Fifty years chlorpromazine: a historical perspective

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Abstract: Chlorpromazine was synthesized in December 1951 in the laboratories of Rhône-Poiulenc, and became available on prescription in France in November 1952. Its effectiveness was reflected in the transformation of disturbed wards; its commercial success stimulated the development of other psychotropic drugs. Recognition of chemical mediation at the site of the synapse, followed by the introduction of the spectrophotofluorimeter first, and receptor assays subsequently, led to the demonstration that chlorpromazine blocks dopamine receptors. Treatment with chlorpromazine focused attention on the heterogeneity of schizophrenia in terms of responsiveness to treatment. By the mid-1980s there was sufficient evidence to believe that resolving this heterogeneity is a prerequisite for developing more effective treatments. Chlorpromazine was instrumental in the development of neuropsychopharmacology, a new discipline dedicated to the study of mental pathology with the employment of centrally acting drugs.

Keywords: chlorpromazine, history, neuropsychopharmacology, pharmacotherapy, psychiatry, schizophrenia.

Introduction

The word "psychopharmacology" was first used in 1920 by David Macht, an American pharmacologist, in the title of his paper describing the effects of the antipyretics, quinine and acetylsalicylic acid, on neuromuscular coordination tests (Macht 1920). Yet, until the 1950s there was no such scientific discipline as psychopharmacology and there was no effective drug therapy for mental illness. In 1952, chlorpromazine (CPZ) appeared on the psychiatric scene in Paris. It was more effective than any of the old drugs, including morphine and scopolamine (hyoscine) combinations, for controlling excitement and agitation, and it could relieve also psychotic symptoms, such as delusions and hallucinations.

Although the psychiatric establishment received CPZ incredulously, for psychiatrists working on the front line it was a miracle drug. Its effectiveness was reflected in the transformation of disturbed wards and psychiatric service. Its commercial success stimulated the development of other psychotropic drugs.

Today, more than 50 years later, psychopharmacology is an established discipline and we have several effective drugs for the treatment of a wide variety of psychiatric disorders (Ban et al 1998).

From synthesis to introduction

Chlorpromazine was synthesized on December 11, 1951 by Paul Charpentier, in the laboratories of Rhône-Poulenc, a French pharmaceutical company, and released for clinical investigation in May 1952 as a possible potentiator of general anesthesia (Charpentier et al 1952).

The potential use of CPZ in psychiatry was first recognized by Henri Laborit (1952), a surgeon and physiologist in the French army, in the course of his research with artificial hibernation in the prevention of surgical shock. In collaboration with

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Huguenard and Alluaume, he employed the drug as an adjunct to surgical anesthetics ("anesthetic cocktail," "lytic cocktail") because of its body temperature lowering effect. He found that CPZ, in the dosage of 50 to 100 mg given intravenously, produced disinterest without loss of consciousness and with only a slight tendency to sleep. His first paper on CPZ was published in the February 13th issue of La Presse Médicale in 1952 with the title "A new vegetative (autonomic) stabilizer" (Laborit et al 1952).

Since cooling with water had been used in France for controlling agitation (Burger 1976), Laborit was able to persuade Hamon, Paraire and Velluz at the neuropsychiatric service of Val de Grâce, the military hospital in Paris, to try CPZ in the treatment of one of their patients (Caldwell 1970). Jacques Lh., a 24-year-old severely agitated psychotic (manic) male was the first psychiatric patient to receive CPZ; he was administered 50 mg of the drug, intravenously, at 10 am, on January 19, 1952. The calming effect of CPZ was immediate but since it lasted only a few hours several treatments were required before the patient's agitation was controlled. Repeated administration of the drug caused venous irritation and perivenous infiltration. Hence, on several occasions barbiturates and electroshock were substituted for CPZ. Nonetheless, after 20 days of treatment, with a total of 855 mg of CPZ, the patient was ready "to resume normal life." The effects of CPZ on Jacques Lh. were reported on February 22, 1952 by Colonel Paraire, at a meeting of the Société Médico-Psychologique in Paris, and, based on this presentation, the first paper on CPZ in psychiatry was published in the March 1952 issue of the Annales Médico-psychologiques, the official journal of the Society (Hamon et al 1952).

