History of Psychopharmacology: From Functional Restitution to Functional Enhancement

Jean-Gaël Barbara

HISTORY OF PSYCHOPHARMACOLOGY – FROM FUNCTIONAL RESTITUTION TO FUNCTIONAL ENHANCEMENT

Version auteur : J.G. Barbara, 2014. « History of Psychopharmacology: From Functional Restitution to Functional Enhancemen», in Handbook of Neuroethics, Jens Clausen and Neil Levy éds., Dordrecht, Springer, 2014, ISBN 978-94-007-4706-7, p. 489-504.

Jean-Gaël Barbara
Université Pierre et Marie Curie, CNRS UMR 7102
Université Paris Diderot, CNRS UMR 7219
jean-gael.barbara@snv.jussieu.fr

TABLE OF CONTENTS

ABSTRACT

The paper presents a very short history of psychopharmacology and attempts to make clear distinctions between (i) the practices of drug administration to insane subjects and the first observations of interactions between diseases and insanity during antiquity, (ii) the concept of psychopharmacology which appears at the end of the 18th C. with the reform of ancient pharmacology focusing on general knowledge and the closer relations established between chemical substances and mental diseases within the first psychopharmacological rationalisms, and (iii) the rise of psychopharmacology as a discipline after the successes of a few advocates of pharmacological psychiatry in the early 1950s, with the successful uses of chlorpromazine, haloperidol or reserpine. At each time period, ethical questions arose as to the dangers of these drugs, addiction risks already being studied in the 19th C., the mental diseases which these drugs can induce being studied by means of animal experimentation, and the non medical uses of some drugs for enhancement behaviours and better life quality especially in children and students. The epistemology of psychopharmacology as a project arising in the early 19th C. has developed continuously more complex methodologies for clinical trials. It is a field of intense progress and current inquiry which in return raises new ethical problems to be solved in future decades in order to guarantee progress in biological psychiatry to all social categories.

Key terms: psychopharmacology; psychiatry; neuroscience; pharmacology; chlorpromazine; haloperidol.

1.0 INTRODUCTION

The history of psychopharmacology is a complex historiographical inquiry, since the historical objects in question are often particularly ill-defined and ambiguous. This historical investigation concerns various time periods, from antiquity to the present time, and many scientific disciplines such as medicine, physiology, pharmacology, behavioural pharmacology, neurochemistry, and psychopharmacology. The particular histories published often make the error of comparing projects of distant time periods with disciplines developed later on.

A clear distinction should be made between the ancient pharmacologies of the mind from antiquity to 18th C., the progress of pharmacological chemical synthesis, the evolution in therapeutic uses of drugs, and the various attempts of different periods in clinical trials on insane patients following methodologies progressively worked out with scientific criteria in the 19th C. Since each time period prepares the following one, the rigorous historical investigation of psychopharmacology of the 1950s must avoid the opposite shortcoming of describing the sudden rise of a new science as being apparently in opposition with anterior knowledge.

Such a study is a sort of challenge as it requires us to avoid these numerous pitfalls and forces the historian to better define his objects and distinguish the practices of psychopharmacology (the history of the uses of drugs, antiquity-18th C.), the concept of psychopharmacology (the behavioural and physiological study of ancient psychotropic drugs and newly synthesized ones in the 19th C.), and the discipline of psychopharmacology (since the 1950s).

At first psychopharmacology appears to be characterized by an evident empiricism which raises many questions concerning the ethical issues of clinical trials and the shift from healing therapies to recent enhancement therapies (crosslink Ethics in Psychiatry) (cross-reference Research in Neuroenhancement). However, the epistemological and ethical issues at stake at different time periods are very different, while many histories written by scientists or historians often have the drawback of connecting these issues with technical histories (uses and synthesis of drugs) and the history of ideas in a similar manner.

The modern historiographical approach to psychopharmacology should aim at working out these issues and better defining the limits of historical continuities and the real changes in each period, concerning not only science itself, but especially epistemology and ethics. The present study only represents a short introduction to such a project hopefully to be expanded in the future.

2.0 FROM ANTIQUITY TO THE 18TH C.

Scipion Pinel, the son of French 19th C. alienist Philippe Pinel, condemned the psychopharmacological practices of past centuries and their false empirical character which justified the use of drugs not by experience, but by bringing into play outdated medical theories : “ […] One must regret the blind belief in disruptive medicines [based on past theories] […] [These theories] are at times the coction of humours, the revulsion and repulsion of peccant matters in the brain, which these impatient doctors fight with powders, extracts, juleps, electuaries, potions, to defeat insanity ; At other times, they prescribe blood letting excessively, with no distinction of the causes and epoch of the disease, showing a

medical doctrine full of prejudice, pedantry and ignorance, at various periods, often supported by the disastrous association of the name of a famous author." (Pinel, 1837, 132; author's translation)

If therapeutic empiricism seems evident in the 19th and 20th C., the psychopharmacological empiricism before the 18th C. was mixed with the sophisticated doctrines of the giant medical systems.

