

History of the Discovery and Clinical Introduction of Chlorpromazine

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Background. *The historical process of discovery and clinical introduction of chlorpromazine, one of the greatest advances of 20th century medicine and history of psychiatry, is analyzed.*

Methods. *In this review, we have studied the original works of pioneers in the discovery and clinical use of chlorpromazine, as well as the contributions of prestigious researchers (historians, pharmacologists, psychiatrists, etc.) about this topic.*

Results. *The discovery of phenothiazines, the first family of antipsychotic agents has its origin in the development of German dye industry, at the end of the 19th century (Graebe, Liebermann, Bernthsen). Up to 1940 they were employed as antiseptics, antihelminthics and antimalarials (Ehrlich, Schulemann, Gilman). Finally, in the context of research on antihistaminic substances in France after World War II (Bovet, Halpern, Ducrot) the chlorpromazine was synthesized at Rhône-Poulenc Laboratories (Charpentier, Courvoisier, Koetschet) in December 1950. Its introduction in anaesthesiology, in the antishock area (lytic cocktails) and “artificial hibernation” techniques, is reviewed (Laborit), and its further psychiatric clinical introduction in 1952, with initial discrepancies between the Parisian Val-de-Grâce (Laborit, Hamon, Paraire) and Sainte-Anne (Delay, Deniker) hospital groups. The first North-American publications on chlorpromazine took place in 1954 (Lehmann, Winkelmann, Bower). The introduction of chlorpromazine in the USA (SKF) was more difficult due to their strong psychoanalytic tradition. The consolidation of the neuroleptic therapy took place in 1955, thanks to a series of scientific events, which confirmed the antipsychotic efficacy of the chlorpromazine.*

Conclusions. *The discovery of the antipsychotic properties of chlorpromazine in the 1950s was a fundamental event for the practice of psychiatry and for the genesis of the so-called “psychopharmacological revolution.”*

Keywords Chlorpromazine, Antipsychotics, Phenothiazines, History of psychiatry, Schizophrenia

INTRODUCTION

Until the middle of the twentieth century, the treatment of psychotic disorders was based on the application of a series of remedies with limited clinical effectiveness, such as the so-

called biological therapies (paludization techniques, application of tuberculine or trementine, insulin or cardiozolic comas, electroconvulsive therapy, etc.) or on certain highly unspecific pharmacological agents (opium, morphine, cocaine, hashish, codeine, digitalis, chloral hydrate, bromide, etc.) (1). In this inhospitable therapeutic framework, at the beginning of the 1950s, was the near-simultaneous appearance in the repertoire of psychiatric therapy of two drugs with totally different origins, namely, chlorpromazine (2,3), a chemically-synthesized

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molecule, and reserpine (4–6), a natural substance obtained from the root of *Rauwolfia serpentina*. The introduction into clinical practice of these two drugs, together with the discovery, a few years earlier (1949), of the antimanic properties of lithium salts by the Australian psychiatrist John Cade (7), marked the beginning of what came to be called the “psychopharmacological revolution” (1,8–22). On August 9th, 1955, just three years after the introduction of chlorpromazine, Mark D. Altschule, a Harvard lecturer and Director of the Laboratory of Clinical Physiology at McLean Hospital (Boston), addressing the Gordon Conference on Medicinal Chemistry at Colby Junior College in New London, affirmed that these two drugs had already “totally changed psychiatric practice” (23).

The advent of chlorpromazine, derided by some of the great figures of psychiatry at the time, such as Henri Ey — who referred to it as “psychiatric aspirin” (24), — represented not only the first selective and effective approach to the treatment of schizophrenic patients, but also opened the way for the synthesis of numerous drugs for treating mental disorders, thus heralding the psychopharmacological era (1,25). The introduction into clinical practice of chlorpromazine can also be considered as the first of three milestones in the history of antipsychotic drugs that would mark the great advance in the treatment of schizophrenia, the others being the synthesis and subsequent use of haloperidol and, finally, the discovery of the atypical characteristics of clozapine, which permitted the development of the second generation (atypical) antipsychotic agents (risperidone, olanzapine, quetiapine, ziprasidone, etc.) (20), with a new pharmacodynamic profile and improved neurological tolerance (26).

Thus, a century and a half after Philippe Pinel physically freed the inmates of the Parisian Hôpital de la Salpêtrière from their chains, French psychiatrists once more released psychiatric patients from the torment of confinement, this time by means of a pharmacological tool, chlorpromazine. In the words of Edward Shorter, “chlorpromazine initiated a revolution in psychiatry, comparable to the introduction of penicillin in general medicine” (27).

THE DISCOVERY OF CHLORPROMAZINE

The discovery of the first family of antipsychotic agents was made within the context of widespread research on antihistaminic substances in France after World War II, and more specifically in that of the work being carried out on phenothiazines. These substances had been known of since the late nineteenth century, having been used by the dyeing industry. Later, in the early 1930s, they were employed as antiseptics and antihelminthics. Finally, in the second half of the 1940s, their antihistaminic properties were studied, though their toxicity made clinical use impossible. Thus, their application to patients with mental illnesses was never directly sought; rather, as Lickey and Gordon so rightly put it, “their introduction in therapeutic use is more like the story of a drug in search of an illness” (28).

Phenothiazines: From the Chemical Dyeing Industry to Anti-infectious Therapy

The first phenothiazinic substances were developed in Germany at the end of the nineteenth century, within the framework of the burgeoning German textile industry (29). The history of these substances began with the work of Carl Graebe and Carl Liebermann, who in 1868 synthesized alizarin, a dye derived from coal tar. The Badische Anilin und Soda Fabrik (BASF) company (Figure 1) undertook its manufacture and commercialization, and further research by the same company resulted in their obtaining a large number of new dyes, including methylene blue, synthesized by Caro in 1876. It was precisely while working on the development of dyes derived from this aniline that the organic chemist August Bernthsen synthesized the first molecule of this family in 1883 (20,30).

The introduction of phenothiazines in medicine coincides with the development of microscopy, and with the need to obtain tinctures that would permit the visualization of histological preparations. It was in this context that the aniline dyes developed in England by William H. Perkin (Figure 2A) were used. Among the pioneers in this field was Paul Ehrlich, who observed that some of these substances had bactericide capacities, and who began studying them with the aim of finding a product capable of destroying pathogenic agents while respecting human cells (the famous “magic bullet”). Thus, in 1907, he discovered trypan red, a lithic substance for parasites of the genus *Trypanosoma*, responsible for sleeping sickness, and subsequently arsphenamine (Salvarsan®), a lethal agent for *Treponema pallidum*, the microorganism that induces syphilis (30).

An indirect but decisive role in the story of the clinical use of phenothiazines was played by the needs and strategies involved in the two World Wars (20). During World War I, the supplements of quinine, the only remedy for malaria at the time, and obtained from the tropical tree *quina cinchona*, were affected by military blockades that made them inaccessible to the German army, so that their researchers undertook to find synthetic derivatives of the substance. Thus, W. Schulemann and his team decided to continue studying the antimalarial effect of methylene blue, a phenothiazine derivative used as a dye in histological dyeing techniques, with which Ehrlich and Guttman had made considerable research progress in 1891. The results of this work led to the synthesis of several derivatives of methylene blue, such as a diethyl-amino-ethyl derivative, with greater antimalarial activity but high toxicity, and finally quinacrine, which became as commonly used against malaria as quinine itself (30). This antimalarial action of phenothiazines continued to be studied until the end of the 1930s, since these substances were found to have a toxic effect on the mosquito larvae, as well as on porcine parasites, and research increased throughout World War II. During that conflict, Japanese expansion in southeast Asia affected the supply of quinine, in this case to the Allied forces, and this obliged scientists



Figure 1 Aerial sight of the chemical plant of the *Badische Anilin und Soda Fabrik* (BASF) company in Ludwigshafen, Germany (1926).

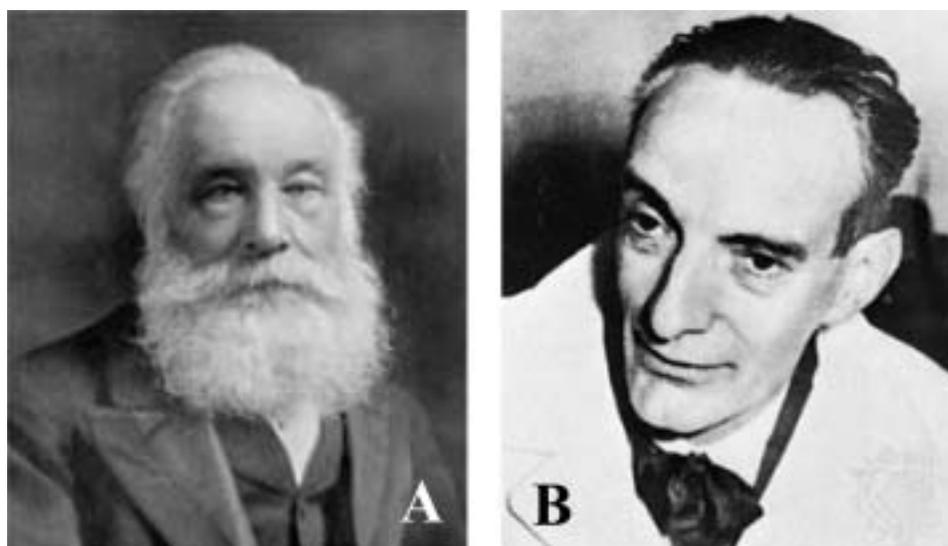


Figure 2 William Henry Perkin (A), pioneer of chemical dyeing industry, and Daniel Bovet (B), researcher of Rhône-Poulenc and 1957 Medicine Nobel Prize.

to seek new therapeutic alternatives, so that they turned once more to phenothiazines. Thus, Gilman and colleagues (31) synthesized a series of compounds, through the addition of amino-alkylate chains to the central nitrogen atom of the phenothiazine ring, although these agents showed a complete absence of anti-malarial activity.

