finally, the potentially powerful placebo effect resulting from the publicity surrounding megavitamin treatment today, must not be altogether disregarded. There does not seem to be sufficient evidence at this time to initiate megavitamin therapy on clinical grounds alone, but its possible negative effects are probably not serious enough to refuse treating a patient with megavitamins—in addition to the generally accepted physical therapeutic approaches in schizophrenia, e.g., pharmacotherapy—if the patient or his family insists on it. Such a compromise must, of course, always remain the personal decision of the psychiatrist in the context of his clinical judgment about the best possible over-all management of his schizophrenic patients.

Hypoglycemic Coma Treatment

This particular form of treatment is only very rarely administered today. It was, however, the first treatment ever to achieve reliable therapeutic results in schizophrenic patients and in that capacity deserves at least more than ordinary historical interest. Its technique has been described in detail in many publications, and for these reasons, reference to it here will be very brief.

The treatment aims at the reduction of cerebral metabolism through the production of insulin-induced hypoglycemia until the patient has reached coma. This state is allowed to last for approximately one hour, after which time the patient is awakened with a sucrose solution, administered by gavage, or with an intravenous injection of glucose, or an intramuscular injection of the hormone glucagon. The treatment is given five times a week, over a period of two to four months.

Mechanisms of Action

It is probable that a combination of factors is responsible for the beneficial effects of insulin coma therapy in schizophrenia. These factors include cerebral hypoxia and multiple physiological defense mechanisms which are being mobilized by the unspecific, systemic shock, as well as probably important psychological effects. The latter are associated with

rendering the patient completely dependent on the nurses and physicians involved in this treatment and then exposing him in this anaclitic situation to a therapeutic re-enactment of early infantile dependence and mothering, but, in contrast to the original real situation, this time with the possibility of therapeutically controlling the "maternal" care given by the nursing and medical personnel.

Clinical Application

The treatment is administered in very few places today. It has been claimed that it is particularly indicated in the management of schizophrenic patients who belong to the simple or hebephrenic subtypes and whose deficit symptoms have failed to respond to pharmacotherapy.

Adverse Reactions

Hypoglycemic coma therapy is potentially more dangerous than most other physical treatments of schizophrenia, since death or permanent brain damage may supervene if the patient is permitted to reach a state of irreversible coma.

Efficacy

As mentioned earlier, it has been shown that hypoglycemic coma

treatment is less effective than pharmacotherapy in unselected schizophrenics. Successes that have been claimed for it in certain patients who were refractory to pharmacotherapy have not been confirmed in controlled studies.

Conclusion

There seems to be little justification for a psychiatric treatment center today to maintain the special facilities and the highly trained staff that would be required for the administration of this type of therapy.

Neurophysiological Treatment

The effective treatment modalities which fall into this category are all characterized by the induction of convulsions. This may be achieved by the intravenous injection of metrazol, or by the inhalation of flurothyl (indoclon), or by the application of an electric current to the head region. The various forms of convulsive therapy have been discussed in detail in another volume of this edition of the Handbook; some of them are mainly of historical interest today. For these reasons, this discussion will be brief and restrict itself to those types of convulsive therapy which still find fairly widespread application in schizophrenia.

Electro-Convulsive Therapy (ECT)

In the standard form of this treatment, electrodes are applied bilaterally to the patient's head, he is given an intravenous injection of a muscle relaxant —usually succinyl chloride— together with an ultra-short-acting barbiturate, and an alternating current of about 120 Volts and 300 milliamperes is then switched on for a period of 0.1 to 1.0 seconds. If necessary, the application of the current may be repeated once or several times within the next minute, until a convulsive reaction has occurred. The peripheral manifestations of the convulsion are, of course, greatly attenuated by the muscle relaxant.

Two modifications of this standard form of ECT have been developed in recent years: unilateral ECT and multiple monitored ECT.

In unilateral ECT both electrodes are placed on the non-dominant side (left in right-handed and right in left-handed persons) of the head. Advantages claimed for this form of treatment include less memory disturbance following a series of treatments, more particularly, less impairment of learning and recall, and less retrograde amnesia, as well as a shorter period of confusion following each seizure.