Clinical investigations with CPZ at Saint-Anne's hospital – at Pierre Deniker's service in Jean Delay's department – in Paris began on March 24, 1952 (Caldwell 1970). Since it was believed that the drug worked by inducing "artificial hibernation," ice packs were used to enhance "cooling." It did not take long to recognize that "cooling" did not contribute to the drug's therapeutic effect (Thuillier 1999). In most patients CPZ alone, in the daily dosage of 75 mg, was sufficient for controlling behavior. Early findings with CPZ at Saint-Anne were presented on May 25, 1952, at the centennial meeting of the Société Médico-Psychologique. (Delay et al 1952a). The six publications of Delay and Deniker during the six months that followed (Delay and Deniker 1952a, 1952b, 1952c; Delay et al 1952a, 1952b, 1952c), set the stage for the introduction of CPZ in psychiatry (Olie 2004). Other publications in 1952 included a report by Follin (1952), on the successful treatment of an aggressive paranoiac patient with CPZ at Montauban mental hospital in France (Caldwell 1970); an article by Rigotti (1952), on 20 psychiatric patients treated with CPZ in Padua, Italy; and a paper by Arnold, Hilt and Solma (1952), on the use of CPZ in psychiatry in Vienna, Austria.

CPZ became available on prescription in France, under the proprietary name of Largactil, ie, large in action, in November 1952 (Caldwell 1970). The proprietary name was chosen to reflect the diversity of pharmacological actions and potential clinical indications of the drug (Courvoisier et al 1953; Burger 1976; Thuillier 2000). Subsequently, within a short period of three years, from 1953 to 1955, CPZ treatment in psychiatry spread around the world. By the end of 1955 there were reports on the effects of CPZ in psychiatric patients from Switzerland (Staehelin and Kielholz 1953; Staehelin 1954); England (Anton-Stephens 1954; Elkes and Elkes 1954); Canada (Lehmann 1954; Lehmann and Hanrahan 1954); Germany (Bente and Itil 1954); Hungary (Kardos and Pertorini 1954); Latin America (Saly y Rosas et al 1954), United States (Winkelman 1954); Australia (Webb 1955); and the USSR (Tarasov 1955). Heinz Lehmann, a German born Canadian psychiatrist at the Verdun Protestant Hospital in Montreal, was first to suggest that CPZ selectively inhibits affective drive (Lehmann 1954). His paper, co-authored by Hanrahan and published in the Archives of Neurology and Psychiatry (USA), had a major impact on the introduction of CPZ in North America (Lehmann and Hanrahan 1954).

The first international colloquium on the therapeutic uses of CPZ in psychiatry was held at Saint-Anne's Hospital in Paris, in October 1955 (Hollister 1994; Thuillier 1999) with 257 participants from 19 countries (Austria, Belgium, Brazil, Canada, Cuba, France, Germany, Great Britain, Holland, Luxembourg, Peru, Portugal, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States and Venezuela). Two years later, in 1957, the importance of CPZ was recognized by the scientific community with the presentation of the American public health association's prestigious Albert Lasker Award to the three key players in the clinical development of the drug: Henri Laborit, for using CPZ as a therapeutic agent first and recognizing its potential for psychiatry; Pierre Deniker, for his leading role in introducing CPZ into psychiatry and demonstrating its influence on the clinical course of psychosis; and Heinz Lehmann, for bringing the full practical significance of CPZ to the attention of the medical community (Ban 1994).