The compounds synthesized by Gilman's team continued to be studied by French researchers at the Société des Usines

Cliniques of Rhône-Poulenc Laboratories (Vitry-sur-Seine, France), who also confirmed that the amino-alkylate derivatives of the phenothiazines had no effect on the symptoms of malaria, but decided to investigate, following the classic research lines, their antihistaminic properties. Thus, the team led by Paul Charpentier at Rhône-Poulenc developed phenothiazine derivatives with an amine chain, similar to that found in molecules with antimalarial activity. The result of this

development process was the synthesis, between 1946 and 1948, of promethazine (RP-3277) and diethazine, subsequently commercialized as Diparcol®.

***Phenothiazines as Antihistamine and Anti-shock Agents:
The Contributions of Henri Laborit***

Concurrently with the developments and events mentioned above, other groups of scientists were researching the antihistamine properties of different substances in relation to the study of shock and stress reactions. Notable among them was the group led by Daniel Bovet (Figure 2B), a Swiss pharmacologist at the Institut Pasteur, which in 1937 was working on the first substance capable of exercising a histaminergic blocking action, 2-isopropyl-5-methylphenoxiethyl-diethylamine, derived from aniline and developed as a dye by Ernest Fourneau in 1910, under the name F-929. Nevertheless, this substance could not be used in clinical practice, in the treatment of allergies, due to its potential toxicity. Following this line of research, in 1944 Bovet's team described the antihistamine properties of pyrilamine maleate, and subsequently, working by now at Société Rhône-Poulenc, Bovet studied (with others, such as Halpern and Ducrot) the antihistamine effects of the phenothiazines synthesized by Fourneau. The result of this research was the clinical introduction, within the field of allergies, of phenbenzamine (RP-2339; Antergan®), diphenhydramine (Benadril®) and, finally, in 1947, of promethazine (RP-3277), whose commercial name was Fenegan®, and which was also used in the treatment of Parkinson's disease. Its sedative effects were also later discovered (13,29).

Some of these antihistamines were even tested in the field of psychiatry. Phenbenzamine was studied by Daumezon, in 1942, in patients with manic-depressive disorder, with the aim of reducing the number of relapses and limiting the use of electroshock, the only therapeutic alternative at the time for this type of patient (32). Although the preliminary results were encouraging, research did not continue. Promethazine was also tested in psychiatry. In July 1950, Paul Guiraud reported his experience with this antihistamine-hypnotic agent in 24 patients with manic-depressive psychosis, though his conclusions (inducement of drowsiness and sedation in agitated psychotic patients or reduction of the duration of manic episodes) were questioned, and made little impact (33).

The early use of phenothiazine compounds as neuroleptic agents resulted from the research of Henri-Marie Laborit (Figure 3A). This French army surgeon, working in 1949 at the Hôpital Maritime in Bizerte (Tunisia), was interested in finding a pharmacological method for preventing surgical shock. According to one of the prevailing hypotheses at the time, proposed by Canadian endocrinologist Hans Selye and defended by French surgeon René Leriche, surgical shock was due to an excessive defensive reaction of the organism to stress, so that a peripheral and/or central inhibition of the autonomic nervous system would be a highly advantageous alternative anti-shock therapy. Thus, Laborit studied from 1947 the ganglionic blocking effect of curare, with the aim of achieving chemical sympathectomy. His idea was received with scepticism by the scientific community at the time, though it did prove successful later on, with the incorporation into the anaesthetic techniques of another ganglioplegic substance, tetraethylammonia. Subsequently, Laborit continued to test different substances

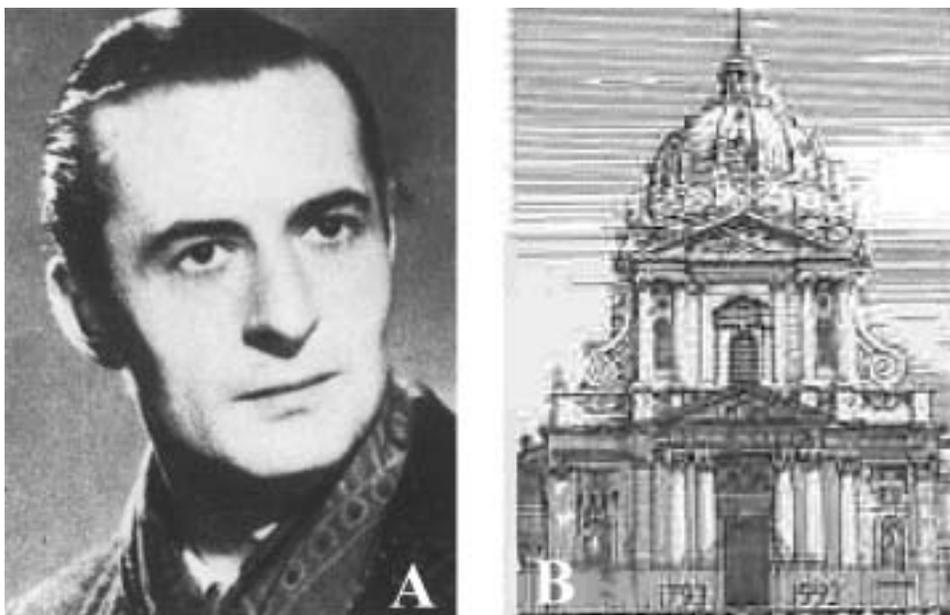


Figure 3 Henri-Marie Laborit (A), and Val-de-Grâce Army Hospital (Paris) (B).

endowed with inhibitory effects of the visceral vasomotor reactions of the vegetative system — substances that included the antihistamines then available. This “Laborit’s idea” was described by Leriche, in 1952, in the preface to a book by Laborit, as “revolutionary, fascinating and extremely promising” (34).

Among the antihistamine drugs of the era under study, Laborit found that promethazine, whose capacity for prolonging the sleep induced by barbiturates had been demonstrated in rodents, had acceptable anti-shock activity, so that he added it to another, morphine-type substance, dolantine (Dolosal[®]), creating the so-called “lytic cocktail,” a landmark in the history of anaesthesia in that it constituted the origin of neuroleptoanalgesia. This early cocktail was widely used in Tunisian women affected by eclampsia. Laborit himself actually predicted the potential psychiatric implications of these agents, and, recalls, in an interview recounted by Swazey, that “I asked an army psychiatrist to watch me operate on some of my tense, anxious Mediterranean-type patients. After surgery, he agreed with me that the patients were remarkably calm and relaxed. But I guess he didn’t think any more about his observations, as they might apply to psychiatric patients” (29).

Subsequently, Laborit’s cocktail would undergo numerous modifications, including the addition of diethazine (Dip-Dol cocktail, Diparcol-Dolosal), or even, later, chlorpromazine. The Dip-Dol cocktail was introduced by a colleague of Laborit, Pierre Huguenard, anaesthetist at the Hôpital de Vaugirard in Paris, who in a nostril operation on a highly agitated patient, to whom he was unable to apply the ether or chloroform mask, administered diethazine mixed with dolantine. The patient underwent general relaxation while remaining conscious, even being capable of answering questions from the hospital staff (35) — a result that some authors described as “pharmacological lobotomy” (36). However, despite the success of the intervention, this cocktail was not applied in psychiatric practice, possibly due to fears that the opiate nature of its formula would create dependence.

The Synthesis of Chlorpromazine and Its Initial Clinical Applications

In the light of these discoveries, Spécia Laboratories at Rhône-Poulenc (Vitry-sur-Seine, France), the company that synthesized and commercialized promethazine, undertook to continue the line of research opened up by Laborit and, in 1950, attempted to find a lytic agent that would prevent surgical shock, through depressant actions on the central nervous system. Thus, Simone Courvoisier analyzed all the phenothiazines synthesized by Paul Charpentier since 1944 as antihistaminic agents. Of these, promazine appeared to be the best option, despite its low antihistaminic activity, so that Charpentier synthesized various derivatives of it. A chlorinated derivative (RP-4560), produced in December 1950, displayed, according to Courvoisier’s test, extraordinary activity, not only of an antihistaminic nature, but also of a parasympathetic and

adrenolytic character, capable of canceling out (at intravenous doses of 1-3 mg/Kg), and even of inverting (at higher doses), the effect of adrenalin on blood pressure (37). Furthermore, it was demonstrated in experiments with rats, such as tests of conditioned avoidance (also carried out by Leonard Cook’s group at SmithKline & French Corporation, Philadelphia, who had designed them), that RP-4560 was capable of extinguishing conditioned reflexes (animals would climb a rope after an auditory stimulus, when this was previously associated with an electrical discharge) without modifying the animal’s strength. Similarly, RP-4560 was capable of prolonging the sleep induced by barbiturates in rodents and preventing the emesis induced by apomorphine in dogs (38). Although the pharmacology of the new product was studied by Courvoisier and Pierre Koetschet in 1951, the first data were not published until 1953, after the publication of the first clinical experience with the substance (37).

The following year, between April and August, RP-4560 was tested by numerous doctors, both French and from other countries. Among those who received samples was Laborit, now working at the Physiology Laboratory of the Val-de-Grâce Military Hospital in Paris (Figure 3B), and who confirmed that this could be the lytic agent he had been seeking for so long. After the statutory studies with experimental animals, Laborit tried the new drug on patients undergoing surgery, at endovenous doses of 50–100 mg. The results as an anaesthetic booster were striking. However, Laborit observed that not only did these patients feel much better during and after the operation, due to the anti-shock action, but they also felt much more relaxed and calm (*désintéressement*) in the pre-operative period, a time associated with intense stress and high levels of anxiety (2). Another interesting property of the product was its hypothermic effect, which allowed reduction of the body temperature to 28–30° C. This effect, attributed by Laborit to a fall in basal metabolism and oxygen consumption, together with the hypnotic properties of the new drug, allowed Laborit and Huguenard to propose, in 1951, the concept of “artificial hibernation” (39), a technique that would make possible greater efficacy of certain types of operation, such as cardiac surgery. Indeed, as Jacobsen (9) relates, the “artificial hibernation” technique was applied on a large scale by Laborit and Huguenard in 1953 in Vietnam, during the French campaign in Indo-China, and permitted them to save the lives of hundreds of soldiers.