Scientific psychopharmacological empiricism, such as the empiricism claimed by Claude Bernard, being used to combat these medical rationalisms and systems which evaded experience and experimentation, cannot easily be found in the periods previous to the 19th C., although local drug experimentation on the insane is not absent from antique and Arabic medicine.

What is often missing before the 19th C. is the pharmacological empiricism based on novel psychopharmacological rationalisms which we define as the convergence between the development of new theoretical ideas on mental diseases, new rational explanations of the actions of drugs and new practices of drug therapies. In the 18th C. these convergences were often based on relations between outdated theories (theory of humours), past and new practices with weak evaluation of treatments and poor attempts to consider new explanations of drug actions.

This is, in my opinion, the way one should consider psychopharmacology from antiquity to the 18th C., as it presents great geographical and chronological heterogeneity in this time period. Nevertheless, I will only consider here a few continuities in the psychopharmacological practices.

Greek medicine failed to build strong correspondences between a unified etiological conception of mental illness and a set of treatments tested with empirical therapeutic trials. However, the Hippocratic corpus described the organic etiology of some mental diseases such as the "sacred disease" (epilepsy), and put forward the theory of humours to explain it, thus leading the way to possible drug treatments able to reduce the excess of phlegm in the brain as observed in the "epileptic goat".

In this area of medicine, Greek doctors gathered interesting clinical observations, noticed and studied further in the following centuries, in order to imagine new ways of treating mental diseases based on some interactions between insanity and pathologies such as fevers which sometimes improved mental health. These observations led to pharmacological treatments up to the 20th C.

Therefore, if the concept of psychopharmacology was absent before the 19th C., a psychopharmacological thinking was on the way locally, in a non systematic, but positive manner. This way of reasoning is relevant to our inquiry since it is in continuity with the treatment of the insane in the following centuries and because it remained heuristic until the rise of the concept of psychopharmacology in the 19th C.

3.0 THE CONCEPT OF PSYCHOPHARMACOLOGY (19TH C.)

3.1 THE RATIONAL REFUSAL OF DRUGS

At the end of the 18th C. Philippe Pinel (France), William Tuke (Great Britain), Vincenzo Chiarugi (Italy), and Benjamin Rush (United-States) attempted to improve the conditions of confinement of the insane, leading the way to moral treatment. This turn came with a mainly moral conception of mental illness, although these doctors did not ignore, whenever possible, lesional causes and interactions with organic pathologies. Therefore, Pinel, for example, did not refrain from prescribing medications to improve the health of his patients. He himself used a short pharmacopoeia with favourite remedies such as wild blackberry and a mixture of camphor (Guislain, 1826).

However, these different types of drugs of the early 19th C. were rather inefficient, as was the massive use of herb tea in asylums until the first half of the 20th C.

Scipion Pinel himself did not deny the value of medications, but the "monstruous polypharmacy" (his term) of the insane asylums was largely disastrous in his opinion, as was the immoderate use of blood letting and the purgatives of ancient medicine.

3.2 NOVEL AND OFTEN NAIVE RATIONALISMS

Although insane asylums kept some specific traditions of old medications in very contrasted manners, with large differences of practices and opinions concerning the efficiency of drugs (Curchod, 1845), a novel rationalism burst on to the scene at the turn of the 19th C., within a context where the conception of mental illness was divided into a moral etiology and an organic etiology.

In parallel to the rise of experimental psychology as a science as early as the 1820s (François Magendie, Pierre Flourens or Luigi Rolando), some alienists with anatomopathological background, and those practicing autopsies, were convinced of the organic etiology of insanity, especially after Antoine Laurent Bayle (1799-1858) managed to demonstrate the organic and syphilitic origin of the general paralysis associated with insanity. These doctors adopted a complex epistemology of the anatomopathology of mental diseases, in line with Franz Joseph Gall, which demanded that primitive organic lesions should be searched for systematically in the autopsies of insane subjects (Barbara, 2011a). They refused the concept of "pure functional lesion" which however surfaced at the end of the 19th C. in Paris during the famous polemics on hysteria in the circles of Jean-Martin Charcot (Barbara, 2011b).