Multiple monitored ECT involves the administration of several electric stimuli during one treatment session while the patient's EEG and ECG are being monitored continuously. From three to five seizures may be produced in 30-45 minutes. This makes it possible to reduce the time required for a full

course of treatment.

Mechanisms of Action

Although ECT has now been in use for more than thirty years, its mechanism of action is virtually unknown. Cerebral hypoxia, systemic "alarm" reaction, psychodynamic speculations about experiencing symbolic death and revival, have all been proposed as explanations of the dramatic effects of ECT on mental processes, but little evidence has been provided for these or any of the many other theories that have been suggested. Kety and his co-workers have shown in animals that electrically induced convulsions increase the turnover rate of biogenic amines in the brain, and a similar mechanism in man may be related to the normalizing effects of ECT in depression or acute psychotic disorders.

Clinical Application

The principal indication for ECT is severe and persistent depression; however, the first successful trials with convulsive treatment were performed on schizophrenic patients, and—after pharmacotherapy—ECT is still the most reliable and most widely accepted physical treatment modality used in the management of schizophrenia. Today, standard ECT, or one of its modifications, is mainly used in schizophrenic patients who have failed to

respond to pharmacotherapy, or when severe agitation and very acute symptoms must be rapidly controlled. Several authors' recommend a combination of ECT with pharmacotherapy as the best approach to schizophrenia, and point out that ECT often breaks through a therapeutic block in drug therapy and makes it possible to reduce the doses of drugs needed to maintain the patient in remission.

Adverse Reactions

The memory disorder occurring with ECT is its most disturbing side-effect. It is in almost every case fully reversible after the treatment has been discontinued for a few weeks, but the patient's improved affect may conceal a still existing objective memory defect for some time, and, particularly in elderly patients, a permanent loss of memory may ensue. Fractures and dislocations were frequent prior to the routine use of muscle relaxants, but can be avoided today. Cardiovascular and respiratory accidents are uncommon. There are no confirmed reports of teratogenic effects of ECT, and its use in pregnant women seems to be relatively safe.

Efficacy

Kalinowsky and Hippius report 68.3 percent remissions in institutionalized schizophrenic patients who had been ill for less than six months, if treated with a minimum of twenty convulsions, but only 9.2

percent in those ill for more than two years. They feel that pharmacotherapy in acutely ill patients may be attempted, but should be tentatively discontinued after several weeks or months; if the patient relapses, he should then be treated with ECT. It should be noted, however, that relapse rates following ECT are about the same as those following the discontinuation of pharmacotherapy, i.e., about 50 percent in twelve months.

Conclusion

ECT results in schizophrenia are often dramatic, but all too often only short-lived. This author's clinical experience has led him to employ pharmacotherapy as the first treatment of choice in acute as well as chronic schizophrenics. Only if the patient's psychotic symptoms have not significantly improved after three months in acute patients or after six months in chronic ones should ECT be given a therapeutic trial. Frequently, six to ten seizures suffice to activate the patient's response to neuroleptics, and he may then be maintained on pharmacotherapy. In more refractory cases, a longer course of up to twenty-five or thirty ECT may be indicated, if the response to pharmacotherapy is unsatisfactory.

Psychosurgery

Psychosurgery is a badly chosen name for the kind of brain surgery which is being performed for the treatment of certain functional psychotic

disorders. It is likely that the term “psychosurgery” will be exchanged for “psychiatric surgery” in the future, since the term designates, of course, not surgery performed on the psyche but on the psychiatric patient.

This kind of treatment has had a bad press for a long time, and merely mentioning its name—or, even more so, that of lobotomy—evokes almost violent emotional reactions in many people. Nevertheless, it may be an effective last resort when every other treatment has failed.

In schizophrenia, psychosurgery enjoyed a brief popularity between 1940 and 1950, when thousands of acute and chronic patients were lobotomized. But the results were often disappointing, because the selection of patients had been inadequate and surgical procedures were still crude.

Today, the development of many refined surgical approaches has reduced adverse reactions and improved therapeutic efficacy; at the same time, much has been learned about selection of appropriate patients for this treatment. All psychosurgical procedures, whether they be frontal lobotomies, cingulotomies, thalamotomies, hypo-thalamotomies, or any other of the many available techniques, aim at a leveling of emotional responsivity, but also at minimal interference with higher nervous functions and basic personality structure.

