NOVAFCSH
FACULDADE DE CIÊNCIAS SOCIAIS E HUMANAS
UNIVERSIDADE NOVA DE LISBOA

The dopamine hypothesis of schizophrenia, an historical approach

Tese de Doutoramento em História

Setembro, 2022

NOVAFCSH
FACULDADE DE CIÊNCIAS SOCIAIS E HUMANAS
UNIVERSIDADE NOVA DE LISBOA

João Tavares

Tese de Doutoramento em História

Setembro, 2022

Tese apresentada para cumprimento dos requisitos necessários à obtenção do grau de Doutor em História, realizada sob a orientação científica de Doutor João Luís Lisboa, Professor catedrático, Departamento de Historia/ FCSH.

Acknowledgements

Constructing knowledge is a community endeavour. As we will see in our research, personal relationships, ocasional encounters and social identities as well as career paths, instruments and artefacts, reflect directly on results and theory. My own project doesn't escape this collective origin.

I'm particularly indebted to this thesis supervisors, João Luis Lisboa and Vincent Barras, but also to those that gracefully accepted to be interviewed, namely Douwe de Boer, Fernand Goffioul, Christian Mormont and Mary Seeman.

Throughout this project, I received insights, criticism, and propositions that changed the course of my research. I am grateful to Elisabetta Basso, Emilie Bovet, Rosa Cipriano, Olivier Darrigol, David Healy, Ivana S. Marková, Jean-Noel Missa, and Cecilia Vaz.

The English version had help from João Aidos and Miguel Cipriano, and was finally revised by Meg Boulton.

A special thanks to Martine Lachaussée, Florence Choquard and Andreas Steck

My sincere gratitude to Mariana Cipriano, for her patience.

The dopamine hypothesis of schizophrenia, an historical approach

A hipótese dopaminérgica para a esquizofrenia, uma abordagem histórica

João Tavares

Abstract

The underlying cause of schizophrenia could be an overacting dopaminergic function at the central nervous system. This hypothesis was first introduced in 1966 by the Dutch pharmacologist Jacques van Rossum. Our project aims to understand the conditions behind the conception of the dopamine hypothesis as well as the process that would place it at the center of psychiatric theory.

Primary sources were mainly published papers during the decade that preceded van Rossum's proposition. Interviews both previously published, and developed during our work, brought additional descriptive elements that helped characterise more informal factors.

Our research illustrates how the dopamine hypothesis emerged from the social history of neuroleptics in general. Haloperidol's development in particular, searching for chlorpromazine- like features and amphetamine antagonism, expanded and transformed the concept of "neuroleptic". The consequence was a change in the way schizophrenia itself was viewed. As haloperidol's use progressed in Europe, and neuroleptics became mostly viewed as antipsychotics, schizophrenia itself suffered major transformations. Those included three similar and parallel processes of *reification* (becoming a more concrete disease, possibly declined into a list of symptoms), *mechanification* (transformation of a complex multilevel interaction into the malfunction of a simple biological pathway) and *cerebralisation* (with an almost exclusive location in the central nervous system). The dopamine hypothesis was a key step confirming, enhancing and accelerating these changes. In the same manner that theory influences drug development, medications construct theory, redefine what we determine as pathological, and reframe research into disease pathophysiology

Pursuing these close relationships between rationalism and empiricism, theory and artefacts, pathophysiology and medication, we unraveled some of the stories that help built the current neuropharmacological academic and industrial complex and analyse the factors that helped shape the current close relationship between industry, academy, and the clinical world.

KEYWORDS: Dopamine hypothesis, History of schizophrenia, History of neuropsychopharmacology, Haloperidol, Neuroleptics, Neurotransmission

Resumo

Um aumento da actividade dopaminérgica ao nível do sistema nervoso central poderia ser a potencial causa da esquizofrenia: esta hipótese foi apresentada pela primeira vez em 1966 pelo farmacologista Holandês Jacques van Rossum. A presente investigação pretende compreender não apenas a origem da hipótese dopaminérgica, como também o processo que a posicionou, desde o início, no centro da construção teórica psiquiátrica.