Some of these alienists, such as Jacques-Joseph Moreau de Tours, developed interesting parallels between the organic action of chemical substances, such as cannabis, and insanity. When back from a journey in the East, Moreau de Tours made self-experimentation with cannabis and described the dreams associated with the drug which he equated with symptoms of insanity. Such a parallel was built over the central idea of the unicity of the etiology of nervous diseases and insanity, which Moreau de Tours suggested after his observations of the nervous and psychic effects of cannabis (Ledermann, 1988). For Moreau, cannabis became a tool for experimental pathology, in the line of experimental physiology, or, in Moreau's terms, of "mental pathogeny". Chemical substances became, as they were during the 1950s, psychopharmacological revolution, a means to build and discover new etiologies of mental illness. More specifically, for Morerau, the drug (cannabis) acted by way of a "substitutive action" on the cause of insanity (the "generator fact" of Moreau). The action of the drug

restored the perturbation induced by the mental defect. Such a toxicologic etiology of insanity can be seen as naive, but it represents a novel psychopharmacological way of thinking and a heuristic path to discovery opened by experimental physiology still widely used today. In the 19th C., a central theme of this strategy was the study of the mechanisms of poisons, such as the "nervous poison" curare (Barbara, 2009).

3.3 NEW DRUGS AND NEW CLINICAL TRIALS

As early as the very beginning of the 19th C., new active plant alkaloids were chemically isolated and used in medicine: morphine, strychnine, caffeine, quinine, veratrine, atropine or cocaine. Then the era of chemical syntheses started with the famous leaderships of French, and then German, chemists, the preparations of new bromides and the chemical synthesis of chloral, chloroform, barbiturates and paraldehyde. Novel animal experimentations tested the physiological actions of new and old drugs, such as Indian poisons used for hunting. In a second perspective, therapeutic trials were progressively widened to include insane subjects Cross-reference : Animal Research and Ethics).

Pharmacology, experimental physiology and the novel toxicology were the scientific disciplines concerned. Before 1806, French physiologist, François Magendie, studied the physiological actions of upas and, some ten years later, he experimented on its active principle, strychnine, just after its chemical isolation. As early as 1826, Pierre-Alexandre Charvet presented his dissertation entitled *Proposal on the mode of action of Opium in man and animals* at the French medical faculty. Deguise, Dupuy and Leuret published their research on morphine in 1824, based on physiological and anatomopathological inquiry on animals Cross-reference : Animal Research and Ethics). In the 1840s, Flourens also worked with a similar perspective on ether and chloroform. Experimental physiologists progressively defined these drugs as "nervous poisons", while they interpreted their actions with the scientific knowledge of nerve physiology (Barbara, 2010).

All these studies did not proceed from a blind empiricism, although chance was a key factor in gathering Indian curares and upas. A profound knowledge of the power of these ancient poisons was scientifically used and tested experimentally and methodically. At the same time, rigorous clinical trials were developed from the end of the 18th C. with old drugs such as opium and morphine, and with a new concern in rationalizing pharmacy which tended to escape general knowledge and to develop regionally. Rational pharmacological trials can be found however earlier in the writings of some medieval and Arabic physicians. But the therapeutic indications of drugs varied greatly and agreements can hardly be found: before ether was used for anaesthesia, it was used for gout, headache or gastric spasms.

Therapeutic trials on the insane were made in some asylums, but few concerning drugs, and more generally involving moral treatments and physical therapies.

Some physicians experimented on the new sedative properties of the drugs studied by physiologists, directly on insane subjects, such as Thomas Smith Clouston (Clouston, 1887) who defined some basic scientific principles, some of them using statistics (Clouston, 1863). Like Moreau de Tours, other physicians developed physiological and pharmacological ideas on insanity which justified their experimentations, such as the clinical trials of ether inhalation on epileptic patients in the 1840s.

The relations outlined by Greek doctors in antiquity between mental illness and diseases led to organicist conceptions of mental diseases favouring medications. German physician

Wilhelm Griesinger widened the conception of a neuropathic origin of mental diseases which led to the idea that, if a central element of the nervous system is altered, medications can act on the nervous peripheral origins and fight the pathological processes invading the brain.

These approaches aiming at a more scientific rationalism compared to the previous decades, especially concerning the use of group subjects, control subjects, averages and statistics, led to very little success, but to a better knowledge of sedation with available drugs until the 1940s.

However, during the 1860s-1880s, physicians refined their practices of drug administration and developed different treatments for each nosographical category of mental diseases (Kraepelin, 1899). Physicians generally followed the first recommendations on the cautious uses of drugs by François Magendie and viewed problems of toxicity and addiction more objectively (crosslink Ethics issues in the treatment of addiction) (cross-reference Addiction and Neuroethics).

4.0 EXPERIMENTS AND NEWLY SYNTHETIZED DRUGS AT THE TURN OF THE 20TH C.

4.1 THE INTRODUCTION OF EXPERIMENTAL PSYCHOLOGY IN PSYCHIATRY

At the turn of the 20th C., a new scientific discipline, namely experimental psychology, took over the objective inquiry of the effects of drugs on the mind and members of psychological faculties, in particular those interested in physiology and psychiatry, such as Kraepelin, Binet and Féré.