Early pharmacology

The pharmacological bridge from "antihistamines" to "antipsychotics" was provided by a test that could detect

the central effect of drugs by the increase in time required for trained rats to climb a vertical rope for food (Winter and Flataker 1951). It was adopted by Simone Courvoisier, in the laboratories of Rhône-Poulenc, for measuring the central effects of phenothiazines, and used later in combination with other behavioral indicators – such as reduction of spontaneous motor activity, induction of cataleptic immobility, antagonism of apomorphine-induced vomiting, inhibition of intracranial self-stimulation – in the pre-clinical screening for drugs with a similar therapeutic profile to CPZ (Courvoisier et al 1953). Leonard Cook, in the pharmacological laboratories of Smith, Kline & French in the United States, was first to develop a behavioral pharmacological test that distinguished CPZ from the barbiturates and other old sedatives. It established that CPZ was different from barbiturates because it selectively blocked the conditioned (behavioral-) avoidance response and left the unconditional (escape-) motor reflex unaffected (Cook 2004a, 2004b). Employment of Cook's test in the screening for CPZ-like compounds led during the late 1950s to a steadily increasing number of antipsychotic drugs.

From CPZ to other antipsychotics

The rapidly growing number of antipsychotics was reflected in the presentations made at the first congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in Rome, Italy, in 1958. Frank Ayd, an American psychiatrist from Baltimore, Maryland, reported on clinical findings of 25 patients, and Hippius and Selbach from Berlin, Germany, reported on clinical findings of 12 patients (Ayd 1959; Hippius and Selbach 1959). By emphasizing that the clinical use of these drugs should be based on the relationship between their therapeutic efficacy and somatic side effects without any theoretical preconception, Hanns Hippius opened the path for a development that led from CPZ to clozapine (Hippius 2004). It was also at the Rome Congress that Pierre Lambert from Lyon, France, first presented the classification of the Comité Lyonnaise, in which antipsychotic phenothiazines were divided into sedative, chlorpromazine-type of drugs, which are less potent on a mg per kg basis, producing drowsiness and lassitude with relatively few extrapyramidal signs (EPS), and incisive, prochlorperazine-type of drugs, which are more potent on a mg per kg basis and produce ataraxy without drowsiness but with frequent and marked EPS (Lambert et al 1959). In 1960, at the 2nd CINP Congress in Basel, Switzerland, confronting the commonly held belief that incisive neuroleptics are also more effective than sedative neuroleptics in the treatment of schizophrenia, Fritz Freyhan, a German born American psychiatrist argued that there is no difference in therapeutic efficacy between the two types of drugs (Freyhan 1961).

Impact on neuropharmacology

Simultaneously with the development of CPZ there was a shift in understanding of the nature of synaptic transmission from a purely electrical to a chemically-mediated event; and by the end of the 1950s, six neurotransmitters were identified in the central nervous system: acetylcholine, dopamine, γ-aminobutyric acid, norepinephrine, serotonin, and substance P (Ban 2001). Recognition of chemical mediation at the site of the synapse, coupled with the introduction of the spectrophotofluorimeter (Bowman et al 1955), an instrument that allowed the chemical analysis of compounds that occur in small amounts in the brain, such as the monoamines and their metabolites, triggered the development of neuropharmacology in the mid-1950s (Carlsson 1998, 2004). There were high expectations that CPZ combined with spectrophotofluorimetry would provide a royal road to the understanding of the pathophysiology of schizophrenia. It was also hoped that there would be feedback from clinical psychopharmacologists to neuropharmacologists, that would help to develop clinically more selective and thereby more effective pharmacological treatments (Ban 1999).

In 1955, Laszlo Gyermek, a Hungarian born pharmacologist, was first to report on the potent antiserotonin effects of CPZ (Gyermek 1955). One year later he demonstrated a relationship between the sedative and the antiserotonin effects of phenothiazines (Gyermek, Lázár and Csák 1956). These findings were contrary to expectations given that in 1954, prior to Gyermek's report, LSD_{25}, a psychotomimetic substance, was found to have potent antiserotonin effects (Woolley and Shaw 1954). Nonetheless, until the early 1960s, antiserotonin effects were perceived as integral part of the mode of action of antipsychotic dugs.