Recorreu-se a diversas fontes históricas, com destaque para os artigos científicos publicados durante a década que precedeu a hipótese de van Rossum. Entrevistas, previamente publicadas ou desenvolvidas no âmbito deste trabalho, acrescentaram elementos descritivos que permitiram caracterizar factores mais informais.

Esta pesquisa revela como a hipótese dopaminérgica resulta directamente da história social dos medicamentos neurolépticos. A construção do haloperidol, procurando por um lado elementos que o aproximassem da cloropromazina, e por outro o antagonismo da anfetamina, expandiu e transformou o conceito de neuroléptico. Tudo isto teve impacto na forma como a esquizofrenia era pensada. À medida que o uso do haloperidol progrediu na Europa continental e que os neurolépticos foram crescentemente vistos como antipsicóticos, a construção da esquizofrenia sofreu importantes transformações. Entre estas encontram-se três processos similares e paralelos, a que chamámos *reificação* (tornando-se uma doença mais concreta, potencialmente reduzida a um declinar de sintomas-chave), *mecanificação* (transformação de uma interação complexa e multidimensional, na disfunção de um simples mecanismo biológico), e *cerebralização* (com uma localização crescentemente exclusiva no sistema nervoso central). A hipótese dopaminérgica foi um elemento chave na confirmação, expansão e aceleração destas mudanças. Da mesma forma que a teoria influencia o desenvolvimento medicamentoso, os medicamentos, eles próprios, tornam-se construtores de teoria, redefinindo o que se considera patológico, e reformulando a pesquisa patofisiológica.

Perseguindo estas relações próximas entre racionalismo e empirismo, teoria e artefacto, patofisiologia e medicação, revelam-se alguma das histórias que ajudaram a construir o actual complexo industrial e académico neurofarmacológico, e analisam-se factores que condicionaram as proximidades actuais entre indústria, academia e clínica.

PALAVRAS-CHAVE: Hipótese dopaminérgica, História da esquizofrenia, História da neuropsicofarmacologia, Haloperidol, Neurolépticos, Neurotransmissão.

Contents

Introduction

In medicine, drugs and theory are sometimes entangled in a way that they become indistinguishable. Substances can become instrumental in the construction of explanatory models, and theory has the ability to reshape drug creation processes. Drugs can emerge as social actors, building theory, and in a similar manner, pathophysiological hypothesis can be viewed as conceptual objects or artefacts, sculpted in a slow and multilayered manner. Our current research uses this apparent inversion of perspectives in order to portray the birth of an exceptional entity – the dopamine hypothesis for schizophrenia.

The history of schizophrenia, as an idea, is both complex and surprising. It is a demonstration of psychiatry's permeability, as a discipline, and its capacity to absorb and integrate mainstream society's ideology and values.

The concept's origin is often traced to degeneration theory (Barrett, 1998a).[1] Benedict Morel's *dégéneration* was grounded in moral and social factors associating physical and mental illness in a hereditary and incurable condition. It had a dreadful prognosis with an inexorable generational decline to sterility. Morel's nosology was essentially etiological, and although heredity played a crucial role, *dégéneration* was multidimensional and multifactorial. Causes included climate, urban surroundings and alcohol intoxication in a complex, and sometimes unique, configuration. Mental illness wasn't an individual phenomenon, and understanding it implicated society at large (Morel, 1860).

Kraepelin's own "dementia praecox", which also defined a gradual decline of a frail minded state, was firmly influenced by his views on masculinity, and embedded in a reductive dichotomy of strong will versus feeblemindedness (to which women, children and primitives were inclined). His idea of degeneration integrated hybrid sources from neuropathological data to a moral conception of human value (Barrett, 1998a). From its first iteration dementia praecox was connected to processes of mental degeneration (*die psychischen entartungsprocesse*), and defined a quick progress to a mostly irreversible mental impairment (Kraepelin, 1893, p. 435).