In relation to Laborit’s work, it is interesting to note the comment of René Leriche, in 1952, in the preface to a work by the naval surgeon, *Réaction organique à l’agression et choc*, that

what is most original in Henri Laborit’s work is the conception he has of therapy for shock. It is frankly revolutionary. Whilst up to now we have tried to reanimate the elements of a life that was dying, he has the idea of putting them into a vegetative sleep, of slowing down all the changes, since it is the vegetative reactions that give rise to and maintain shock (34).

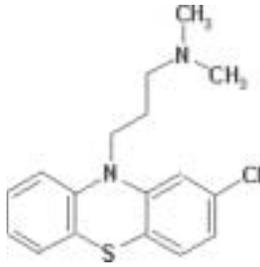


Figure 4 Chlorpromazine chemical structure.

The new drug, described by numerous authors at the time as “Laborit’s drug,” was called chlorpromazine (Figure 4), and was commercialized in France by Rhône-Poulenc in 1952. Its commercial name, Largactil® (“large” = broad; “acti*” = activity), was designed to reflect its wide spectrum of pharmacological activities; gangliolytic, adrenolytic, antifibrillatory, antiedema, antipyretic, anti-shock, anticonvulsant, antiemetic, and so on (38).

PERIOD OF CLINICAL PSYCHIATRIC INTRODUCTION OF CHLORPROMAZINE IN EUROPE (1952–1955)

Laborit’s observations allowed him to hypothesize other therapeutic uses for the new drug, which he called a “vegetative stabilizer” (2) (Figure 5A), including, in addition to the boosting of anaesthesia, the management of surgical stress, serious burns, cardiovascular disorders (such as Raynaud’s disease) and psychiatric disorders. Thus, in November 1951, Laborit and Montassut administered a dose of chlorpromazine intravenously to Cornelia Quarti, a fellow psychiatrist acting as a healthy volunteer at the Villejuif mental hospital. Although there were no effects worthy of mention, save a certain sensation of indifference, on getting up to go to the toilet, Quarti fainted; as a result, the head of the hospital’s Psychiatric Service decided to discontinue experimentation with the substance (10,40).

In spite of these events, in one of his first publications on the surgical results obtained with RP-4560, in early February of 1952, Laborit argued that the observations made “may anticipate certain indications for the use of this compound in psychiatry, possibly related to sleep cures with barbiturates” (41). Thus, during a meal in the canteen at the Hôpital Val-de-Grâce, he persuaded his colleagues from the Neuropsychiatry Service, headed by Joseph Hamon, to test the drug in psychotic patients, though, as Swazey (29) recounts, the psychiatrists were not initially enthusiastic about Laborit’s proposal. On January 19, 1952, it was administered for the first time, as an adjunct to an opiate (petidine), a barbiturate (pentotal) and electroconvulsive therapy, to Jacques Lh., an extremely agitated manic patient aged 24, who rapidly began to calm down, maintaining a state of calm for several hours. By February 7, Jacques had calmed down sufficiently to be able to play bridge and carry out

normal activities, though he maintained certain hypomanic attitudes. Finally, after a 3-week treatment, with a total quantity of 855 mg of RP-4560 administered, the patient was discharged from hospital. Colonel Jean Paraire presented these data on February 25, at a meeting of the *Société Médico-Psychologique in Paris*, and they were published in March of that same year of 1952 (Figure 5B). In prophetic tone, he said: “We have quite probably introduced a series of products that will enrich psychiatric therapy” (42). This event marked the culmination of what may constitute one of the most important landmarks in the history of psychopharmacology, since this was the first time chlorpromazine had been administered in the field of psychiatry, even though, as Shen and Giesler (43) point out, reference to this contribution has been omitted by many researchers, due possibly to the multiple therapeutic drugs used.

The Crucial Contribution of Jean Delay and Pierre Deniker

There soon began to appear in the literature scientific works on clinical experience in psychiatry with chlorpromazine, notable among which are the pioneering studies by Jean Delay (Professor of Psychiatry at the Sorbonne and Director of the Hôpital Sainte-Anne in Paris) (Figure 6A) and Pierre Deniker (Men’s Service Chief at the same hospital) (Figure 6B). Deniker heard about Laborit’s hibernation experiments from his brother-in-law, who was a surgeon, and ordered from Specia Rhône-Poulenc some samples of the substance RP-4560 for administration to psychiatric patients. Doctor Beal, head of clinical research at Rhône-Poulenc, sent him some of the product, together with a brief note on its pharmacological characteristics and instructions for the hibernation technique. Thus, Deniker and Delay, several weeks after Paraire’s presentation, administered chlorpromazine alone, with no other drug in combination, for the first time, and confirmed its great efficacy as a tranquillizing agent in psychotic or agitated patients (3). Furthermore, they observed that the dosage of chlorpromazine employed by Laborit in his hibernation techniques was insufficient when the drug was used alone, and that dosages 4 to 6 times higher were necessary for an antipsychotic effect (75–100 mg/day).

In 1952, Delay and Deniker described the clinical condition caused by the administration of an injection of 15–100 mg of chlorpromazine, which was characterized by a slowing down of motor activity, affective indifference and emotional neutrality, a condition they referred to as “neuroleptic syndrome” (44). According to Ginestet (45), in January 1955, Jean Delay proposed to the French Académie Nationale de Médecine the term neuroleptic (from the Greek: “that take the nerve”) to designate chlorpromazine and all the drugs producing a similar motor side effect. The term neuroleptic was widely accepted in Europe, but not in America, where it was considered inappropriate to define a family of drugs by their adverse effects, rather than by their therapeutic qualities. Thus, the preferred

se laisse pas véritablement impressionner directement par la situation qui est devant lui, mais qu'il agit plutôt dans le groupe ; tant en ce qui concerne le lapsus d'être du malade que les réactions psychopathologiques, et par conséquent aussi dans ce qui concerne autre apparence, des différences peuvent exister entre ces deux situations.

Les termes « végétatif » et « végétal » renvoient aux pléonasmes et à des faits qui diffèrent les uns des autres, non seulement pour ce qui est des actions, mais en leur essence même. Ces termes sont très vagues, très commodes également des manifestations végétales qui apparaissent à la suite de processus morbides. Le cas de Van Dyck semble d'être supporté. On se peut de voir, être consensuelle uniforme, appaître globalement et sans distinction à toutes les manifestations végétales, lorsque peut-être quelques réactions.

M. P. GAZDAR. — Cette communication présente l'intérêt de nous offrir le cas de quatre dépressions principales, dont le délire évolue d'après pour son usage, surtout une situation différente dans chaque cas. Le seul élément collectif est le caractère consensuel à ces délires d'avoir un thème végétal, qui diffère d'ailleurs, quoique dans un cas il est question de la Vierge, dans un autre de Saint-Régis. Dans les délires collectifs, habituellement, il y a un caractère de dérivé principal dans les autres, influencés, partageant les caractéristiques.

Il y aurait lieu, à nos yeux, d'établir une distinction entre la « végétation végétale » et la « végétation », d'une part, et, d'autre part, entre la « végétation végétale » et la « végétation végétale ».

Remarque sur l'action du 4560 R.P. sur l'agitation maniaque, par MM. HANON, PARAIN et VELLEZ.

Les ganglioplegiques sont à l'ordre du jour en thérapeutique. Certains d'entre eux commencent à être utilisés dans les accidents hémorragiques cérébraux de l'hypertension ou pour modifier le régime de la circulation cérébrale dans les interventions neuro-chirurgicales. D'autres sont capables d'exalter l'action des anesthésiques ou de bloquer le système neuro-végétatif.

Un de ces agents médicamenteux, le 4560 R.P., préconalidolamine et stabilisateur végétatif, est étudié par Janeline et Laborit, au laboratoire central du service de santé et a permis à Laborit de mettre au point sa technique d'hypertonie artificielle.

Le 4560 R.P. est un corps chimique, dérivé de la diéthylamino-paralidolamine, et dont la structure est voisine de celle du dipérool et du paralidol. C'est un ganglioplegique, un sympatholytique et, à un moindre degré, un vagolytique.

La toxicité, expérimentée chez les souris, s'est montrée comparable à celle du phénothène. Il n'est pas anti-histaminique. Il a une action potentialisatrice à l'égard des anesthésiques, des analgésiques, des hypnotiques et des barbituriques. Injecté seul, il produit une hypotension artérielle, associée à un état de somnolence et de « déshydratation ». Il est également hypotenseur et, pour certains,

RESUME

Les auteurs ont étudié expérimentalement l'action de certains agents végétatifs et de certains médicaments. Ils ont constaté que les effets de ces agents sont très variables et dépendent de la dose, de la voie d'administration, de l'état de santé du sujet, etc. Ils ont également constaté que les effets de ces agents sont souvent transitoires et peuvent être modifiés par l'administration de certains médicaments.

ACTUALITÉS THÉRAPEUTIQUES

UN NOUVEAU STABILISATEUR VÉGÉTATIF (LE 4560 RP)

Les troubles mentaux (1) sont caractérisés par une grande instabilité et par une grande variabilité. Ils sont souvent accompagnés de troubles somatiques et de troubles végétatifs. Les auteurs ont étudié expérimentalement l'action de certains agents végétatifs et de certains médicaments. Ils ont constaté que les effets de ces agents sont très variables et dépendent de la dose, de la voie d'administration, de l'état de santé du sujet, etc. Ils ont également constaté que les effets de ces agents sont souvent transitoires et peuvent être modifiés par l'administration de certains médicaments.

Populiste psychotrope

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Figure 5 Publications that were a milestone in the history of chlorpromazine clinical introduction (1): Laborit et al, 1952 (2) (A), and Hamon et al, 1952 (42) (B).

B

A



Figure 6 Jean Delay (A) and Pierre Deniker (B).

term in the USA was initially “tranquillizer,” and this was replaced by the expression “major tranquillizer” before the introduction of the current term “antipsychotic” drug (46).