In the mid-1960s Carlsson and Lindqvist (1963) found that the administration of CPZ and haloperidol, the first butyrophenone neuroleptic, stimulated the turnover of catecholamines in the brain of the mice. They attributed their findings to a compensatory increase of tyrosine hydroxylase activity and hypothesized that the drugs blocked catecholamine receptors. Arvid Carlsson's postulation of a possible relationship between DA receptor blockade and antipsychotic effects (Carlsson 2004) shifted interest from antiserotonin to antidopamine effects and led to the introduction of a series of tests, based on the antagonism to DA agonists, eg, antagonism to amphetamine – induced stereotypes, in the

pharmacological screening for antipsychotic drugs (Janssen 1998). It also provided the rationale for research that led to the demonstration, with the employment of receptor bindings assays (Seeman et al 1975), that antipsychotic drugs block DA receptors (Creese et al 1975).

Pharmacotherapy of schizophrenia

The introduction of CPZ focused attention on the heterogeneity of schizophrenia in terms of responsiveness to treatment (Ban 1969, 1972, 1986). Was the difference in responsiveness due to individual idiosyncrasies in reacting to neuroleptics, or to differences in the biology of the different forms of the disease? To answer this question Frank Fish, a British professor of psychiatry, examined the therapeutic response profile of neuroleptics (Fish 1964) in different forms of schizophrenia using the classification of Karl Leonhard, a German professor of psychiatry (Leonhard 1957). The significant differences he found in responsiveness to neuroleptics between some of the groups could not be explained by idiosyncratic individual variations in responsiveness to the drugs. The differences were so great that in one group (affect-laden paraphrenia, one of the three forms of unsystematic schizophrenia in Leonhard's classification), more than 4 in 5 patients responded markedly or moderately to treatment, whereas in another group (systematic hebephrenia, one of the three categories of systematic schizophrenia), less than 1 responded in 4. Fish published his findings in 1964 in Encephale, a French journal, but as a result of his untimely death, coupled with reservations towards Leonhard's classification, his findings remained isolated from the main stream. Nevertheless, by the end of the 1960s it was clear that ignoring the heterogeneity of schizophrenia deprived neuropharmacology of the necessary feedback for developing clinically more selective, and thereby more effective treatments (Ban 1969). Furthermore, by the mid-1980s, there was sufficient evidence to conclude that resolving the heterogeneity of schizophrenia is an essential prerequisite for progress in the understanding of the biology of the different illnesses pooled together in the diagnostic concept of schizophrenia (Ban et al 1986; Ban 1987, 1990).

Concluding remarks

Since the introduction of CPZ more than 50 years have passed; and pharmacotherapy has become the primary treatment in psychiatry. The therapeutic success of CPZ was instrumental in the reintegration of psychiatry with the other medical disciplines. It turned psychiatrists from caregivers to full-fledged physicians who can help their patients and not only listen to their problems (Lambert 1998).

Introduction of CPZ was also instrumental in the development of neuropsychopharmacology, a new discipline that provided the necessary methodology for psychiatry to examine and change its theoretical framework. By the end of the 20th century, Wilhelm Griesinger's contention that mental illness is a symptom of brain disease (Griesinger 1845) has become an accepted reality, and Joseph Moreau de Tours' vision of understanding mental pathology by studying the effect of centrally acting drugs (Moreau de Tours 1845) an accepted methodology in psychiatry. But in spite of all the progress made in the understanding of signal transduction in the brain, and designing drugs which fit like keys in their locks, none of the newer antipsychotic drugs has surpassed the effectiveness of CPZ (Ban 2004; Lieberman et al 2005). Hence, if an agitated and aggressive psychotic patient in the emergency fails to respond to some of the excellent new medications which may offer distinct advantages in terms of one or another side effect, one should not hesitate in prescribing good old CPZ that has remained even after 50 years one of the most reliable antipsychotic drugs.

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References

Anton-Stephens D. 1954. Preliminary observations on the psychiatric uses of chlorpromazine (Largactil). *Journal of Mental Science,* 100:543–57.