Bleuler's formulation, *schizophrenia,* followed a different trend. Influenced by Romanticism, german academics since Griesinger identified a failure of inner unity, a divided

[1] It should be noted that this genealogy is strongly contested. Among other conceptual aspects, Chapter 2.7 further explores the doubts concerning the impact of Morel's contribution.

person, as the culmination of mental illness. For some authors (Barrett, 1998b), Bleuler proposed *associative splitting* as the primary core pathology to schizophrenia following these XIXth century cultural tropes. More than a constellation of symptoms, schizophrenia was a global transformation of the self (Bleuler, 1937, p. 313).

In 1958 schizophrenia was understood to be a combination of these two tendencies. Leopold Bellak's collaborative effort "Schizophrenia: a review of the syndrome" was critically acclaimed and became a major influence on psychiatrists in training at the time (D. Burnham, 1960; Rosenfeld, 1961; Stengel, 1960). In that work, schizophrenia was defined as a severe disturbance of the ego (used here in an explicitly Freudian sense), combining altered relation to reality, poor drive control, disturbance in object relation, thought processes and defensive functions. It was a multi-factored, multidimensional condition, with a complex variety of etiological components from psychodynamic to traumatic, or genetic, all merging in a particular and specific pattern. This kind of definition used hybrid discourse importing concepts from psychoanalysis, clinical medicine, and biology (Bellak, 1958, pp. 3-24).

Soon afterwards, in 1966, Jacques van Rossum proposed an etiological theory that would radically change this conceptual frame. The dopamine hypothesis for schizophrenia suggested that overstimulation of dopamine receptors in the neuronal synaptic gap could be a part of the etiology for schizophrenia. This could be mediated by direct dopamine increase, by substances with similar dopaminergic action, or even by altered receptor susceptibility. The implications of this hypothesis were phenomenal and in the decade following the dopamine hypothesis became the most influential psychiatric theory conditioning everything from drug production, to clinical practice. Thus, the dopamine hypothesis not only changed psychiatry, but also reconstructed the way we, and society at large, relate to mental illness.

The dopamine hypothesis is arguably a grounding exemplar of a certain psychiatry, a way of thinking and practicing psychiatry that has been called "biological psychiatry". It can be said that this hypothesis served as a model for other neurochemical reasonings, and helped foster an ambitious research program in neurochemistry. Allies of the hypothesis point to its productive capacity, and uphold its ambition of creating an unique bridge between basic neuroscience and clinical practice (Javitt & Laruelle, 2006; Lau, Wang, Hsu, & Liu, 2013). This biological movement can be integrated in a broader ideological trend that retains an individualistic concept of modern identity and places it exclusively in the brain (Vidal, 2009).

This neuroscientific research program has an ambitious and unlimited object of attention - all human experience, from the organisation of the social world, to concepts of morality, art, or personality (Gold & Stoljar, 1999).

The main question of this research is how was the dopamine hypothesis created? What were the conditions for its emergence? What kind of forces were at play? What changed forcibly and what remained the same?

Our research doesn't want to be an empty contemplation of the past, on the contrary we see a hidden power in this line of inquiry. Understanding how a conceptual object was created is a way of grasping the conditions to its present preponderance. Further, it is a way to unnaturalise what has become self-evident and to discern the contested interior of the hypothesis, acknowledging some of its forces and fragilities. It is also a way of learning to recognise how similar objects can be constructed in our time. Looking at the way psychiatry produced its current knowledge anchors present practices in a more reflexive manner, but is also the first step in searching for alternative knowledge production procedures. In the last decades of psychiatric research, feminist authors have explored emancipatory psychiatry, promoting a more dialogical knowledge formation process, emphasizing collectivity through integrative approaches. Ethnopsychiatric approaches have refuted ethnocentrism and social psychiatry has explored the economic and social aspects of psychiatric illness. As patients organize politically, their voice starts being heard, at least on an organisational level. My research shares in this effort of reconstructing a more diverse and inclusive knowledge and practice. This being so, understanding the forces and agents at play behind our most powerful hypothesis, is, it seems to me, a fundamental first step.