In the 1880s, alienists, such as Clouston, claimed that medical psychology should help psychiatry in its new physiological perspective, thus evading the single previous philosophical framework that made psychology a branch of philosophy (Clouston, 1887). This era marked by experimental physiology enabled experimental psychology and psychiatry to claim legitimacy for their medical investigations of the mind, evading the purely spiritualist perspective, and taking the lessons of experimental psychologists such as Kraeplin, who trained with Wilhelm Wundt on the measure and interpretation of reaction times.

One of the new experimental approaches used the Mosso ergograph to study muscular fatigue and psychism, when a muscle is exhausted by intense work and nevertheless recruited again by a surge of lasting psychical force. This type of work was taken over by experimental psychologists and adopted in the study of the effects of drugs on psychism, in particular in learning and memory (Kraepelin, Benedict; see Lashley, 1917). This was the way to the concept of behavioural pharmacology, a discipline adopting reflex tests, capacity tests of psychic faculties, control subjects and simple statistical analyses.

4.2 THE NEW PROJECT OF PSYCHOBIOLOGY

Psychologists, alienists and physiologists, individually or collectively and interdisciplinarily, not only claimed the experimental study of the mind, but they also advocated and tried novel forms of cooperation between disciplines in a new interdisciplinary perspective.

The term “psychobiology” never became the label of a clearly defined approach to psychology, but nevertheless, in the early 20th C., it designated a diversity of opinions on what the relationship between experimental psychology and biology should be.

According to Dewsbury, such opinions all shared a common point of view in their wish to bring psychology closer to biology in a holistic vision of the organism, in a manner analogous to the wish of biologists such as neurophysiologists Ralph Gerard (USA) or Alfred Fessard (France) to always keep in mind a “large picture” of the scientific problems, while biology turned to the systematic study of the elementary mechanisms of nervous phenomena (Edgar Adrian), and the minute molecular structures (Jean Nageotte, Francis O. Schmitt) (Dewsbury, 1991).

Therefore, psychobiologists expressed the parallel wishes to preserve psychology from biological reductionism adopted uncritically, while taking advantage of the advances of biomedical disciplines. However, these psychobiological projects never became united, and were often aborted, such as the journal *Psychobiology* of K. Dunlap, with only two issues published in 1917 and 1920. Some of these projects however showed a great anticipation of the spirit of the neurosciences, as for example in France, where Henri Wallon created a “*laboratoire de psychobiologie de l’enfant*” (laboratory of child psychobiology) in a primary school in the Parisian suburbs in 1925 (Galifret, 1979).

One can clearly see, in the perspective of Henri Wallon or that of K. Dunlap, the wish to take advantage of the advances in the study of the “histological details” in the field of psychology and in the desire to explicate their psychological and functional significance in the classical perspective of “physiological psychology”. In a broader perspective, those researchers claiming a psychobiological project did not put up any opposition between the study of forms and that of functions. These theoretical opinions favoured studies on the effect of drugs on the psychic functions of normal subjects and diseased patients.

The new orientations of psychology in the 1920s and 1930s offered a new ground for interdisciplinary projects with biologists, physiologists and physicians, some of them massively funded by the Rockefeller Foundation.

4.3 PSYCHOPHARMACOLOGY AS A PROJECT

In the 1920s, one can observe a burst of new studies on the effects of drugs on psychic faculties in animals and man (Cross-reference : Animal Research and Ethics). In this psychobiological context, David Israel Macht (1882-1961), pharmacologist of Russian origin at Johns Hopkins University, started experimental research on behavioural pharmacology on mice, developing a motor skill using a rope or circular mazes (Macht, 1920a). In one of his articles, he designated his emergent research program, in the line of the previous studies of experimental psychology of the 1890s, under the label “psychopharmacology”, although the term – or similar ones – had previously been used by others (Macht, 1920b). Macht defined his investigations very simply as the study of the effects of drugs on psychological functions, with not much new from the previous psychopharmacological concept.

The interdisciplinary character of the study of Macht, and of others at the same time, clearly appeared since those projects not only involved physicians, but also physiologists and pharmacologists. This is in striking opposition to the *Pharmakopsychologie* of Kraepelin which largely remained programmatic (Kraepelin, 1892).

4.4 THE EMPIRISM OF SHOCK THERAPIES AND PHARMACOLOGICAL CURES

In parallel to the development of a scientific project in psychiatry, a new path of therapeutic empiricism emerged at the turn of the 20th C., aiming at understanding the effects of drugs on the mind.

