Discoveries in Biological Psychiatry

Edited by
FRANK J. AYD, JR., MD, FAPA
Editor: *International Drug Therapy Newsletter*
Medical-Moral Newsletter

and

BARRY BLACKWELL, MD, DPM
Associate Professor of Psychiatry and Pharmacology, University of Cincinnati, Group Director, Psychiatric Clinical Research, The Wm. S. Merrell Company, Cincinnati

1970

J. B. LIPPINCOTT COMPANY
Philadelphia/Toronto

CHAPTER

12

Introduction of Neuroleptic Chemotherapy Into Psychiatry

PIERRE DENIKER, MD *

MEDICAL DISCOVERIES are frequently attributed to chance, luck, or even error. In our case, progress might be more accurately attributed to the synthesis of new compounds serving the hypothesis that it is possible to treat mental disorders in a strictly medical sense.

BEFORE CHLORPROMAZINE

Twenty years ago, such an idea might have seemed unrealistic, since, even today, there are psychiatrists who think it impossible to act on the mind by means other than the spoken word. Even before 1952, when chlorpromazine was introduced, several fundamental advances had been made in treating psychoses. They included electroshock or shock induced by fever, Metrazol, or insulin, which are nonspecific therapies or medications, like antibiotics for the treatment of syphilis, affecting the etiological agent rather than the resulting disorders. However, definite etiologies are not known for most psychoses.

The quest for knowledge was as marked 20 years ago as it is today. This was evidenced by the first World Psychiatric Congress held in Paris in 1950. Certain trends among the many quite "unsophisticated" research efforts led to the discovery of modern chemotherapy. Initial studies attempted to analyze the mechanism of

* Professor agrégé, Clinique des Maladies Mentales et de l'Encéphale, Paris.

action of shock therapy. Thus, our first communication on chlorpromazine was presented at the centennial of the French Medico-Psychological Society, which covered shock therapy methods. Jean Delay reviewed them in the light of his studies on the common effects of these different methods on diencephalic centers. Accordingly, they resembled Selye's alarm reaction. This explains our immediate interest in "artificial hibernation," developed by my friend Laborit, because it acts on the mechanisms and structures affected by shock therapy. However, the method we proposed, together with Jean Delay and J. M. Harl,† employed neither hibernation nor sleep therapy.

Another research trend involved attempts to find psychiatric applications for new drugs introduced into general therapy: for instance, the use of procaine and procainamide ‡ for the treatment of hallucinatory psychoses, and, in particular, trials with new antihistamines such as the American investigations with diphenhydramine and the French work with promethazine, a percursor of chlorpromazine. Studies on compounds modifying the nerve cell, such as dinitriles, or application of the psychic effects of certain drugs in psychiatry were also included. For example, by 1952, isoniazid-induced psychic stimulation in tubercular patients led to the use of this iproniazid precursor in depressions.

Although producing more or less negative results, other research contributed to progress by preventing further work in certain fields. For example, the use of opiates and belladonna derivatives, bromides and chloral hydrate, paraldehyde and barbiturates resulted in as many disappointments as hopes. Sleep treatments induce only prolonged sleep whether they are deep narcotherapies, which were developed in Switzerland in 1930, or "conditioned" sleep therapies inspired by Pavlovian ideas. Their indications are neuroses and psychosomatic disorders rather than psychoses.

Drugs with new activity were quickly recognized because of familiarity with available agents. The "lytic cocktail" developed by Laborit combined three drugs: pethidine, a morphine-like derivative; promethazine, an antihistamine; and chlorpromazine. Psychiatrists knew the first two; therefore, interest centered on the last.

† Before his premature death in a mountain accident, he was an intern in our department.

‡ These attempts precede the introduction of substituted benzamides as neuroleptics by 20 years.

CHLORPROMAZINE

In 1950, Charpentier at Rhône Poulenc Laboratories synthesized this phenothiazine, which is related to antiparkinsonian agents and antihistamines. It might still be sitting on the shelf of some chemical laboratory if Laborit had not sought a compound with more central effects than promethazine. With chlorpromazine, he actually reproduced in warm-blooded animals conditions existing in cold-blooded or hibernating ones. However, the possibility seemed remote that the drug might produce in humans the cold-bloodedness, "indifference," or ataraxia extolled by the Stoics. It was Laborit who predicted that the new agent would be used in psychiatry. His colleagues, psychiatrists at the military hospital of Val De Grâce, tried his drug mixture in manic patients. They found its effects interesting but not strong enough and returned to electroshock therapy.