My main question isn't about truth, nor reality, it isn't a clinical question, nor an empirical question. I don't wish to revise experimental data, favouring or contradicting the dopamine hypothesis (for that see (p.e Howes & Kapur, 2009; Kendler & Schaffner, 2011; Moncrieff, 2009; Philip Seeman, 2013). I am not seeking to question its scientific validity. Finally, I should clarify, I am not personally a believer in the dopamine hypothesis, nor am I a denier, a polarisation current psychiatry sometimes promotes. I prefer to stand in a place of suspended belief.

This is an historical research project. As questions linger about how neurochemical hypotheses emerged, our approach will examine and analyse a corpus of primary sources,

from scientific papers, to written interviews. Trying to find a clearer perspective on the way the dopamine hypothesis for schizophrenia was formed includes understanding the social and intelectual conditions necessary for its construction, as well as the reasons for its success and resilience. In doing so, the project wishes to contribute to the present reflection about knowledge construction in psychiatry, and its impact on mainstream society's popular discourses.

My thesis is structured in a mostly chronological manner. We will start in 1958 with the emergence of a new neuroleptic drug (haloperidol) that would become a decisive medication for schizophrenia. This singular creation process is said to have been the main influence behind the dopamine hypothesis by van Rossum himself. Our attention will be centred in the eight years that separate haloperidol from van Rossum's seminal proposition. Important protagonists and events precede 1958 and whenever that's the case we will explore their importance, detail their precedence or their impact on the events that interest us. Again, in a similar way, events post 1966 may be included if they have a direct impact on the way we think about the timespan we are pursuing.

Until the 1950s psychiatry can arguably be described as mostly fractured along regional or national lines. The United States' psychiatry of that time, for example, has been repeatedly described as strongly influenced by psychoanalysis in ways that maybe European continental psychiatry was not (E. Shorter, 2021, p. 34).[2] In continental Europe, nosology and clinical procedures seemed to follow the most influential linguistic traditions: namely, those of the French (France, Belgium and Latin countries from Portugal to Romania), German (Germany and Austria) and English language (UK, Ireland, the Netherlands)(Sartorius & Sartorius, 2020). The prevalence and durability of national concepts, along with the difficulty in exporting specific linguistic terms such as the French "boufées délirantes" or the scandinavian "reactive psychosis", are examples of organisation by spheres of influence that affect this area of study from a historiographic perspective (Pichot, 1985, 1986).

There were no major international associations for psychopharmacology, individual psychiatrists international contacts were mainly sparse personal acquaintances (Sartorius & Sartorius, 2020). The first congress of the World Psychiatric Association was in 1950, in

[2] In the german speaking world, for example, psychoanalysis, after its America expansion, is said to have dwindled, restricted to Switzerland, Viena, and "Kretschmer's circle" (Janzarik, 1985).

Paris, mostly through the dedication of the French (including Jean Delay, Henry Ey and Pierre Pichot) (Sartorius & Sartorius, 2020). The second meeting was only 7 years later, in 1957, and still in Europe (Zurich), but the formal founding of the World Psychiatric Association would wait until 1961, falling within the timespan that interests us.