Classical histories of biological psychiatry often focus on the first very successful psychiatric treatment: the malariatherapy of von Jauregg. However, the success of the treatment of neurosyphilis by inoculation of a malaria clone of low virulence in order to provoke fever represented the end product of a very long series of trials to induce a great variety of diseases, some of them dangerous, to alleviate insanity.

One should reconsider those efficient clinical trials in the larger framework of the medical empiricism used in healing insanity, where physical and chemical treatments of all sorts were considered, such as the prolonged narcosis with bromide prescribed in order to reorganise functional nervous activities. This empiricism was characterized by the poor ethical concerns of trials, and the lack of means to evaluate the benefit of treatments (crosslink Relation of Risks and Benefits in Research with Mentally Ill Persons). But scientific justifications are nevertheless elaborated with reference to a biomedical rationalism still based on nervous physiology and the emerging neurone doctrine.

4.5 NAIVE RATIONALISMS OF SHOCK THERAPIES AND PHARMACOLOGICAL CURES

The histories of shock therapies and prolonged pharmaceutical treatments used in psychiatry refer to other rationalisms responsible for the choice of inducing agents, but also to the scientific explanation of their positive effects which justify their use - with little proof however.

The deep sleep therapy of Macleod, that of Epifanio using barbiturates and of Klaesi are all based on the belief that putting a stop to psychic activities in the nerve centres enables a better start upon wakening and the associated functional reorganisation of neuronal connections, which explained the improvement of the observed psychic state of the patients, in a similar manner to the sleep theory proposed by Matthias Duval in the 19th C.

Hungarian anatomopathologist Meduna, trained in psychiatry, developed a psychobiological rationalism based on his histological investigations. His observations of glial cells on epileptic and schizophrenic patients led him to think that if epilepsy induces a glial reaction, those cells tend to disappear in patients with schizophrenia. Meduna inferred that, in schizophrenic patients, glial cells could be reactivated with the artificial induction of epileptic convulsions. For this purpose, he used the intravenous administration of a convulsant, camphor, which led him to the rationalism of the cardiazol treatment and convulsive therapy.

Sakel also used this rationalism at the turn of the 20th C., along with the doctrine of Ramón y Cajal, in order to explain the benefit of the insulin treatment where the induction of a coma

was believed to stop the degenerating processes accounting for altered cells and to enable the regeneration of their connections.

These types of reasoning were not much more elaborated than those of the malariatherapy, which leads epistemologists to infer that those researches were profoundly empirical. However, their empirical character rather results from ad hoc explanations, based on theoretical frameworks with mediate relations to the facts observed, and which remain largely hypothetical.

5.0 THE BEGINNING OF PSYCHOPHARMACOLOGICAL THERAPIES

5.1 LIMITS OF THE CLASSICAL PHARMACOLOGY OF THE MIND

The pharmacology of mental diseases still remained very unsatisfactory until the 1950s. Some progress was made during the 1940s, but pharmacological innovation often continued to be homemade in small family industries, in spite of the development of large pharmaceutical groups at the international level.

The pharmacology of the mind was a poorly developed branch of psychiatry which nevertheless tried to make legitimate and somewhat efficient uses of narcosis, psychosurgery and shock therapies on patients, with the aim of sedating them to secure psychotherapy and occupational therapy.

This failure to create new pharmacologically efficient treatments explains the impossibility of psychiatrists to find any consensus in the explanation of the effects of drugs and in psychogenic theories of mental diseases. This situation was more or less the one that prevailed over the previous centuries.

Locally, research groups managed to improve the efficiency or reduce the toxicity of some drugs, as was the case for specific classes of antiepileptic drugs, such as hydantoines. LSD or low doses of curare were tested on human subjects during the Second World War and on patients with mental diseases, while shock therapies still remained in wider use in asylums.

However, in the 1940s, some psychiatric departments embarked in therapeutic pharmacological empiricism (Jean Delay in France, Joel Elkes in Great Britain), after the rise of pharmaceutical industries opened an era of great enthusiasm in medicine, with dominant economical positions acquired during the Second World War, and following the discovery and massive use of new antibiotics, steroids and antituberculosis drugs.

Therefore, the 1930s and 1940s should not be considered as a non profitable period for pharmacology and psychiatry, although the great success of neuroleptics in the 1950s overshadowed the new prescriptions of barbiturates, which replaced bromides, and the introduction of antiepileptics and anticonvulsants, such as phenytoin and trimethadione.

5.2 PSYCHIATRY AND PHARMACEUTICAL INNOVATION

In the 1940s, a few neurologists and psychiatrists started experimentations on animals and new clinical trials on their patients, with little ethical commitments, trying new drugs and

sometimes modifying the chemical structure of molecules themselves (Cross-reference : Animal Research and Ethics).