We decided to use the drug without concomitant agents; this may be the first rule of clinical pharmacology. Doses considered high at that time, 75 mg to 150 mg per day, were administered "continuously" in four daily injections. This continuity, which today applies to most psychiatric chemotherapy, was a decisive factor in our success.

Our initial experimental data were very limited. The good pharmacological work of Mrs. Courvoisier and Koetschet *et al.*, as well as Dell's experiments with the reticular formation, was published in 1953. We had only received a few typed sheets in 1952. They were a brief summary for the clinician's use and were distributed with the ampules and tablets. It is disturbing to think that certain effects of the drug were observed in humans before being noted in animals.

Despite great progress, psychiatric wards of 20 years ago still included agitated patients who did not respond to common therapeutic procedures. Pinel had eliminated chains, but existing treatments could not abolish straitjackets and cells. If we were to recreate the atmosphere of an agitated ward for our students' instruction, they would laugh or become skeptical just as if a Western were projected in an operating room. Nevertheless, neuroleptic chemotherapy originated in that atmosphere. Logically, a new drug was tried in cases resistant to all existing therapies. We had scarcely treated 10 patients—with all due respect to the fervent adherents

of statistics—when our conviction proved correct. It was supported by the sudden, great interest of the nursing personnel, who had always been reserved about innovations.

From May to July 1952, Delay and I published our observations on chlorpromazine. There were only 38 cases, and our data dealt with the therapeutic indications as well as the inherent effects of the drug. Since then, we have learned from others, but have not changed our initial opinion about chlorpromazine in acute psychoses. Manic excitation and, more generally, psychotic agitation, which were often resistant to shock or sleep therapy, immediately became indications of choice. This effect of the drug became noticeable in the wards and, to us, it is still a pharmacodynamic test for neuroleptic activity.

The antipsychotic activity of the drug was also evident in the treatment of mental confusion. It differed from the sedative effects because drugs reducing mental alertness generally aggravate disorders of wakeful consciousness. In contrast, chlorpromazine only had symptomatic effects in depression. Its sedative and hypnotic activity cannot correct underlying depressions. True antidepressants were discovered later by R. Kuhn and N. Kline.

Agitation, aggressiveness, and delusive conditions of schizophrenics improved. Contact with the patients could be reestablished, but deficiency symptoms did not change markedly. We are still of the same opinion. The great international confrontations of 1955 on chlorpromazine and neuroleptics were necessary to affirm their efficacy in chronic psychoses. The first inhibition-releasing effects in schizophrenia were observed following the introduction of new phenothiazines. (This point will be discussed later.)

However, even the first few clinical observations yielded considerable information on the novel central activity of the drug. It affected regulation of body temperature, pulse, and blood pressure, gastrointestinal motility, blood count, etc. But the impact of the most significant finding was not immediately recognized. It was the characteristic psychomotor indifference that chlorpromazine caused in treated subjects. Later, it was classified as akinesia.

After initial trials, specialists were particularly impressed by the potent sedative activity of the drug. It was more marked than that of any known agent, was accompanied by relatively mild hypnotic activity, and caused reversible sleep. This was the real beginning of research on drugs that would soon increase in number and would

be referred to as "tranquilizers." Chlorpromazine was characterized by not only its action on mental alertness but also its ability to induce a new, neuropsychic condition related to akinesia. The development of the class of drugs for which we proposed the name "neuroleptics" was based on these findings.

IDENTIFICATION OF NEUROLEPTICS

Until then, our research had required no particular technical skill. Any clinician using the latest therapeutic agent available, observing its effects especially when they were unexpected, and recording physical and psychic changes, was merely doing what an honest physician should do. Further developments proved more interesting by relating classic knowledge to new observations, which makes research more rewarding.

Cardiologists noted that reserpine caused psychic indifference. This finding led us to study the drug after Nathan Kline and at the same time as Weber and Noce *et al.* Using doses 10 times those commonly given in treating arterial hypertension, we reported in 1954, with Delay and Y. Tardieu, several observations on the similarities and differences in the therapeutic effects and inherent actions of reserpine and chlorpromazine. In the same year, Professor Steck of Lausanne made an important observation. He reported that patients treated with either drug may develop syndromes resembling parkinsonism, and that reserpine may cause restlessness and make it impossible for the subjects to remain seated (akathisia). These symptoms were also seen in lethargic encephalitis after World War I.