As we will see, many of the events in our research are in a close geographical vicinity, near the language frontier in central Europe, namely: Beerse, Liège, Utrecht and Dusseldorf. These are at a distance of little more than 100 km from each other. From this local origin the dopamine hypothesis grew into an international success. Understanding the basis for this internationalisation, the social mechanisms it used, how it followed a broader internationalisation movement within the discipline, is one of the main objectives of our research. Even so, our research will be mostly limited to Western Europe, the United States and Canada. This, I believe, reflects the geographical location of the primary events that contributed to the emergence of the dopamine hypothesis, but is also possibly conditioned by our own limited language skills (English, German, French and Portuguese). Other psychiatric, and mental health, traditions exist, of course, and historical approaches of subaltern practices are fundamental to broaden our understanding of the field. As our research interests itself with the center of the discipline, looking for the origin of the most hegemonic concepts, it may neglect some more peripheral contributions.

The first part of the thesis addresses major previous works that relate to our main questions, explores our principal arguments and research objectives, as well as setting out our methodological strategies.

The second part traces the path that a substance takes in order to become a drug. Created as R 1625 in Paul Janssen's thriving new pharmaceutical company, haloperidol still had a long way to go before becoming a drug. This part of the thesis interprets how theoretical considerations and practical concerns conditioned haloperidol's construction process. It portrays the first trials in Liège and explores how they led to the establishment of a partnership between Liège's university and Paul Janssen. Still in Belgium, the Dave trials were the next fundamental step in the construction of haloperidol's anti-delusional and halucinolitic effects. From there, our research describes the drug's first septs of internationalisation and demonstrates how they were carefully organised by Janssen pharmaceuticals. In the end, this second part reveals how a picture of a potent drug starts to

emerge in the European published literature, and how this powerful social construction was, in turn, related to transformations of schizophrenia itself.

The third part of the thesis explores an Atlantic divide in the reception of haloperidol, and how this reshuffled theoretical construction around neuroleptics. It describes the diverse conditions of the first clinical trials outside continental Europe, first in Manhattan, then in England and Montreal, showing how haloperidol was considered less potent than what had been described in continental Europe, and more significantly, how side-effects were considered numerous and disturbing. This part lays out how these secondary side-effects (that began by being seen as incapacitating) became an opportunity and were transformed in an essential piece of the mechanism of action. This transformation, we argue, was crucial in the construction of the dopamine hypothesis for schizophrenia. The research then uncovers the story of these side-effects, how they were called extra-piramidal, and how, through a collaboration with a young German doctor Hans-Joachim Haase, Paul Janssen found a new identity between therapeutic action and side effects.

The forth part of the thesis follows these drugs, neuroleptics, as they went back to the laboratory. As the drugs found growing legitimacy in clinical wards and asylums, an important validation was missing: an explanation for the way they worked in clinical practice. This compelled a return to the laboratory. There we identify a new background but also new actors. The research reveals how instruments like the spectrophotofluorometer changed the way substances could be identified, and their presence verified. In the end of the forth part, we can see how new biochemical hypothesis were being proposed and in the same process a new model of chemical neurotransmission was gaining growing support.

The fifth part of the thesis depicts how the Dutch scientist van Rossum found himself in an unique place, wherein he was able to synthesise and articulate both Janssen and Haase's contributions about haloperidol's mechanism of action with the new ideas in chemical neurotransmission, alongside his own previous work on psychostimulants.

Of course schizophrenia is more than simply an idea. It has real impact in patient's lives, sometimes even limiting their liberties and autonomy, but also conditioning medical practices, techniques and artefacts (from buildings to drugs). During our research, when we think of schizophrenia primarily as a construct, we have no intent to invalidate personal suffering, nor exclude any possible explanatory model for that suffering be it biological,

psychoanalytical, or other. Furthermore, we can clarify that our research doesn't approach lived experiences of patients directly, but is mostly interested in their descriptions, interpretations and other theoretical underpinnings formulated in academic discourse and mostly published in specialty papers. In this sense we don't use the descriptors *mental health survivors*, or *mental health service users,* sometimes used in social studies of psychiatry, and prefer to use expressions that are closer to our sources but that are still respectful like *patients*. We avoid the term *schizophrenic* as we feel it can be derogatory by creating an identity between person and illness

1.1. Psychiatry as an historical object

The purpose and value of writing the history of psychiatry is a recurring question. Its persistence in our collective discourse may suggest that history of psychiatry, as a discipline, is an epistemologically fragile endeavour, that needs to find a purpose to claim an identity. Between the various available examples, we chose three different papers that express contrasting views of this field of study (Mora, 1970) (Huertas, 2001) (Beveridge, 2014). Although they aren't representative of an expanding field, they express the diversity of answers to our first question: Why write a history of psychiatry?