New effects of drugs unknown until then, but suggested by scarce and incomplete observation, were tested on specific categories of patients, as was the case for hydantoines, LSD and disulfiram.

Past therapeutic empiricism met with a novel enthusiasm. Such empiricism had been forgotten when the therapeutic properties observed in the newly synthesised drugs were often different by far from those expected.

The path to discovery of the antihistaminic drugs saw the phenothiazines previously recognized as insecticides, antihelminth drugs, and then antimalaria drugs. The French military surgeon, Henri Laborit, experimented on the action of the antihistaminic properties of drugs in the potentiation of anaesthesia to reduce anaesthetic agent doses and prevent postsurgical shock and anaesthetic shock.

5.3 NOVEL PSYCHOPHARMACOLOGICAL RATIONALISMS AND THE NEUROLEPTIC CONCEPT

New phenothiazines, the drugs which were to later become Antergan®, Neoantergan®, Phenergan® and Multergan® were synthesized in France in the 1940s and showed interesting antihistaminic properties. Phenergan ® was tested at Sainte-Anne hospital in Paris by Dr Paul Guiraud, as a sedative and hypnotic drug.

The fabric of the neuroleptic concept and the making of chlorpromazine as a drug against psychoses was a tortuous path pursued when Laborit, joined by French pharmacologist Pierre Huguenard, introduced a lytic cocktail with Phenergan®-Dipacol® which was shown to induce “artificial hibernation” and used to protect wounded soldiers from traumatic shock during the French Indochina War.

In these studies, Laborit tried a promethazine from the French pharmaceutical industry, Rhône-Poulenc, namely chlorpromazine. Laborit rapidly noticed the antipsychotic action of the molecule which nevertheless remained unnoticed by psychiatrists from Val-de-Grâce military hospital where Laborit worked. Chance was partially involved in the discovery by Pierre Denicker and Jean Delay at Sainte-Anne hospital of the antipsychotic properties of chlorpromazine used alone, at a time when drugs were generally used in combination or with other physical treatments, such as sedation by lowering the body temperature with ice. The discovery occurred when the sedation with ice was abruptly interrupted, without notice to the doctors, because of an ice shortage in the hospital, but with no consequence on the benefit of the chlorpromazine treatment.

5.4 THE CLINICS OF CHLORPROMAZINE

The great, but slow, worldwide success of the discovery of the neuroleptic effect of chlorpromazine triggered enthusiasm among some pharmacologists and psychiatrists. The rationalism of antihistaminic drugs with expected anti-shock properties, given that they

prevent anaphylactic shock, could lead other researchers to use a similar simple reasoning to find new psychiatric medications.

Delay visited laboratories abroad and was actively involved in the diffusion of his discovery of the effects of chlorpromazine. The molecule was progressively adopted in many countries and radically changed the life of psychiatric departments when the sedation of patients allowed social therapy.

Chlorpromazine slowly became a neuroleptic medication, but for numerous years after its discovery it remained advertised, commercialised and prescribed only as a sedative drug. The sedative chlorpromazine replaced hyoscine or amytal, and led however to the withdrawal of polytherapies, since it was efficient when used alone. Chlorpromazine as a neuroleptic drug required many international meetings and international scientific prizes to advertise the new medication as such.

Therefore, one should always remember that a medication possesses an essence radically different from that of its constituting molecule. Chlorpromazine made possible the manufacture of Largactil ® as a neuroleptic medication after ten years of use worldwide.

Psychopharmacology as a scientific and medical discipline was born from this slow revolution, when a new drug was discovered to be efficient alone, and this ultimately paved the way to new explanations of psychosis. The revolution did not involve any radical change in pharmacological rationalism, but in the status of psychiatry in medicine and society with the new and markedly recognized efficacy of psychiatrists.

5.5 NEW FRAMEWORKS OF PSYCHOPHARMACOLOGY AND THEORIES

The discovery of haloperidol by Paul Janssen followed a rationalism different from that of chlorpromazine, but as simple and efficient, which was described by philosopher and historian Jean-Noël Missa after an interview with Janssen (Missa, 2006). A friend of his practicing high level biking informed him of the psychogenic effects of the amphetamines used for doping. Janssen felt he could discover anti-amphetamine drugs with possible antipsychotic effects, and this is how he managed to synthesize and test haloperidol. As for chlorpromazine, the new molecule was first adopted as a sedative drug, and Janssen had to fight and convince psychiatrists to specifically search for the antipsychotic properties of the Largactil ® commercialized form.

In this context, many psychiatrists tried their luck testing old drugs or new molecules, such as reserpine, LSD, monoamine oxidase inhibitors or benzodiazepines.

