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History of the Discovery and Clinical Introduction of Chlorpromazine

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Abstract

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, Winkelman, 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 molecule, and reserpine ([4], [5][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], [9] [10] [11][12][13][14][15][16][17][18][19] [20][21][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]).

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

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]).

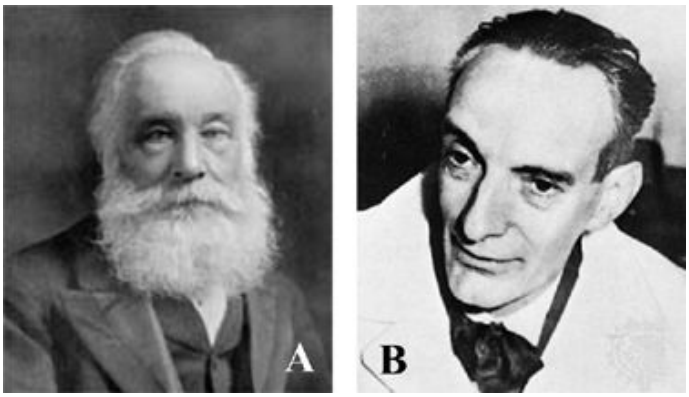

Figure 2 **William Henry Perkin (A), pioneer of chemical dyeing industry, and Daniel Bovet (B), researcher of Rhône-Poulenc and 1957 Medicine Nobel Prize.**

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 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-alkilate chains to the central nitrogen atom of the phenothiazine ring, although these agents showed a complete absence of antimalarial 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-alkilate 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 aminate 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-methylphenoxiethyldiethylamine, 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 Fenergan®, 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 electro-shock, 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 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]).

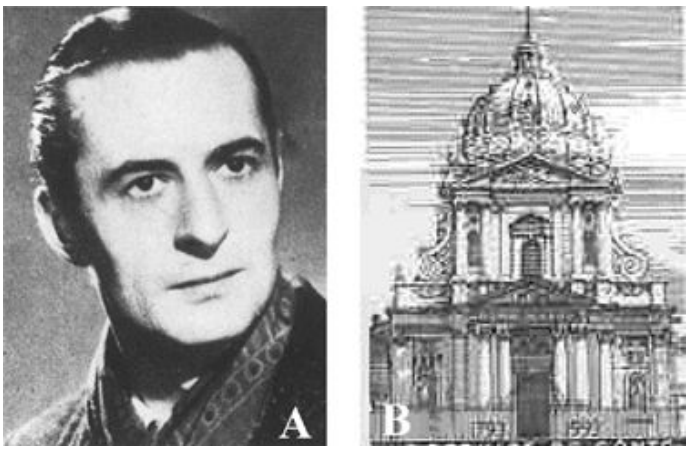

Figure 3 **Henri-Marie Laborit (A), and Val-de-Grâce Army Hospital (Paris) (B).**

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, Specia 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 lityc 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 28–30º 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]).

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]).

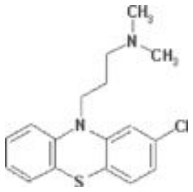

Figure 4 **Chlorpromazine chemical structure.**

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

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