Between May and July 1952, Delay and Deniker, together with the interns J.M. Harl and A. Grasset, presented six clinical reports containing the results of chlorpromazine use in 38 patients in states of agitation and excitation, mania, or mental confusion, or undergoing acute psychotic processes. They confirmed therapeutic effectiveness in these patients, as well as the poor response in cases of depression and to the negative symptoms of schizophrenia. Case 1 is a good illustration (47), and referred to Giovanni A., a 57-year-old manual worker with a long history of mental pathology, admitted for “giving improvised political speeches, getting into fights with strangers and walking along the street with a plant pot on his head proclaiming his love of liberty.” After a 9-day treatment with chlorpromazine, he was able to maintain a normal conversation, and within 3 weeks he was in such a calm state that he was able to be discharged.

The first of the reports, presented on the May 22 at the centenary meeting of the Société Médico-Psychologique and dealing with “shock and reactions of alarm,” was published a month later in the prestigious French journal *Annales Médico-Psychologiques* (3) (Figure 7A). Curiously, the article made no reference whatsoever to the research and previous experience of Laborit, nor to the work of Hamon, Paraire and Velluz, suggesting that there was some degree of conflict between the two groups. On June 26 the group presented its second report at a meeting of the same society (47), and the third was presented on July 7 (48). Both were published in the same review as the first. The end of July saw the presentation of the three remaining

studies within the framework of the 50th French Congress of Psychiatry and Neurology, held in Luxembourg (44,49,50). Table 1, taken from Deniker (10), shows all the publications on chlorpromazine from the year 1952.

Delay and Deniker’s influence was decisive for the future of psychopharmacology and psychiatry, for not only did they assess the therapeutic importance of chlorpromazine, they also helped to propagate its use and developed the initial regimes for the administration of this first antipsychotic drug. Nevertheless, the figure of Henri Laborit should be reconsidered, from the historical point of view, since he carried out the essential research that laid the foundations for the later work of the psychiatrists at Sainte-Anne. Indeed, in 1957 the American Public Health Association awarded the prestigious Lasker Prize for Medicine to Laborit and Deniker, together with Heinz Lehmann, a Canadian psychiatrist, for the discovery of the antipsychotic effect of chlorpromazine. The plinth of Deniker’s award bore the inscription: “Prize awarded for the introduction of chlorpromazine in psychiatry and the demonstration that a medication can influence the clinical course of the major psychoses.” Nevertheless, the disputes between the groups from Val-de-Grâce and Sainte-Anne and the subsequent controversy over the discovery of the antipsychotic properties of chlorpromazine deprived these researchers, as noted by Pichot (51), of winning the Nobel Prize, for which they were nominated in view of the great clinical significance of their contribution, since the Swedish Academy preferred not to give the award to either so as to avoid problems within the French scientific community; this was indeed an even more obvious outcome if we take into account that Delay was at the time a foreign member of the Academy.

Table 1 Publications on Chlorpromazine in 1952, Year of Its Clinical Introduction, under Chronological Order

Date		Authors	Title	Reference
February 13	1	Laborit et al.	Un nouveau stabilisateur végétatif (le 4560 RP)	<i>Presse Med</i> 60: 206-8
February 25	2	Hamon et al.	Remarques sur l'action du 4560 RP sur l'agitation maniaque	<i>Ann Med Psychol</i> 110: 331-5
March 8	2	Pocidalo et al.	Action sur l'excitabilité sympathique du 4560 RP	<i>CR Soc Biol</i> 146: 368-70
May 26	2	Delay et al.	Utilisation en thérapeutique psychiatrique d'une phénothiazine d'action centrale élective	<i>Ann Med Psychol</i> 110: 112-7
June 21	2	Deschamps	Hibernation artificielle en psychiatrie	<i>Presse Med</i> 60: 944-5
June 23	2	Abely et al.	Suite aux essais de rééquilibration instinctivo-affective: essai de traitement par le B.T.E.A. en comparaison avec le 4560 RP et C 9295	<i>Ann Med Psychol</i> 110: 262-7
June 23	2	Delay et al.	Traitement des états d'excitation et d'agitation par une méthode médicamenteuse dérivée de l'hibernothérapie	<i>Ann Med Psychol</i> 110: 267-73
July 7	2	Delay et al.	Traitements des états confusionnels par le chlor ^{te} de deméthylaminoprppyl-N-chloro-phénothiazine (4560 RP)	<i>Ann Med Psychol</i> 110: 398-03
July 7	2	Hamon et al.	Etats anxieux et barbituriques potentialisés	<i>Ann Med Psychol</i> 110: 403-7
July 27	2	Delay y Deniker	Le traitement des psychoses par une méthode neurolytique dérivée de l'hibernothérapie (le 4560 RP utilisé seul en cure prolongée et continue)	<i>CR 50° Congrès Aliénist Neurol Langue Fse</i> 495-502
July 27	2	Delay y Deniker	38 cas de psychoses traitées par la cure prolongée et continue de 4560 RP	<i>CR 50° Congrès Aliénist Neurol Langue Fse</i> 503-13
July 27	2	Delay y Deniker	Réactions biologiques observées au cours du traitement par le chlor ^{te} de deméthylaminoprppyl-N-chlorophénothiazine	<i>CR 50° Congrès Aliénist Neurol Langue Fse</i> 514-8
July 27	2	Gachkel y Brisset	La cure de sommeil en psychiatrie	<i>CR 50° Congrès Aliénist Neurol Langue Fse</i> 491-6
October 18	1	Deschamps	Les ganglioplégiques en thérapeutique psychiatrique	<i>Sem Med</i> 650-3
December	1	Arnold et al.	Ueber die Anwendung eines zentral vegetativen Hemmungsstoffes in der psychiatrischen Therapie	<i>Wiener Med Wochenschr</i> 102: 965-9

1 (date of the journal publication); 2 (date of the communication). Modified from Deniker (10).

Other French Contributions in the Period of the Clinical Introduction of Chlorpromazine

Although Delay and Deniker showed already in 1952 the rapid improvement experienced by their psychotic patients, the use of chlorpromazine by French doctors was delayed for longer than might have been expected, with a few exceptions, such as the group led by J. Sigwald and D. Bouttier (Hospice Paul-Brousse, Paris), who began treating psychotic and “neurotic” patients with chlorpromazine alone on February 18, 1952, even though they did not publish their results (with 48 patients) until 1953 (52). Another exception was the case of Andrée Deschamps (Fleury-les-Aubrais Asylum), who in 1952 published the results of a modification of the “artificial hibernation” method with chlorpromazine, promethazine and barbiturates in 6 agitated psychotic patients (53). These works, although published around the same time as those of Hamon, Delay and Deniker, had received less attention by historians.

In this regard, Lempérière (54) recalls that there was indeed great scepticism toward the new drug at first among French psychiatrists, who saw it as no more than a simple sedative agent, like chloral hydrate or barbiturates, and that Delay and Deniker had great difficulty in persuading their colleagues that chlorpromazine possessed certain specific antipsychotic features. Acceptance of its antipsychotic properties was more widespread among the younger psychiatrists, and indeed, in the

majority of psychiatry departments, it was actually introduced by residents. Some authors have blamed this delay in the clinical introduction of chlorpromazine on the pharmaceuticals industry, since, given the low amount of scientific research carried out in the 1940s, numerous drugs were presented as the panacea for the treatment of mental illness, even though their true efficacy was minimal or null (1,27,55).

Despite this early scepticism, a scientific association was set up in 1954 in Lyon, by the name of “Le Comité Lyonnais de Recherches Thérapeutiques en Psychiatrie.” Its members were specialists at the two local hospitals (Hôpital Psychiatrique de Bassens and Hôpital du Vinatier), and it was chaired by Professor Louis Revol, whose initial objective was to combine the experience of the two institutions in relation to patients treated with chlorpromazine. Thus, at the *Colloque International sur la Chlorpromazine et les Médicaments Neuroleptiques en Thérapeutique Psychiatrique*, organized in Paris in 1955 by Delay and Deniker, data were presented on 458 chronic psychotic patients treated at the Hôpital de Bassens (56); the following year, the joint experience of the two hospitals (over 1,400 patients) was reported in a publication entitled *La Thérapeutique par la Chlorpromazine en Pratique Psychiatrique* (57). For more than 20 years, as Lambert (58) recounts, there was a state of healthy rivalry in French psychiatry between the Parisian Hôpital de Sainte-Anne and the Lyon school, represented by Le Comité lyonnais, a rivalry that

generated considerable debate at congresses, meetings, and so on and greatly enriched the development of psychopharmacology.

European Expansion of the Use of Chlorpromazine

It was Swiss psychiatrists who were most receptive to the introduction of the new drug, so that it was no coincidence that the first important scientific meeting on the subject of chlorpromazine was organized there: the Largactil-Symposium, held at the Psychiatrische Universitätsklinik in Friedmatt Hospital (Basel) on November 28, 1953, and chaired by John Eugen Stähelin, Head of Outpatients Service in that institution. Stähelin had a year earlier sent one of his assistants, Felix Labhardt, to the Hôpital Sainte-Anne, so that he could become familiarized with the use of the new drug. After Labhardt's return to Basel in 1953, chlorpromazine soon began to replace the biological therapies that were being used up to that point at the Psychiatrische Universitätsklinik (59). Labhardt himself, drawing on his experience in France, carried out a large-scale study with schizophrenic patients, and published the first data on treatment with chlorpromazine at the Largactil-Symposium. The results obtained were more than satisfactory, since, of 46 patients with a history of psychosis of 1 to 5 years, 48% improved their symptoms with the neuroleptic, and 41% presented social or total remission. Furthermore, in 106 schizophrenics with over 5 years' history of the illness, 26% presented slight improvement, 40% substantial improvement, and 18% total remission (60). Labhardt later published a report of the experience accumulated between 1953 and 1955, with a total sample of 373 psychotic patients treated with chlorpromazine (61).