In 1955, Delay and I proposed that the two drugs with completely different chemical structures be classified under the same name: "neuroleptic," literally: that which takes the neuron. In 1956, a new piperazine phenothiazine, prochlorperazine, was reported to cause strange hysterical attacks both in women suspected of being neurotic and in soldiers during training. We made an important correlation with "hysteriform" conditions, described between 1920 and 1930 as sequelae of lethargic encephalitis. The new drug caused various types of unusual dyskinesia. Roumanian authors, in particular, had previously described it as an extrapyramidal disorder or disease. But the syndrome that we observed appeared upon administration of the compound and disappeared when treatment was discontinued.

It was found that neuroleptics could experimentally reproduce almost all symptoms of lethargic encephalitis. In fact, it would be possible to cause true encephalitis epidemics with the new drugs. Symptoms progressed from reversible somnolence to all types of dyskinesia and hyperkinesia, and finally to parkinsonism. The symptoms seemed reversible on interruption of medication. Like the encephalitis virus, the drugs acted via the mesodiencephalic extrapyramidal centers.

In 1957, we proposed a general definition of neuroleptics based on similarities between compounds then known, which later would include many chemical groups with different structures. In 1958, a sulfamide phenothiazine became available, which caused very marked akinetic, hypertonic, and hyperkinetic syndromes characteristic of postencephalitic symptoms. At the same time, the drug showed marked therapeutic activity even in chronic psychoses.

In the same year, Belgian investigators tested a new compound, haloperidol. It was selected by Laboratoires Janssen because it caused dyskinesia in animals. These authors furnished additional proof that neurological effects were more important than the chemical structure in characterizing the effects of the drug. In 1960, we showed that the fundamental characteristic of neuroleptics was a combination of antipsychotic and essentially neurological effects.

Since then, the class of neuroleptics has increased by several chemical types: the phenothiazines have different effects depending on the structure of their side chains and substituted radicals. Compounds with aliphatic chains, the chlorpromazine type, have sedative activity mainly accompanied by extrapyramidal and especially autonomic effects. Compounds with piperazine chains, the prochlorperazine type, have inhibition-releasing properties and cause very marked dyskinesia. Those with piperidine chains, the thioridazine type, have moderate activity and slight neurological effects, but they cause endocrine-metabolic changes of central origin. Butyrophenones, already quite numerous—thioxanthenes, dibenzothiazepines, substituted benzamides, several piperazine derivatives, etc. —were developed in addition to phenothiazines and reserpine derivatives. As a result, the list of compounds following chlorpromazine continues to grow.

THERAPEUTIC ACTIVITY AND NEUROLOGICAL EFFECTS

We thought it would be possible to establish a relationship between the therapeutic activity of neuroleptics and their ability to

cause specific neurological syndromes. This is one of the most controversial aspects of our studies. Generally, agents used for biological treatment in psychiatry are precisely those that cause "therapeutic diseases" of CNS regulatory mechanisms. This applied to fever in malaria therapy, for which Wagner von Jauregg received the Nobel Prize, and to lobotomy, which induces an organic frontal syndrome, for which Egaz Moniz received the same award. It is also true for insulin, which causes coma, as well as Metrazol and electroshock, which induce artificial epileptic seizures. Neuroleptics cause extrapyramidal syndromes, which minor tranquilizers never induce. Similarly, antidepressants have their own neurological effects: the tremor-dysarthria syndrome of the tricyclic compounds and, more generally, the convulsant activity of various agents of this type.

On the other hand, it must also be admitted that neuroleptics may act without causing neurological symptoms. Although the therapeutic activity of chlorpromazine and reserpine was known before their neurological effects, autonomic changes and akinesia were immediately noted. It was then found that all drugs producing the characteristic neurological syndromes had similar antipsychotic activity. In contrast, compounds of the same chemical group that did not cause neurological effects had almost no therapeutic activity in psychoses.

Sound arguments contradict our neurological theory. Chiefly, no relationship has been established between therapeutic activity and the intensity of neurological symptoms, although better results are sometimes obtained when marked neurological syndromes are systematically induced. Neurological symptoms indicate that there are effects on nervous structures, which are probably involved in the therapeutic process, and perhaps also in the pathology of psychoses. Lethargic encephalitis was known to cause syndromes resembling hebephrenia and catatonia. Cases have also been reported where the occurrence of encephalitis during schizophrenia favorably affected the mental disease.

However, present reasoning involves biochemical factors. The greater sensitivity of certain nervous structures to neuroleptics depends on their particular chemical activity. Research in this area is just beginning and clinicians can make their modest contributions. Cazzullo *et al.* showed that adenosine triphosphate, ATP, prevented histological lesions induced in the animal nervous system by very high doses of neuroleptics. We demonstrated in humans that ATP

infusions reduced the hypertonic syndrome. This was experimentally confirmed further. Because of the detailed analysis of changes in facial expression and facial muscle tone, we considered the temporal amygdala to be among the centers affected even by weak neuroleptic treatment.