Arnold OH, Hilt S, Solma W. 1952. Über die Anwendung eines vegatativen Hemmungs stoffes in der psychiatrischen Therapie. *Wiener Medizinische Wochenschrift,* 102:965–9.

Ayd FJ. 1959. A clinical analysis of the differential effects of phenothiazine derivatives. In Bradley PB, Deniker P, Radouco-Thomas C (eds). Neuropsychopharmacology. Amsterdam: Elsevier. pp 487–8.

Ban TA. 1969. Psychopharmacology. Baltimore: Williams & Wilkins. p 431.

Ban TA. 1972. Schizophrenia: A Psychopharmacological Approach. Springfield: Charles C. Thomas. pp 68–70.

Ban TA. 1987. Prolegomenon to the clinical prerequisite. Psychopharmacology and the classification of mental disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry,* 11:527–80.

Ban TA. 1990.Clinical pharmacology and Leonhard's classification of endogenous psychoses. *Psychopathology,* 23:331–8.

Ban TA. 1994. Nobel Prize and Albert Lasker Award. In Ban TA, Hippius H (eds.). Towards CINP. Brentwood: JM Productions. pp 8–14.

Ban TA. 1999. Selective drugs versus heterogeneous diagnoses: towards a new methodology in psychopharmacological research. *Psiquiatria Biologica,* 7:177–89.

Ban TA. 2001. Pharmacotherapy of mental illness. A historical analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry,* 25:709–27.

Ban TA. 2004. Neuropsychopharmacology and the history of pharmacotherapy in psychiatry. A review of developments in the 20th century. In Ban TA, Healy D, Shorter E (eds.). *Reflections on Twentieth-Century Psychopharmacology*. Budapest: Animula. pp 697–720.

Ban TA, Guy W, Wilson WH. 1986. Research methodology and the pharmacology of the chronic schizophrenias. *Psychopharmacology Bulletin,* 22:36–41.

Ban TA, Healy D, Shorter E. 1998. Preface. In Ban TA, Healy D, Shorter E (eds). The rise of psychhopharmacology and the story of CINP. Budapest: Animula. pp VII–VIII.

Bente D, Itil TM. 1954. Zur Wirkung des Phenothiazin Körpers Megaphen auf das menschliche Hirnströmbild. *Arzneimeittel Forschung,* 4:418–23.

Bowman RL, Caulfield PA, Udenfriend S. 1955. Spectrophotometric assay in the visible and ultraviolet. *Science,* 122:32–3.

Burger A. 1976. History. In Usdin E, Forrest IS (eds). Psychotherapeutic Drugs. Part I Principles. New York and Basel: Marcel Dekker. pp 11–57.

Caldwell AE. 1970. Origins of Psychopharmacology From CPZ to LSD. Springfield: Charles C. Thomas. pp 23–35.

Carlsson A. 1998. Neuropsychopharmacology. In Ban TA, Healy D, Shorter E (eds). The Rise of Psychopharmacology and the Story of CINP. Budapest: Animula. pp 124–8.

Carlsson A. 2004. The discovery of chlorpromazine – Impact on basic research. *The International Journal of Neuropsychopharnacology,* 7 (supplement 1):22.

Carlsson A, Lindqvist M. 1963. Effect of chlorpromazine and haloperidol on formation of 3-methoxytyramine and normetanephrine on mouse brain. *Acta Pharmacologica et Toxicologica,* 20:140–4.

Charpentier P, Gailliot P, Jacob R, et al. 1952. Recherches sur les diméthylaminopropyl-N phénothiazines substituées. *Comptes rendus de l'Académie des sciences (Paris),* 235:59–60.

Cook L. 2004a. Reflections on the introduction of chlorpromazine in the United States. In Ban TA, Healy D, Shorter E (eds). Reflections on Twentieth-Century Psychopharmacology. Budapest: Animula. pp 178–81.

Cook L. 2004b. Early pharmacology of chlorpromazine. *The International Journal of Neuropsychopharmacology,* 7 (supplement 1):21.