In 1954, Joel Elkes and his wife, Charmian Elkes, from the Department of Experimental Psychiatry at the University of Birmingham (England), published the first controlled test with chlorpromazine (62), in a study that can be described as historic, not only because it was widely cited by later authors, but also because it introduced into psychiatry the methodology of trials randomized and controlled with placebo. That study included 27 hospitalized hyperactive chronic psychotic patients, monitored for 22 weeks, who were given alternatively (every 6 weeks) chlorpromazine (in relatively small doses; 250–300 mg/day) and placebo. The design was blind, and the patients themselves acted as controls. Evaluation of the treatment's effectiveness was based on daily observations of the patients' behavior by nurses and a weekly clinical examination by a doctor. This information was given scores in a report especially designed for the study by one of the researchers. The results indicated complete recovery in 25.9% of the patients and a partial improvement in 40.7%. The authors stressed the fact that "... in no case was the content of the psychosis changed. The schizophrenic and paraphrenic patients continued to be subject to delusions and hallucinations, though they appeared to be less disturbed by them." Moreover, for the first time subjects treated with neuroleptics gained weight (9 patients increased their weight over the 22 weeks, in a range of

5–15 kg). The contribution of Joel Elkes to the development of new clinical research models in the psychiatric field and to the implementation of psychopharmacology in the USA would become evident in the years to come, especially after he began working at Johns Hopkins University (Baltimore), where he became the first chairman of the American College of Neuro-psychopharmacology (ACNP), as well as an important figure within the Collegium Internationale Neuropsychopharmacologium (CINP). In Ayd's opinion (12), the publication of the Elkes and Elkes article marks the birth of a new discipline — psychopharmacology.

In Spain, Professor Ramón Sarró presented, in 1955, within the framework of the *I Coloquio Internacional sobre la Terapéutica Narcobiótica* (Barcelona), a pioneering work in Europe, entitled *Técnica, complicaciones y resultados de la terapéutica con clorpromazina*, published, together with the rest of the contributions, in Number 3 of the *Revista de Psiquiatría y Psicología Médica de Europa y América Latina*. This study includes the results of his experience with chlorpromazine, begun in 1952 at the Instituto Pedro Mata in Reus (Spain) and continued at the Clínica Psiquiátrica Universitaria in Barcelona, with the collaboration of Joan Obiols. It is in this work that the term "orthotimic" was proposed for referring to chlorpromazine, given its normalizing effect on mood (63).

THE CLINICAL INTRODUCTION OF CHLORPROMAZINE IN NORTH AMERICA (1953–1955)

Canada as Chlorpromazine's Route of Entry into America: The Contribution of Heinz Lehmann

The route of entry of introducing chlorpromazine in North America was Canada (11,18). Although unknown to the majority of researchers, Griffin (64) recovered for history the name of the person who was quite possibly responsible for introducing chlorpromazine into North American psychiatric practice. Ruth Koeppel-Kajander was a German who emigrated to Canada, and in 1953 was a psychiatry resident at the Mental Hospital in London (Ontario). During that year, she obtained permission to administer chlorpromazine to 25 patients, and reported her study results at a psychiatry meeting near Toronto in November 1953. However, she never managed to publish those results. The drug, said Koeppel-Kajander (27), "calms excited or overactive patients, without sedating them to the level where they could not function. Patients lost their agitation level, but not their consciousness. They could talk about themselves and eat and sleep without difficulty."

A similar case was that of Hassan Azima and William Ogle, two psychiatrists at the Allan Memorial Institute, part of McGill University (Montreal), who began using chlorpromazine in the treatment of different mental disorders, but delayed excessively, according to Sarwer-Forner (65), the reporting of their data. Thus it was that Azima and Ogle's (66)

publication appeared 4 months after that of Lehmann and Hanrahan's pioneering work.

Despite the contributions of Koeppe-Kajander, Azima and Ogle, the name that has gone down in history as the introducer of chlorpromazine in North America is Heinz Lehmann (Figure 8), who was responsible for one of the first North American publications on this antipsychotic (67). Lehmann, a Berlin psychiatrist who, as a refugee from Nazi Germany, was employed at the Verdun Protestant Hospital in Montreal (now the Douglas Hospital), considered, in the late 1940s, that the origin of the mental illness of patients in his hospital must have some biological substrate. Consequently, he used as therapeutic tools numerous pharmacological substances (high doses of caffeine, nitric oxide, insulin, hypophysary extracts, typhoidal toxins, turpentine, etc.) (11). Lehmann recalls how one day in 1953 a representative from Poulenc Ltd., a subsidiary of the Rhône-Poulenc company with a branch in Montreal, arrived at his office, and since he was too busy to attend to him, he gave instructions to his secretary to receive the documentation the representative had brought. The representative, according to Lehmann, told the secretary: "*it isn't necessary* [to speak directly to Lehmann], I'll leave this here, this is something new and so good I don't have to explain it to him, he will certainly pay attention to it once he reads it" (11,68). At first, Lehmann considered that it was just another nonbarbiturate sedative, but on reading some of the articles by Delay and Deniker, which accompanied the documentation, he was attracted by the claim that chlorpromazine acted "like a chemical lobotomy." Thus, he decided to try the French drug, initially, on nursing students at his hospital who had volunteered for the tests. At small doses, the nurses felt an effect of drowsiness, but no intellec-

tual functions were affected, as occurred with barbiturates (11). Thus, he began using the new drug, working with a resident (Gorman E. Hanrahan), in some of his patients, to whom he administered chlorpromazine between May and July of 1953.

Compared to his French colleagues, Lehmann progressed to using much higher doses (up to 800 mg per day), in 71 patients aged between 18 and 82, with different psychiatric conditions, all characterized by psychomotor agitation (schizophrenia, schizo-affective disorders, senile psychosis, acute and chronic manic conditions, and psychoneurotic, post-lobotomy and mentally deficient patients). He observed, with continuous treatment (4 months), a positive response in approximately 66% of patients. The best results were obtained in manic-depressive patients, whose psychomotor agitation improved significantly after 24 hours of treatment, while the poorest were found in chronic schizophrenic subjects, whose condition actually worsened. The results of this study were published in March 1954 (67) (Figure 7B). The authors recommended that chlorpromazine be administered under strict medical supervision, given the risk of possible toxic effects, and compared the advantages of chlorpromazine with the standard treatments for agitated patients: electroconvulsive therapy and sleep cures. With regard to the former, relapses were much less frequent with the drug, which also had fewer effects on the higher brain functions (memory, alertness, etc.). As regards the latter, based on the use of barbiturates, scopolamine, insulin, etc., chlorpromazine did not have a prolonged adverse effect on the capacity of losing consciousness, was safer in the long term, and was easier to administer. Finally, it should be stressed that this publication contributed the first data on the use of chlorpromazine in a chronic fashion.

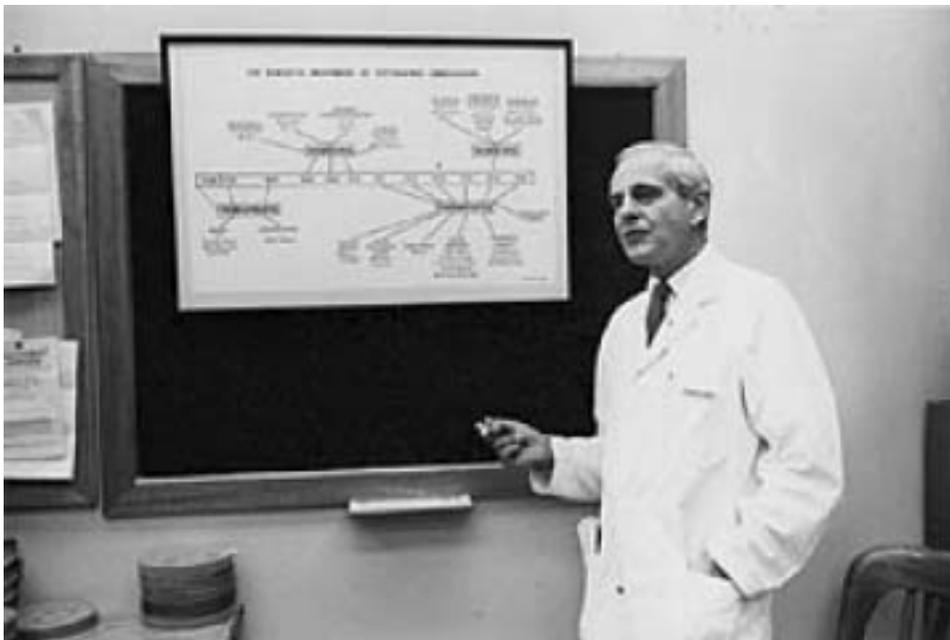


Figure 8 Heinz Lehmann.

The Introduction of Chlorpromazine in the United States

The introduction of chlorpromazine onto the U.S. market was more difficult than in Canada, and as slow as in Europe. The licence for the sale of the drug in the U.S. was granted by Rhône-Poulenc to a pharmaceutical company recently incorporated into the sector, the SmithKline & French Corporation (SKF), based in Philadelphia. Its new chairman, Francis Boyer, traveled to France in the spring of 1952 to obtain the licence for the new anaesthetic agent from Rhône-Poulenc, unaware of its potential for the field of psychiatry (27,69). Thus, after a period of clinical trials lasting two years, the drug came onto the market, in May 1954, with the name Thorazine[®], though the Food and Drugs Agency (FDA) initially only approved its use as an antiemetic. In fact, as in France, the first use of chlorpromazine in the U.S. was as a hypothermic agent in heart surgery, by Dr. Ribstein of the Maimonides Hospital in Brooklyn, to which SKF supplied the drug during its process of clinical development, before the establishment of its psychiatric indications (69).

In the field of psychiatry, pressure from the families of schizophrenic patients, together with the promotional work of SKF, led some years later to the official approval of its use as an antipsychotic. In the U.S. at the time when the first antipsychotic agents appeared, there was a strong psychoanalytic tradition, a direct inheritance of the great influence of Freud on American psychiatry. It was precisely the loyalty of disciples to the Masstro's theories that hindered the early use of these psychoactive drugs, even though everyone was aware that psychoanalysis *per se* was not capable of curing schizophrenia, as underlined by Freud himself. Indeed, the definitive victory of psychoactive drugs did not arrive until around 1970, as American psychiatrist W. Reich recounts: "psychodynamic environmentalism [dominant before World War II], sustained by an ingenuous optimism and boundless hope, had led to failure. The expected cures had come to nought, and at the beginning of the 1970s a new generation of American psychiatrists started to turn towards psychobiology. It was a fresh perspective that would become a source of hope and renewed optimism" (70).