Psychiatrists, physiologists and pharmacologists joined into common projects. In the US, Seymour Kety became director of a new and important interdisciplinary psychiatric centre at NIH. Those scientific interactions enabled common interpretations of the new efficient treatments and the rise of new biological theories of mental diseases based on the depletion of neurotransmitters (catecholaminergic theory of depression by Axelrod, serotoninergic theory of depression by George Ashcroft and Donald Eccleston), or the hypersensitivity to others (dopaminergic theory of psychosis by Carlson).

These new theories appeared a few years after the great controversy surrounding the chemical theory of neurotransmission, and represented an extension of this latter theory in the medical field.

5.6 PSYCHOPHARMACOLOGY AS A SCIENTIFIC DISCIPLINE

Psychopharmacology as a discipline was born from a small group of psychiatrists, pharmacologists, neurochemists, one neurologist, and one surgeon who, in the 1940s, chose to follow the path of pharmacological empiricism to treat mental illness.

Only after the early successes of the 1940s, and mainly the 1950s, did this little community gather in international congresses and decide to found a new society, the *Collegium internationale psychopharmacologicum*.

From the very early 1950s onwards, they organised interdisciplinary meetings on psychiatric drugs and their mode of action (Jean Delay, 1950, Paris; US NAS, Semour Kety, 1954; NIH, 1956, Ralph Gerard; Macy foundation, 1954-1959, Harold Abramson).

Following the introduction of radiolabelled neurotransmitters and the rise of neurochemistry, biological psychiatry, psychopharmacology, neurochemistry and neuropharmacology became much more than individual disciplines. They became real scientific networks overlapping and paving the way to new forms of interdisciplinarity in the underground neuroscience project on its way in the late 1950s.

6.0 ETHICS OF PSYCHOPHARMACOLOGY

6.1 ETHICS OF CLINICAL TRIALS AND DRUG EVALUATION

Chlorpromazine and haloperidol were tested on the patients of psychiatric departments with few ethical procedures, at a time when shock therapies were still in use, in spite of the Nuremberg code which was not strictly applied, and in a scientific way not very far from standard physiological experimentation.

In September 1956, in Washington D.C., a meeting focused on Psychopharmacology and the problems in evaluation, under the presidency of Ralph Gerard. The main issues concerned scientific and ethical questions dealing with patient categories, the evaluation of treatment benefit, adequate statistical analyses, conflicts of interest, the risk of side effects, problems of the autonomy of subjects, and of the equity of access to treatment among patients.

While psychopharmacology was progressing, local ethical committees were constituted in institutions in order to guarantee an evaluation independent of the actions of pharmaceutical companies. Historians and sociologists of science have shown how mental diseases and their treatments could be seen as social constructs dependent on the economy, the social characteristics of nations, the interests of pharmaceutical industries and the degree of the infiltration of psychiatry by psychoanalysis.

Questions on the autonomy, consent and the selection of patients are still complex today in the fields of psychopharmacology (crosslink Informed consent in the mentally ill). A controversy still occurring today concerns the use of electroconvulsive therapy. Although the techniques have been used for decades and advocated as a safe method particularly suited to treat psychotic depressions, some patients report traumatizing memory loss. For each therapy specific issues should guarantee an equitable negotiation of the consent form between patients and doctors.

In order to test the negative side effects of treatments and their unsuspected psychological consequences, some psychiatrists have practiced autoexperimentation with electroshock. Those experiments have shown to the medical community deleterious psychological consequences, more pronounced that those which could be evaluated by simply recording the improvement in the psychiatric state of the patients. These practices helped to justify the inclusion of healthy subjects in clinical trials, and since 1976 the American College of neuropsychopharmacology enounced some restrictions on the conditions concerning the inclusion of such subjects.

6.2 ENHANCEMENT

In the previous years, sociologists and philosophers have studied the social consumption of psychiatric drugs for enhancement of cognitive capacities, in particular among children and teenagers during schooling (crosslink Neuroenhancement; Reflections of Neuroenhancements) (cross-reference Research in Neuroenhancement)..

In a more general manner, non medical psychiatric drug consumption is an old theme of 19th C. medicine with the denunciation of addiction risks (crosslink Addiction and Neuroethics) (cross-reference Addiction and Neuroethics).

People are deceived when some drugs are advertised, by pharmaceutical companies and society, as efficient treatments to a selective health problem. They consider science as a means to improve their quality of life but with no critical analysis, which should be adequately provided by professionals, physicians, drugstores and drug makers.

France is the leader in antidepressant and anxiolytic drugs. Modafinil ® is used in the US against narcolepsy and mild sleep disorders to enhance cognitive capacities. The consumption of Ritaline ® by children seems medically justified in only about 10% of the subjects (crosslink Pediatric psychopharm) (cross-reference Research in Neuroenhancement)..