Courvoisier S, Fournel J, Ducrot R, et al. 1953. Propriétés pharmacodynamiques du chlorhydrate de chloro-3-(diméthylamino-3'-propyl)-10-phénothazine (4560 RP). Étude expérimentale d'un niveau corps utilisé dans l'anesthésie potentialisée et dans l'hibernation artificielle. *Archives internationales de pharmacodymnamie et de thérapie,* 92:305–361.

Creese I, Burt R, Snyder SH. 1975. Dopamine receptor binding; differentiation of agonist and antagonist states with ^{3}H-dopamine and ^{3}H-haloperidol. *Life Science,* 17:993–1001.

Delay J, Deniker P. 1952a. Le traitments de psychoses par une méthode neurolytique dérivée de l'hibernothérapie; le 4560 RP utilisée seul en cure prolongée et continue. *CR Congr Méd Alién Neurol (France),* 50:497–502.

Delay J, Deniker P. 1952b. 38 cas de psychoses traitèes par la cure prolongèe et continuè de 4560 RP. *CR Congr Méd Alién Neurol (France),* 50:503–13.

Delay J, Deniker P. 1952c. Réactions biologiques observées au cours du traitement par l'chlorhydrate de deméthylaminopropyl-N-chlorophénothiazine. *CR Congr Méd Alién Neurol (France),* 50:514–8.

Delay J, Deniker P, Harl JM**.** 1952a. Utilisation en thérapeutique d'une phénothiazine d'action centrale selective. *Annales Médico-psychologiques,* 110:112–7.

Delay J, Deniker P, Harl JM. 1952b. Traitement des ètats d'excitation et d'agitation par une méthode médicamenteuse dérivè de l'hibernothèrapie. *Annales Médico-psychologiques,* 110:267–73.

Delay J, Deniker P, Harl JM, et al. 1952c. Traitements d'ètats confusionnels par l'chlorhydrate de diméthylaminopropyl – N – chlorophénothiazine (4560 RP). *Annales Médico-psychologiques,* 110:112–7.

Elkes J, Elkes Ch. 1954. Effects of chlorpromazine on the behavior of chronically overactive psychotic patients. *British Medical Journal,* 2:560–76.

Fish FJ 1964. The influence of the tranquilizers on the Leonhard schizophrenic syndromes. *Encephale,* 53:245–9.

Follin S. 1952. Discussion. *Annales Médico-psychologiques,* 110:126–7.

Freyhan F. 1961. The influence of specific and non-specific factors on the clinical effects of psychotropic drugs. In Rothlin E (ed). Neuropsychopharmacology 2. Amsterdam: Elsevier. pp 183–8.

Griesinger W. 1845. Die pathologie und therapie des psychischen krankheiten. Wreden: Braunschweig.

Gyermek L. 1955. Chlorpromazine: A serotonin antagonist? *The Lancet* 2:724.

Gyermek L, Lázár GT, Csák Zs. 1956. The antiserotonin action of chlorpromazine and some other phenothiazine derivatives. *Arch Int Pharmacodyn,* 107:62–74.

Hamon J, Paraire J, Velluz J. 1952. Remarques sur l'action du 4560 RP sur l'agitation maniaque. *Annales Médico-psychologiques (Paris).* 110:331–5.

Hippius H. 2004. From chlorpromazine to modern ("atypical") antipsychotics. *The International Journal of Neuropsychopharmacology,* 7 (supplement 1):21–2.

Hippius H, Selbach H. 1959. On the correlation of the pharmacologically effective qualities of a drug to its therapeutic effect in psychoses. In Bradley PB, Deniker P, Radouco-Thomas C (eds). Neuropsychopharmacology (pp.598–601). Amsterdam: Elsevier. pp 598–601.

Hollister LE. 1994. Review of International Colloquium on Chlorpromazine. In: Ban TA, Hippius H (eds). Towards CINP. Brentwood: JM Productions.pp 18–23.

Janssen PAJ. 1998. Function and dysfunction of the basal ganglia. In Ban TA, Healy D, Shorter E (eds). The Rise of Psychopharmacology and the Story of CINP. Budapest: Animula. pp 63–8.