Moreover, the therapeutic exports from Europe did not make many converts in America; for example, Kläsi's sleep cure, widely used in central Europe, was attributed with an excessively high mortality rate by North American psychiatrists (13). Thus, in order to encourage acceptance of the new drug in a country with a clear preference for psychoanalysis, SmithKline & French created a "task force" to raise awareness among the psychiatric fraternity, and had to invite Pierre Deniker to help them in the difficult task of trying to convince his North American colleagues of the advantages of the new pharmacological tools (Figure 9). In fact, the first psychiatrist to test chlorpromazine in the U.S.A. was William Long, at the time Medical Director at SKF. As John Young, then a member of the SKF board, recalls, in an interview with Edward Shorter, one of the first patients treated by Long was "a severely disturbed nun, ... at the edge of violence and using extremely coarse language. He was very concerned about the patient. He gave her some of this stuff. The result? He couldn't

believe it. She had been extraordinarily abusive with most nun-like behavior. In the afternoon she was calm" (27).

The first studies carried out in the U.S. such as those of N. William Winkelman (Sidney Hillman Medical Center, Philadelphia), published in 1954 in the *Journal of the American Medical Association* (71), or Willis H. Bower (McLean Hospital, Boston), published in the same year in the *New England Journal of Medicine* (72), demonstrated to their North American colleagues the utility of the new drug in the management of different neuropsychiatric disorders (states of severe agitation and anxiety, manic conditions, obsessive-compulsive and phobic disorders, and conditions involving hallucinations). The study by Winkelman, a psychiatrist from the psychoanalytic tradition, used a sample of 142 patients, who were treated with chlorpromazine at various doses of between 75 and 150 mg/day for a period of 2–8 months. Despite the clinical effectiveness of the new antipsychotic drug, Winkelman still maintained that this type of approach should never be considered as a substitute for psychoanalytic techniques, and that he did not see it becoming a panacea for all psychiatric illness. Even so, he did not share the initial negative opinion of some of his colleagues, since he did not consider the drug to constitute a "chemical straitjacket," and felt that it showed substantial effectiveness in reducing severe anxiety, phobias and obsessions, paranoid psychoses and manic crises, as well as making hostile and agitated patients calmer and much easier to handle (71).

From that point on, chlorpromazine was used by a large number of prestigious North American psychiatrists, such as Kinross-Wright (Houston), Goldman (Cincinnati), Kline (New York), Freyhan (Delaware), Ayd (Baltimore) and Harris (Galveston). The last-named of these, Titus Harris, Head of the Psychiatry Department at the University of Texas, was, as Ayd (12) recalls, one of the pioneers of American biological psychiatry, and soon saw the therapeutic potential concealed in the new drug from France. Harris charged one of his assistants, Irving Cohen, with setting up a study dealing specifically with this drug, some of the conclusions of which (referring to hepatic complications with chlorpromazine) were published (73) a little after Winkelman's findings.

Once SKF had managed to achieve acceptance of the new drug by the medical and academic class in the U.S. the next step was its progressive introduction in public psychiatric hospitals, often using quite modern-sounding arguments for those times, referring to health economics and cost-cutting. Within a short time, the battle against the conceptualists of psychoanalysis had been won. Shorter recalls the remarks made in *Time* of March 7, 1955: "The ivory-tower critics argue that the red-brick pragmatists—state hospitals—are not getting to the patient's 'underlying psychopathology' and so there can be no cure. These doctors want to know whether he withdrew from the world because of unconscious conflict over incestuous urges or stealing from his brother's piggy bank at the age of five. In the world of red-bricks, this is like arguing about the number of angels on the point of a pin" (27).

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"Thorazine" is especially effective when the psychotic episode is triggered by delusions or hallucinations.

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A reminder advertisement... For prescribing information, please see PDS of antibiotic literature.

Figure 9 Publicity advertisement of Thorazine® (chlorpromazine) of the pharmaceutical company SmithKline and French Laboratories.

The success of the introduction into the American psychiatric market of Thorazine® was such that in 1955 alone SKF grossed 75 million dollars; this obviously soon encouraged other pharmaceutical companies to plunge wholeheartedly into this new market (55).

PERIOD OF CONSOLIDATION OF CHLORPROMAZINE THERAPY (1955–1964)

The Role of the Colloque International sur la Chlorpromazine in Paris (1955)

In the story of chlorpromazine, the year 1955 marks a point of no return. In addition to the publication of the first random-

ized and controlled clinical trial with the drug, by Elkes and Elkes, that year saw the celebration of a series of important scientific events. Between March 29 and April 1, there took place in Barcelona the first international conference on this neuroleptic (*I Coloquio Internacional sobre la Terapéutica Narcobiótica*), organized by Professor Sarró. In June, a symposium set up by SmithKline & French in Philadelphia assembled 117 psychiatrists under the title *Chlorpromazine and Mental Health*. In September and October there were plenary conferences in Italy on chlorpromazine and reserpine, respectively (*Convegno Nazionale su Sonno prolungato, Ibernazione artificiale, Neuroplegici in Neuropsichiatria*, Vercelli, and *Symposium Nazionale sulla Reserpina e la Chlorpromazina in Neuropsichiatria*, Milan). Finally, also in October, Delay and his assistant Deniker organized, at the Hôpital Sainte-Anne in

Paris, the *I Colloque International sur la Chlorpromazine et les Médicaments Neuroleptiques en Thérapeutique Psychiatrique* (20–22 October 1955). This last meeting, considered by many authors as the first event of a new era in the field of psychiatry and psychopharmacology, was attended by over 400 specialists from 22 countries, who debated at length on the new chemical tools (chlorpromazine and reserpine) in the treatment of psychoses. The scientific result of the Colloquium amounted to more than 150 papers, all published in a special issue of almost 1000 pages of the journal *L'Encéphale* in 1956 (Figure 10).

The principal conclusions drawn at the meeting were reported by Delay and Deniker in 1956. Chlorpromazine appeared to mark the beginning of a new era in the treatment of mental disorders, bringing important advantages with respect to the existing biological treatments, especially shock thera-

pies, though the participants recognized the importance of taking into account the support of psychotherapy and the crucial role of the patient's psychosocial readaptation. In comparison with reserpine, chlorpromazine also seemed to offer a series of advantages, according to the majority of participants, such as more rapid onset of its action and a more powerful, regular and constant antipsychotic effect. Nevertheless, it was also confirmed that treatment with chlorpromazine was not innocuous, from the point of view of tolerance, even if the balance between benefits and risks was clearly in its favor. Despite the large number of scientific contributions, the Colloquium failed to reach a consensus on the recommended dosage, which was deemed to depend on individual susceptibility to the product, on the nature of the pathology and on the technique employed (hibernation techniques, sleep cure inducement therapy, or treatment of psychotic patients in monotherapy, also called by some participants "neuroleptic cures"). The range of doses to be employed was set at 150 to 500 mg/day (74).

Moreover, this Colloquium provided an opportunity for the presentation and discussion of the possible therapeutic indications of the new drug. The efficacy of this antipsychotic in manic-depressive conditions was evident, especially in the manic phases, in which the percentage improvement surpassed 85% of patients treated, the duration of the attacks being clearly reduced. On the other hand, in depressive and melancholic states, the effectiveness of chlorpromazine was practically null, and it was necessary to turn to electroconvulsive techniques. Even so, the drug was also extremely useful in the treatment of acute processes associated with psychoses, such as "syndromes of excitation, agitation, anxiety or aggression; states of mental confusion; attacks of delirium" (74). As regards schizophrenia, paranoid forms seemed to benefit more from the therapy than "hebephrenic or hebephrenocatonic" forms. Finally, in the field of the "neuroses," the drug's potential appeared more controversial, it being of some use "in neurotic tension and in sleep disorders." In spite of this, the only randomized, controlled study with placebo presented at the Colloquium evaluated the efficacy of chlorpromazine in 100 patients with anxiety disorders, and although its anxiolytic effectiveness was demonstrated, the nature of the adverse effects led to many patients dropping out of therapy (75).

Finally, the Colloquium provided the occasion for numerous contributions on the possible action mechanism of chlorpromazine, and on its profile of adverse effects. These will be discussed presently.

Confirmation of Chlorpromazine as a New and Revolutionary Agent of Psychiatric Assistance

The contribution of chlorpromazine to psychiatric assistance was clear from the very moment of its clinical introduction. In this regard, Professor Juan José López Ibor (Hospital Provincial de Madrid), one of Europe's pioneers in the use of chlorpromazine, remarked, in relation to the new neuroleptic



Figure 10 Cover of the journal *L'Encéphale* (1956), containing the scientific contributions to the *I Colloque International sur la Chlorpromazine et les Médicaments Neuroleptiques en Thérapeutique Psychiatrique* (Paris, 20–22 October 1955).

agents and schizophrenic conditions, that “although the [neuroleptic] therapies do no more than mitigate the morbid course [of schizophrenia], they are of great social and biological value” (76).

Judith Swazey, in her work *Chlorpromazine in Psychiatry*, recalls the impact on mental health professionals of the anti-psychotic effects of the new drug:

It is a practically unanimous opinion that after administration of the drug, patients who showed great psychomotor activity, aggression, hostility and negative attitude present a reduction in their motor activity (movements). The patients are less agitated, perfectly capable of remaining seated calmly, less aggressive and destructive, and are neat and polite. Subjectively, their anxiety is markedly reduced. They have a clear mind, are oriented in their environment and are capable of speaking calmly and with a considerable degree of objectivity about their hallucinations and delirium” (29).

Likewise, Caldwell refers to the spectacular effect of chlorpromazine in the context of psychiatric hospitals in France: “By May 1953, the atmosphere in the disturbed wards of mental hospitals in Paris was transformed: straitjackets, psychohydraulic packs and noise were things of the past! Once more, Paris psychiatrists who long ago unchained the chained, become pioneers in liberating their patients, this time from inner torments, and with a drug: chlorpromazine. It accomplished the pharmacologic revolution of psychiatry” (8).