Separated by 44 years, a period of important changes in the historical and methodological approaches of psychiatry, we can nevertheless find common concerns and continuities across these sources. One central element of all these papers is the idea of a history made for the present, the joint refusal of an antiquarian history, the rejection of a history of curiosities serving only the validation of the current practices. Mora, Huertas and Beveridge share this sense of history as powerfully transforming reality, a sense shared by this study. As stated by Mora:

> History, then, ceases to be merely an arbitrary selection of events of the past and becomes instead - no matter to what philosophy of history one subscribes - a meaningful interpretation of events of the past in the context of their relevance for the present and the future. (Mora, 1970)

George Mora had been a student of Gregory Zilboorg, the author of "The History of Medical Psychology", an influential work sometimes criticised for its strong psychoanalytic perspective (Wallace & Gach, 2010, p. xiv). In Mora's paper from 1970, this history for the present can be framed as a desire for a profound knowledge of human experience, as a contribution to the understanding of ourselves. History's capacity to act in present psychiatry, for Mora, came from this ability to purpose a broad interpretative frame, that was sometimes explicitly psychodynamic.

Huertas (2001), writing at the turn of the century, becomes liberated from such psychoanalytic principles. His case for a history for the present is mostly epistemological, seen as an instrument for analysing the internal validity of current constructs and practices. Understanding the context where "our" concepts were founded is a way of grasping its

purpose in the scientific discourse. An-historical psychiatry, a discipline forgetting its past, would risk combining concepts of different contextual origins, with divergent meanings.

Our last example, Beveridge (2014), defends psychiatric history as a way of increasing our critical posture, and expanding our understanding of the patient. He writes from an iconoclastic stance, where the current psychiatric discourse is seen as naturalised, incapable of engaging with patients views. History, for Beveridge, offers a new critical distance, highlighting contexts and power relations, as a way of creating space for the patients' perspective.

Arguably, as with all histories, we can see these three examples as responding to the doubts and fears of their time. The purpose and value assigned to the history of psychiatry being, in many ways, dependent on their epistemological stance. Nevertheless, in the intersection of their perspectives we can find a solid argument, which our research also shares, that assigns, to the study of the past, the ability to change our present. Recognising the capacity of historical knowledge to produce changes in our current perception of reality is a core part of this thesis. In our research, specifically, we try to grasp the origins of the dopamine hypothesis in the hopes that this understanding can influence the way we look upon, not only dopamine, but also other pathophysiological hypotheses in psychiatry. Furthermore, we hope to contribute to a reflection about the wider process of knowledge creation within the discipline.

But where to find the motor of history? Who could qualify as agents of change, as constructers of knowledge within the discipline?

During the first half of the XXth century historiographical traditions placed men as the central figures of narratives of psychiatry. The psychiatrist lifted from the anonymous masses, moved by moral imperatives of work and charity, was solely responsible for forming theory and practices. This tradition, of which Rene Semelaigne (1932) is an example, is in many senses a biographical exercise. Such a biographical historicising model often details the elitist origin, from the educated Bourgeoisie, highlighting their faith, their dedication, and their good intentions. The psychiatrists emerged in these narratives as the center of power, the only agents capable of creating change, in their hands psychiatry hold the promise of progress – they became the monoliths around which the history of the discipline is formed.