Kardos G, Pertorini R. 1955. Largactil a psychiátriában. *Ideggyogyászati Szemle,* 8:65–9.

Laborit H, Huguenard P, Alluaume R. 1952. Un noveau stabilisateur végétatif (le 4560 RP). *La Presse Médicale,* 60:206–8.

Lambert P. 1998. Chlorpromazine: A true story of the progress affected by this drug. In: Ban TA, Healy D, Shorter E. (eds). The Rise of Psychopharmacology and the Story of CINP. Budapest: Animula. pp 237–43.

Lambert P, Perrin J, Revol L, et al. 1959. Essai de classification des neuroleptiques d'après leurs activités psycho-pharmacologiques et cliniques. In Bradley PB, Deniker P, Radouco-Thomas C (eds). Neuropsychopharmacology. Amsterdam: Elsevier. pp 619–24.

Lehmann HE. 1954. Selective inhibition of affective drive by pharmacological means. *American Journal of Psychiatry,* 110:856–7.

Lehmann HE, Hanrahan GE. 1954. Chlorpromazine, new inhibiting agent for psychomotor exctietemnt and manic states. *Archives of Neurology and Psychiatry (Chicago),* 71:227–37.

Leonhard K. 1957. Aufteilung der endogenen Psychosen Berlin: Academie Verlag. pp 155–396.

Lieberman JA, Stroup TS, McEvoy JP, et al. 2005. Effectiveness of antipsychotic drugs in chronic schizophrenia. *New England Journal of Medicine,* 353:1209–13.

Macht DL. 1920. Contributions to psychopharmacology. *Johns Hopkins Hospital. Bulletin*, 31:167–73.

Moreau de Tours J. 1845. Du Hachich et de L'Alienation Mentale. Etude Psychologiques. Paris: Fortin & Mason.

Olie JP. 2004. The discovery of chlorpromazine: A historical account. *The International Joirnal of Neuropsychopharmacology,* 7(suppl 1):21.

Rigotti S. 1952. Del blocco del SN vegetativo all'ibernazione artificiale primi risultati di un nuevo indirizzo di terapia psichiatrica. *Rassegna di neurologia vegetative,* 9:197–210.

Sal y Rosas F, Jerí R, Sanchez J. 1954. Chlorpromzine in neuropsychiatry *Journal of the American Medical Association,* 156:558.

Seeman P, Chau-Wong M, Tedesco J, Wong K. 1975. Brain receptors for antipsychotic drugs and dopamine: direct binding assays. *Proceedings of the National Academy of Sciences (USA),* 72:4376–80.

Staehelin JE. 1954. Einige allgemeine Bemerkungen uber die Largactiltherapie in der psychiatrischen Universitatsklinik Basel. *Schweizerische Archives für Neurologie und Psychiatrie,* 73:288–91.

Staehelin JE, Kielholz P. 1953. Largactil, ein neues vegatativen Dämpfungsmittel bei psychischen Störungen. *Schweizerische Medizinische Wochenschrift,* 83:581–6.

Tarasov GK. 1955. Aminazine, review of the literature on the psychiatric use of a phenothiazine derivative. *Zhurnal Nevropatologii i Psikhiatria Korsakov,* 55:296–310.

Thuillier J. 1999. Ten Years That Changed the Face of Mental Illness London: Martin Dunitz. PP 111–23.
Webb RR. 1955. Largactil in psychiatry. *The Medical Journal of Australia* 1:759–61.
Winkelman NW. 1954. Chlorpromazine in the treatment of neuropsychiatric disorders. *Journal of the American Medical Association,* 155:18–21.
Winter CA, Flataker L. 1951. The effect of antihistaminic drugs upon the performance of trained rats. *Journal of Pharmacology and Experimental Therapeutics,* 101:156–62.
Woolley DW, Shaw E. 1954. A biochemical and pharmacological suggestion about certain mental disorders. *Proceedings of the National Academy of Sciences (USA*), 40:228–31