The impact of the introduction of chlorpromazine and its derivatives can be evaluated by considering some data on the hospitalization of psychiatric patients. During the first half of the twentieth century, the number of patients admitted to psychiatric hospitals in the U.S. increased alarmingly, from 150,000 to 500,000; it was estimated in 1955 that half the total number of hospital beds were occupied by this type of patient. However, after 1956, first year of the massive use of antipsychotic drugs, the trend of hospitalizations became reversed, and by 1975 the number of inpatients had fallen to 200,000 (77,78). Between 1954 and 1996, the official figure for inpatients at public psychiatric hospitals in the U.S. fell by 89%, whilst the number of these institutions decreased by 34% between 1954 and 1988, according to Geller (79). As a European example, at the University Psychiatric Hospital in Basel (Switzerland), the mean number of days’ stay per patient fell from 150 in 1950 to 95 in 1960 (59).

Other clear indications of the enormous importance of the clinical introduction of chlorpromazine are the large numbers of patients who benefited from its use, which rose, just in the decade 1955–1965, to more than 50 million (80,81), or the more than 10,000 publications on chlorpromazine that appeared in the same period (80).

The First Controlled Clinical Studies with Chlorpromazine

It is a well-documented fact that in the early days of the psychopharmacological era there were numerous limitations on the methodology of clinical research in the field of mental

health. By way of example, it suffices to recall the tremendous limitation of samples in the initial studies with chlorpromazine, which frequently numbered no more than 20 patients. As Leonard Hollister points out, these tiny samples led to the sophism “not different from ..., consequently, the same as ...” (82). In fact, Lehmann recalls the terms in which the study that led to the first North American publication on chlorpromazine was carried out: with no established protocol for the study, without requesting the authorization of the health administration, without informed consent, without the permission of the hospital director, without any type of financial compensation, and so on. Simply “I thought I should do” (11). Even in 1956, Altschule remarked on the problems for evaluating objectively the effects of the new psychoactive drugs, given the scarcity of evolution scales and the involvement of the psychiatrist’s personal judgment in their use (23).

It would not be until the beginning of the 1960s that the first trials were carried out with an adequate methodological design and a substantial sample, in order to assess the anti-psychotic effectiveness of chlorpromazine. Among such studies were that of the U.S. Veterans Administration Collaborative Study Group (83,84), or the project designed by Jonathan Cole and his colleagues at the Psychopharmacology Service of the U.S. National Institute of Mental Health (NIMH), begun in April 1961 and published in 1964 (85). The latter was a multi-center study (nine hospitals), randomized, double-blind and controlled with placebo, which assessed the efficacy of three antipsychotics (chlorpromazine, fluphenazine and thioridazine) in 344 patients recently admitted to hospital and diagnosed with schizophrenia, after 6 weeks of treatment. The results of the trial, shown in Figure 11, indicated the clear effectiveness of the new drugs, since approximately three quarters of the patients had by the end of the treatment experienced at least a moderate improvement, while in the placebo group one third of the patients had to abandon the study due to lack of response, and around a quarter of them showed some improvement. This last result led to the false conclusion that the placebo effect was very high in schizophrenic patients, or that there was a very high incidence of spontaneous remission. Nevertheless, authors such as Hollister argue that in this study there could be considerable diagnostic bias, since at that time diagnostic criteria were not perfectly defined (the DSM-III had not yet been published), so that those classified as chronic schizophrenic patients might include manic patients who experienced spontaneous remission (86). On the other hand, no statistical differences were observed between the three antipsychotics in the efficacy parameters evaluated. The results of this trial confirmed that the symptoms that best responded to the treatment were disorganization and confusion (incoherent speech, personal hygiene, attention to requirements, etc.), as opposed to reasoning disorders, which responded more poorly. Moreover, it was confirmed that the development of extrapyramidal effects was not necessarily associated, as it had been believed, with greater clinical effectiveness.

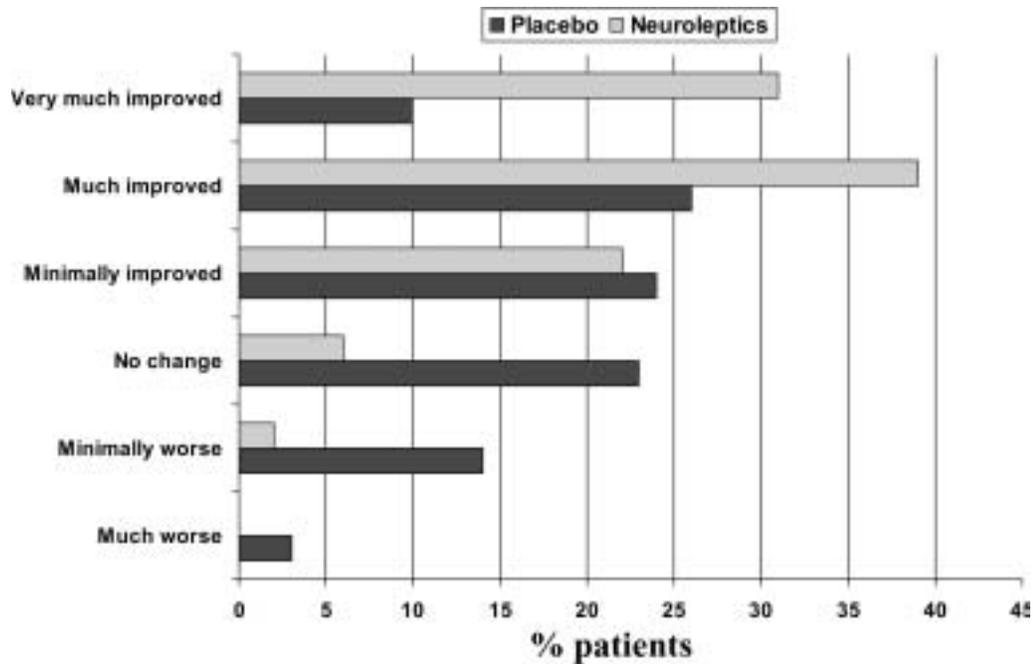


Figure 11 NIMH (1964) study results: effect of neuroleptics administration in schizophrenic patients, evaluated by the researcher by means of the *Global Rating of Improvement*. Modified from Cole et al. (85).

The efficacy of the new antipsychotic drugs was also compared with psychological therapies. Phillip R.A. May, Professor of Psychiatry at the University of California (Los Angeles), published in 1968 the results of a comparative study, evaluated by third parties, in which 228 schizophrenic patients were divided, at random, into five treatment groups: one group received antipsychotics, another individual psychotherapy, another occupational therapy, another psychotherapy and antipsychotics, and a fifth electroconvulsive therapy (87). The results showed the psychological techniques to be totally ineffective, in contrast to the antipsychotic medication. But moreover, the author himself, in a study published later (88), monitored these same patients (once they had completed an outpatient phase) for five years, in order to demonstrate a series of additional advantages of the drugs in the long term. Thus, he was able to observe that the patients who took the antipsychotics were readmitted to hospital less frequently than those who had received psychotherapy, and that, moreover, the duration of their stay was considerably shorter. Thus, the idea circulating in the early years of the psychopharmacological era, that neuroleptic drugs produced “revolving door” patients — that is, patients who went home only to return to hospital shortly afterwards — began to lose credibility.

Despite the large number of classic antipsychotic agents introduced into clinical practice, the antipsychotic efficacy of chlorpromazine was never surpassed, as McKenna and Bailey (89) recognize. It is clear, then, that the classic antipsychotics are effective against acute psychotic symptoms, at the same time as preventing relapses. In this regard, the importance of

these agents is highlighted in a relatively recent review of the literature (90), which covers a total of 4,365 patients, from 66 clinical studies, and in which the cumulative mean rate of relapse was 53% among the patients that abandoned the medication, versus 16% among those that continued with neuroleptic treatment over a period of 9 months.

Studies on the Action Mechanism of Chlorpromazine and Its Relationship to the Etiology of Schizophrenia

In the countries of southern Europe, the first attempts to work out the action mechanism of chlorpromazine were based on their traditional neuromorphological schools (91–96). According to these authors, the action of chlorpromazine, as an exponent of the so-called “neurolytic” or “narcobiotic” drugs, was dual: a depressant action of the bulbo-mesencephalo-diencephalic reticular formations, which would halt the activating stimuli of this system (91,92), either of a peripheral or descendant (cortico-reticular) nature, and an inverting activity of the peripheral actions of adrenaline (93,94). Some authors also proposed direct action on the hypothalamus-hypophysis axis (95).

As regards the action on the ascendant reticular formation, a hypothesis initially proposed by Hrayr Terzian, Professor at the Clinic for Nervous and Mental Illnesses at the University of Padua (Italy), chlorpromazine produced the same effects on the behavior of rhesus monkeys and the same electroencephalographic changes in these animals as surgical section of this pathway would have done. Moreover, this action of chlorpromazine,

demonstrated through studies of electrical activity in the “isolated brain,” appeared to be relatively specific, and different from the action of other drugs with central depressant action, such as barbiturates (97). For their part, the team at the Physiology Laboratory of the Hôpital Henri Rousselle in Paris defended the hypothesis of the involvement of peripheral circulating noradrenaline in control of the activity of the noradrenergic neurons of the brainstem reticular formations (98). Thus, any pharmacological substance that modifies the plasma levels of noradrenaline could exercise a central action on these anatomical structures (94). This would be the case of chlorpromazine, whose adrenergic action (or even anti-adrenalinosecretory — on the part of the suprarenal glands) had already been reported by Courvoisier et al. (37). Thus, the blocking exercised by chlorpromazine on the intrareticular adrenergic mechanisms would cause a reduction in spontaneous reticular activity, and therefore, a decrease in the capacity for response to external stimuli, including electrical stimuli, and sensory afferences, all typical effects of the neuroleptic.