At present, cerebral amine metabolism is of great interest. It is markedly but differently modified by various neuroleptics. The role of these amines in Parkinson's disease is also known. The effects of our drugs may originate in the basal ganglia, where the biogenic amines are highly concentrated. However, modern biochemistry may consider our agents too crude and their effects too massive for them to be analyzed in detail. We have passed from simple therapeutic observations to rudimentary but sound hypotheses about the mechanisms of action. These hypotheses provide, by way of introduction, a valid methodology in the search for new effective drugs.

The recent introduction of long-acting neuroleptics has shown that equivalent and even better therapeutic effects are possible with much lower doses. The drug quantity once used in a single day now suffices for two to three weeks of treatment, because the drug is slowly released. Thus, the question arose about the kinetics of neuroleptic metabolism in the organism and the brain. Pertinent studies are under way.

POSITIVE AND NEGATIVE ASPECTS

Neuroleptic agents are produced in great quantity and are taken by millions of patients. Thus, an evaluation may be attempted. Simple drugs have facilitated extensive therapy in psychiatric institutions where previously only a few patients benefited from active treatment. If those in charge of American mental health are correct, the generalized use of chemical agents, neuroleptics and others, has decisively influenced overcrowded psychiatric hospitals and facilitated more liberal treatment and its continuation under outpatient conditions.

The discovery of chemotherapeutic agents coincided in all developed countries with a movement supporting better institutional organization for the patients' rehabilitation. Paradoxically, someone assumed a certain opposition between chemotherapy and, on the other hand, sociotherapy and psychotherapy. They actually benefit from one another and are inseparable. We only need to know the

role and usefulness of each method in terms of saving human life. Chemotherapy is relatively precise, choice among the different agents is delicate, and strict medical control is indispensable. It may have excellent therapeutic effects in chronic psychoses; however, they are basically transitory because relapses occur when medication is interrupted for a few weeks. This shows the significance of the cooperation between the psychiatrist and the family physician, and the importance of adequately informing the patient's everyday contacts.

These drugs are now widely distributed and very cautiously marketed. Thus, it may seem surprising that the originally unsophisticated psychopharmacological research did not cause more accidents or catastrophes. Although such possibilities did arise, they were generally averted. Furthermore, it might have been feared that these drugs, whose action compares with that of encephalitis and parkinsonism, might eventually induce irreversible secondary neurological syndromes. Such effects cannot be denied: it has been known for some years that permanent dyskinesia may occur in patients treated with neuroleptics and drugs with neurological activity. These phenomena must be recognized in time and treated correctly. Also, they are not absolutely irreversible because they can be relieved by treatment with another appropriate neuroleptic. Ocular and dermatological complications have received much attention, especially in America; I am referring to the "purple people." These disorders occurred in patients who received high doses for a very long time without adequate supervision. This finding supports our statements about strict medical control. Finally, in certain predisposed subjects, potent neuroleptics may cause actual "malignant" syndromes with hyperthermia. When discovered in time, they can always be checked by discontinuing the causal agent and using appropriate treatment.

Overall, neuroleptics are more useful than dangerous when treatment is suitably administered and supervised. A more theoretical aspect of the new chemotherapeutic agents is their contribution to the development of a more medically and scientifically oriented psychiatry since their use requires more comprehensive and advanced training for physicians and nursing personnel. Any stimulation of psychiatrists and their collaborators that prompts them to further their medical and psychological knowledge simultaneously expands the future possibilities of our discipline.

Another point should be observed. Almost 20 years ago, a simple drug was found to act directly on a psychopathological process. This finding was very important, although the precise etiology of this process was still unknown. It is now established that mental disorders may be chemically induced, for example pharmacopsychoses, and then relieved by means that are effective in both artificial and natural psychoses. This theory supports the biochemical origin of psychoses.

Neuroleptics are only part of the new field of psychopharmacology in which remarkable discoveries have been made, such as antidepressants. Psychopharmacology has probably existed as long as physicians have been searching for drugs affecting insanity. The introduction of neuroleptics at a crucial time when shock therapy had achieved all its objectives decisively influenced present-day psychiatry. Despite the development of more scientific therapy—the term clinical psychopharmacology is currently used—we must not forget that experimental subjects are human beings suffering from the worst disorders. They are not an anonymous "clinical material" to be treated with questionnaires that are evaluated by computers only.