Philosophers and ethicians tend to broaden the debate on these dangerous behaviours and present enhancement as a long standing cultural reality. What really matters is the risk of selling drugs to consumers to combat, for example, memory loss, in the same manner as aspirin is provided against fever. The concepts of drug and enhancing agent are close and the boundary between the two is sometimes difficult to see for users who feel the right to correct minor impairments with pharmacological treatments without the help of responsible, not hypocritical, physicians.

6.3 FUTURE QUESTIONS

The ethics of psychopharmacology remains a vast and often difficult domain of inquiry because of the dilemmas occurring on account of the application of antagonist principles of clinical trials which must simultaneously respect the autonomy of the subjects and guarantee a benefit, while giving access to new treatments to all social categories.

One of the major issues at stake deals with the trials of underrepresented social categories for which obtaining consent is complex, as for children (minors), teenagers (respect of their autonomy), pregnant women (risks for the baby), minorities (possible lack of confidence and understanding). An ethical controversy concerns random trials with placebo controls using randomized withdrawals of patients. This is in opposition to the benefit principle, but it remains a key condition to evaluate this benefit.

For these reasons clinical trial methodologies become more and more complex and tend to be based on large international networks with rigorous follow-up meetings. These networks should remain independent which is a difficulty given the necessary funding by industries and possible conflicts of interests.

The ethics of psychopharmacology is still an advanced domain of bioethics where much research and negotiation are still necessary. Historians of science are not excluded since a historical perspective can show very recent abuses and instrumentalisations of psychopharmacological knowledge by politicians, military institutions and industries.

Acknowledgement

The author thanks Chantal Barbara, Jean-Noël Missa and Frank Stahnisch for helpful comments and suggestions.

REFERENCES

Barbara, Jean-Gaël. 2009. Claude Bernard et la question du curare : Enjeux épistémologiques », Soc Biol, 203, 227-234.

Barbara, Jean-Gaël. 2010. La naissance du neurone, Paris, Vrin, 2010.

Barbara, Jean-Gaël. 2011a. Ouvrir le corps des fous et des criminels : science et enjeux philosophiques d'hier et d'aujourd'hui », in Crime et Folie, Laura Bossi, ed., Les Cahiers de la NRF, Sixième volume des « Entretiens de la fondation des Treilles », Paris, Gallimard.

Barbara, Jean-Gaël. 2011b. Relations Médecine – Sciences dans l'individualisation des maladies à la Salpêtrière à la fin du XIXe siècle, Revue d'Histoire des Sciences, 63, 369-407.

Clouston, Thomas, Smith. 1887. Clinical lectures on mental diseases, London, Churchill, 1887.

Clouston, Thomas, Smith. 1863. Contributions to the study of insanity and its treatment, London, 1863.

Curchod, Henri. De l'aliénation mentale et des établissements destinés aux aliénés dans la Grande Bretagne, Lausanne, Bridel, 1845.

Deguise, Dupuy, Leuret. 1824. Recherches et expériences sur les effets de l'acétate de morphine, Paris, Crevot, 1824.

Dewsbury, D.A. 1991. "Psychobiology". American Psychologist, 46, 198-205.

Dunlap, K. 1914. An outline of psychobiology. Baltimore, The Johns Hopkins Press, 1914.

Galifret, Yves. 1979. Le biologique dans la psychologie de Wallon. *Enfance*, 32, 355-362.

Guislain, Joseph. 1826. Traité sur l'aliénation mentale et sur les hospices des aliénés, Amsterdam, J. van der Hey et fils, Les héritiers H. Gartman, 1826.

Kraepelin, Emil. 1892. *Über the Beeinflussung einfacher psychischer Vörgange durch einige Arzneimittel*. Jena, G. Fischer, 1892, p. 227.

Kraepelin, Emil. 1899. Psychiatrie: ein Lehrbuch für Studirende und Aerzte, 1899.

Lashley, K.S. 1917. The effect of strychnine and caffeine upon the rate of learning. Psychobiology, 1, 141-170.

Ledermann, François. 1988. Pharmacie, médicaments et psychiatrie vers 1850 : le cas de Jacques-Joseph Moreau de Tours, Revue d'histoire de la pharmacie, 276, 67-76.

Macht D.I., Mora C.F. 1920a. Effect of opium alkaloids on the behaviour of rats in the circular maze. J Pharmacol Exp Ther, 16, 219-235.

Macht D.I. 1920b. The effect of some antipyretics on the threshold of hearing. Journal of Pharmacy and Experimental Therapeutics, 15, 1920, 149-165.

Missa, Jean-Noël. 2006. Naissance de la psychiatrie biologique, Paris, PUF, 2006.

Pinel, Scipion. 1837. Traité complet du régime sanitaire des aliénés, Bruxelles, Société encyclographique des sciences médicales, 1837.