For his part, in the first article published in the U.S. on the clinical efficacy of chlorpromazine, Winkelman (71) defends the action mechanism proposed by Laborit, in the sense that chlorpromazine would in some way modify the synaptic transmission (changes in the cellular concentration of ions of potassium) of the pathways connecting the diencephalon with cortical areas, so that the effect of massive doses of the neuroleptic, parenterally, would be quite similar to that of frontal lobotomy. Notable among the pharmacological actions mentioned by Winkelman are depression of the nervous system, alterations of the conditioned responses of experimental animals, fall in blood pressure and body temperature, blocking of vomit induced by apomorphine, and an intensification of the effect of barbiturates, ether, narcotics, muscle relaxants and ethyl alcohol.

Table 2, a modification of Decourt (96), shows the principal pharmacodynamic actions of chlorpromazine, in comparison with the rest of the synthetic drugs employed in psychiatric therapy in the first half of the 1950s.

From the biochemical perspective, during the second half of the 1950s, different hypotheses were postulated on the action mechanism of chlorpromazine, all of them related to the mistaken etiopathogenic bases of schizophrenia prevailing at the time, and which attempted to explain psychoses as a toxic phenomenon. Thus, it was believed that chlorpromazine might interfere with the enzymatic system of N-methyl-transferase, with the consequent reduction in the synthesis of noradrenaline (99), or that it decreased the use of adenosine-triphosphate, resulting in psychotoxic residues, such as dimethylated indoleamines (100). There was also speculation about a stabilizing mechanism of the cellular membrane, protective against the action of alpha-2-globuline, a plasmatic factor involved in the origin of psychoses (101), and about a drop in general metabolism, on reducing the cellular needs for oxygen (50).

After having studied laboratory animals' brain, Swedish psychopharmacologists, Arvid Carlsson and Margit Lindqvist (Göteborg) in 1963 discovered that chlorpromazine and haloperidol can bind postsynaptic dopamine receptors and prevent dopamine released from presynaptic neurons from binding the postsynaptic neurons (102). Later, Carlsson shared with other two scientists the 2000 Noble Prize for this important work and others. With the help of available dopamine agonists, more scientists had studied synthesis, storage, release and metabolism of the dopamine neurons. Based on all the laboratory results, Solomon Snyder of Johns Hopkins University (Baltimore) proposed the dopamine hypothesis of schizophrenia in 1974 (103). The oversimplified points of this hypothesis consists of: (a) excessive dopamine in the brain through the use of dopamine agonists (such as amphetamine) causes psychotic symptoms,

Table 2 Main Pharmacodynamic Actions of the Four Groups of Synthesis Substances Used in Psychiatry During the First Years of the “Psychopharmacological Era”

	ACTIVITY			
	Hypnotic	Adrenolytic	Anticholinergic	Narcobiotic
Barbiturates				
Phenobarbital	+++	0	0	0
Butobarbital	+++	0	0	0
Benzodioxan-derivates				
883-F	++	+++	+/-	+
933-F	++	+++	+/-	+
Benzhydrol-derivates				
N-68	(-)	0-	0	+++
Meratran	--	0		?
Phenothiazines				
Diethazine	+++	+	+	++
Promethazine	+++	+	+	++
Chlorpromazine	(++)	++	+/-	+++

Modified from Decourt (96).

(b) the blockage of dopamine receptors in the postsynaptic neurons through the use of antipsychotics (such as haloperidol) can improve psychotic symptoms, and (c) the brain of a schizophrenic patient has more dopamine receptors to bind a dopamine ligand as compared to that of the normal controls (20). This hypothesis dominated the field for 15 years till the advent of the second generation antipsychotic drugs (20).

Knowledge of the Adverse Effects of Chlorpromazine

The first adverse effects reported in published studies on chlorpromazine were lethargy, orthostatic hypotension, jaundice, painful induration at the sites of injection, dryness of the mouth and the development of Parkinsonian syndrome (104). Of less frequent mention were phlebitis, with risk of cardiac or pulmonary infarct, rheumatoid arthritis, dermatitis, galactorrhoea, blurred vision and the emergence of depressive conditions.

Nevertheless, from the perspective of tolerance, the most important characteristic of the so-called classic antipsychotics, which include chlorpromazine, is the induction of adverse motor effects of an extrapyramidal nature. As early as 1952, Delay and Deniker described a syndrome of psychomotor indifference (50) similar to the akinetic syndrome identified by Lhermitte in patients with encephalitis lethargica (105). Two years later, Labhardt (106) described an extrapyramidal syndrome in patients treated with chlorpromazine, and Lehmann and Hanrahan (67), in the first North American study, also reported these effects, especially at high doses. The patients described by the mentioned authors presented motor inhibition, with unstable gait and a lack of facial expression, a situation reminiscent of Parkinson's disease victims, but without the muscular rigidity. These extrapyramidal conditions (trembling and bradykinesia), of reversible nature, and also brought on by reserpine, were, in the opinion of Swiss psychiatrist Hans Steck (Director of the University Psychiatric Hospital in Lausanne), similar to the irreversible processes of encephalitis lethargica, described after World War I (107), and were attributed initially to a circulatory problem of the cephalorrhachidian liquid, together with an alteration of the blood-brain barrier, and subsequently to the action of the drug on the extrapyramidal and diencephalic system. At the Paris Colloquium of 1955, Steck presented data on the incidence of extrapyramidal syndrome induced by chlorpromazine in his series of patients of 44.5% in men (n=137) and 42.4% in women (n=340) (108).

A great advance in the knowledge of extrapyramidal reactions took place when, in 1956, Broussolle and Dubor, two Lyon psychiatrists, observed how the first piperazine phenothiazine, prochlorperazine, caused attacks of hysteria both in women affected by neurotic conditions and in soldiers when it was used as an antiemetic during naval disembarkation exercises (109). These phenomena were quite similar, according to Delay and Deniker, to the "hysteriform" conditions described

by Marie and Levy, under the name "excito-motor syndrome," as residual effects in the encephalitis lethargica cases found between 1920 and 1935. These symptoms began with a pronounced drowsiness that gave way to different types of dyskinesias and hyperkinesias, leading finally to a Parkinsonian condition. However, in contrast to the case of encephalitis, the syndrome described was observed while the drug was administered, and disappeared when the treatment was discontinued (10). In a paper delivered at the International Meeting in Milan in 1957, reproduced in the work *Psychotropic Drugs*, Delay and Deniker state that "we are inclined to conclude that the neuroleptics have the same trophism as von Economo's encephalitis virus, in that they produce a selective impregnation of the meso-diencephalic centres of the base of the brain" (110).

In November 1960 there took place in Montreal a monographic scientific meeting on neuroleptics and the extrapyramidal system, and in 1961, Ayd published the first epidemiological data on the adverse extrapyramidal effects of neuroleptics, which were estimated to affect 38.9% of patients treated (111). At the same time as these events, as Deniker (10) recounts, the group led by Sigwald, in France, and Uhrbrand and Faurbye, in Denmark, reported the first descriptions of the long-term extrapyramidal effects, even after the suspension of the neuroleptic therapy, which basically involved tardive dyskinesia (112).

As has been mentioned, these adverse extrapyramidal effects of chlorpromazine and its phenothiazine derivatives were known ever since the drugs had been used, and they were related in such a way that many were convinced that the therapeutic effect of the neuroleptic depended on the extrapyramidal motor effect (113,114). Some authors, such as the Swiss Steck and the German Haase, even went so far as to consider this "neuroleptic impregnation" as a "*conditio sine qua non*" for obtaining antipsychotic efficacy (115). In fact, it was noted how other substances from the same chemical family as phenothiazines, such as promethazine, which lacked antipsychotic effect, also failed to have adverse neurological effects (10). In this regard, the experimental tests on the clinical potency of possible neuroleptic agents were measured in accordance with the precise dosage for the inducement of extrapyramidalism. Nevertheless, from the early 1960s, controlled trials invalidated these hypotheses. In 1961, Freyham reviewed the case histories of 1,000 institutionalized schizophrenic or manic patients, treated with the different neuroleptics available up to 1960 (basically phenothiazines), and found no relation between the appearance of extrapyramidalism and positive antipsychotic response (116). Finally, in 1965, Bishop and his team carried out a controlled trial, of double-blind design, with 223 schizophrenic patients. Their conclusions — no association was found between clinical improvement with neuroleptics and extrapyramidal effects — put an end to debate on the matter (117).

Worthy of note among the adverse effects of neuroleptic agents is an infrequent but tremendously serious and potentially

fatal disorder that actually includes their description in its name: malignant neuroleptic syndrome, described for the first time in the early 1960s by Delay's group (118). Nevertheless, despite its close relationship with the classic antipsychotic drugs and its characteristic clinical symptoms (rise in body temperature, vegetative alteration, muscular rigidity and extrapyramidal neurological effects), it was not definitely recognized in the English-speaking scientific world until the publication of Caroff's classic review in 1980 (119).

CONCLUSION: HISTORICAL IMPORTANCE OF THE CLINICAL INTRODUCTION OF CHLORPROMAZINE

The discovery of the antipsychotic properties of chlorpromazine in the 1950s was a fundamental event for the practice of psychiatry and for the genesis of the so-called "psychopharmacological revolution." Arriving as it did in a desert landscape as far as therapy was concerned, chlorpromazine made it clear that mental illness could be treated effectively by chemical means. It also paved the way for the clinical use of new psychoactive drugs, such as lithium salts, imipramine or chlordiazepoxide, which continue, at the dawn of the 21st century, to be of great therapeutic, conceptual and practical importance.

The introduction of chlorpromazine made possible a series of great clinical, healthcare and scientific advances (25,120): it led to the phenomenon of deinstitutionalization of psychiatric patients and permitted many of them to be attended in their family environment and by their general physicians, thus putting them on an equal footing with others, both socially and in relation to work, and undoubtedly contributing to reducing the stigma associated with schizophrenia; it attracted interest from researchers and from the pharmaceuticals industry in the development of new psychoactive drugs in general and antipsychotic agents in particular; it opened the door to the neurobiological concept of schizophrenia and other psychoses; it permitted an improvement in the methodology of clinical psychiatric research, and it contributed, at a nosological level, to categorizing the design of a new set of diagnostic criteria. All of this makes chlorpromazine a fundamental element in the consolidation of modern psychiatry.

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