The operation must be chosen and performed by a neurosurgeon, while

the diagnosis and recommendation for psychosurgery are the responsibility of a psychiatrist.

Mechanisms of Action

How improvement of psychiatric disorders may be brought about by surgical interference with cerebral structures is very poorly understood. On the other hand, this type of treatment is the only one which was originally based on theoretical extrapolations of observations made in experimental studies on animals. Admittedly somewhat simplistic, the hypothesis was that a consistent calming effect, which was observed following certain neurosurgical procedures performed on the frontal thalamic or limbic systems in animals, e.g., a reduction of anxiety or aggressive responses, without significant interference with cognitive and perceptual functions, might also occur in man and would reduce psychotic manifestations, if they were present.

Clinical Applications

Any psychosurgical procedure should be considered only as the last resort in those exceptional cases where all other treatments have failed and the patient has been ill for at least two years without remission. When these conditions are fulfilled, this form of treatment is frequently successful in

states of severe, chronic anxiety, depression, or obsessive-compulsive pathology. Its indications in schizophrenia are questionable, because acute schizophrenic patients who may respond well to psychosurgery are also excellent prospects for pharmacotherapy; and chronic schizophrenics have a much poorer record of success. One group of patients in whom psychosurgery has shown good results is that of the pseudoneurotic schizophrenics. The only other indication for psychosurgery in schizophrenia today might exist in those extremely rare cases where severe agitation, anxiety, or aggression has consistently failed to respond to energetic treatment with neuroleptic drugs and ECT.

Adverse Reactions

Mortality, which was comparatively high in the early operations, has today been very considerably reduced and must no longer be considered a serious risk of psychosurgery. The same is true for the incidence of convulsions in the post-treatment phase. Likewise, the gross and unfavorable personality changes, which were not uncommon following the early frontal lobotomies and are responsible for the bad image psychosurgery has acquired, are almost never seen any more.

Nevertheless, psychosurgery is the only psychiatric treatment that aims at the production of irreversible changes in the central nervous system, and

permanent neurological deficits or undesirable psychological changes may remain as sequelae of the treatment.

Efficacy

A recent follow-up survey of 210 patients suffering from long-standing, intractable psychiatric illness after bi-frontal stereotactic tractotomy reports no favorable results in the chronic schizophrenic patients of this population. But a short-term study of nine treatment-resistant, chronic schizophrenics after stereotactic cingulotomy reports at least gratifying reduction of anxiety and a positive activating effect. Freeman, reporting up to thirty-year follow-ups on 415 *early* schizophrenics (less than one year hospitalized) whom he treated with frontal lobotomy, found that 57.4 percent were employed or keeping house, 24.5 percent were living at home unemployed, and only 18.2 percent were in hospital.

Conclusion

Psychosurgery in schizophrenic patients has only very limited application. It may be considered in pseudoneurotic schizophrenia if the patient is greatly distressed, has shown no spontaneous remission for at least two years, and has failed to respond to adequate trials with every other accepted treatment method, including psychotherapy. In rare cases, psychosurgery may be indicated for chronic schizophrenics whose anxiety

and agitation have remained refractory to adequate pharmacotherapy and ECT.

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Notes

1 Although this treatment was unsuccessful and soon abandoned, it is interesting to note that manganese will, in toxic amounts, produce extrapyramidal symptoms, and in this unusual aspect resembles all those drugs which until now have been shown to be effective in the treatment of schizophrenia.

2 For instance, in one large NIMH collaborative study with acute schizophrenic patients, the investigators concluded, from regression equations based on symptoms present before treatment, that chlorpromazine was most effective for "core" symptoms of schizophrenia (e.g., slowness of speech, poor self-care, indifference to environment), Acetophenazine for "bizarre," and fluphenazine for "depressive" symptoms. Casework interviews with these same patients later revealed that fluphenazine was relatively more effective in patients whose premorbid history would suggest a poor prognosis, and less effective in patients where good prognostic conditions existed; in this latter case, Acetophenazine appeared to cause greater improvement.