In the 1960's, with works from Erving Goffman (1961), and later in France with Robert Castel (1971), the main force within psychiatric history, the agent behind the historical event, as it were, stoped being these honourable men and became, instead, the "institution". The asylum ceased being the scenery against which everything was enacted and became the protagonist pushing the narrative. The psychiatrist lost his name, he lost his right to good intentions, and was diluted in his social role. Instead, the institution itself constructed the specialised psychiatric discourses, the institution itself distributed power. This newfound object is reflected in multiple historical works as Andrew Scull's *Madness and segregative control: the rise of the asylum* (1977).

In a similar manner to the foregrounding of the institution, artefacts, in the broader context of the material turn, have also been the center of attention in the history of psychiatry. *La baignoire, le lit et la porte* (Majerus, 2011), is an example of this understanding of objects as active social agents, structuring day-to-day life in the psychiatric institution. This biographical approach to objects, from their initial conception to their changing uses, underscores their capacity to transform psychiatric practices, and their history.

In a more recent example (Morrison, 2016), the central object of study is again displaced, as relational aspects become the key to understanding psychiatric history. Both patient's and psychiatrist's narratives were built within the same encounter, negotiated through power and agency. Psychiatric discourse was constructed in this "mutually dependent" manner, where the clinician's capacity to penetrate the patient's intimate lived-experiences depends on the patient's disposition to disclose.

These different examples of focus show us that changing the central object changes our whole perspective of the phenomenon, including changes in methodology and ideological compromise. By highlighting different agents of change, contrasting views emerge of the forces that built the discipline. Going from the psychiatrist or the institutions, to objects or relationships, we can see more clearly the diversity of historical approaches to psychiatry. Maybe these transformations also reflect broader societal changes, as both identity and agency are increasingly seen as fragmented and negotiated.

Our research object, centred in a pathophysiological hypothesis, has been traditionally overlooked. One example is Emilie Bovet's work on the diencephalic hypothesis of mental illness (2012). The author highlights elements of theoretical continuity within

psychiatry, during the rise of neuroleptic therapy, events often previously described as serendipitous and revolutionary. Bovet contributed to change the way we look at psychiatric knowledge construction in the 1950's, and we will return to her work during our research.

Although we are mainly interested in a conceptual creation, we expect to recognise different actors in this process. In this context, biographical elements seem relevant, as they expose personal identities, from class to nationality, as well as personal ambitions - be they financial or academic. We also recognise the capacity of objects for transporting theory and transforming reality. Be it instruments, as the spectrophotofluorometer, or substances, as R 1625, objects retain the capacity to materialize theory and condition new hypothesis construction.

In the 1960's the glorious progressive internalist narratives of psychiatry were deposed by new iconoclastic approaches, including Michel Foucault's (1961) transformative work. There was an increased emphasis on discontinuity, on the patients' silenced voices, and the therapeutical techniques' function of control. New approaches from social sciences started to look for external forces in the construction of psychiatric concepts. Lanteri-Laura's (1972) study of chronicity, as a concept emerging in psychiatric diagnostic classification during the second half of the XIXth century, is a good example of this trend. Connecting psychiatric nosology to the reshaping of the social and economic determinants of the asylum, Lanteri-Laura transformed the origin story of psychiatry. Concepts like "délire chronique à évolution progressive" took definitive form in the writings of psychiatrists like Magnan, but the forces creating them were the needs of the institution. Psychiatric knowledge construction could then be seen as directly dependent on financial forces.

Barrett's (1998a) synthesis of the origin of schizophrenia as a construct, in the midst of XIXth century degeneration theory, to which we have referred previously, is another example of external analysis of knowledge creation. Concepts that organise nosology were seen as subsidiary of broader cultural trends.

As we approach our research we keep in mind these lessons from past historiographical works. As we look at the origins of the dopamine hypothesis we will pay close attention to how economic forces could shape theory, namely how research was funded, the role of private industry, as well as the geopolitical interests of western states in the aftermath of the second-world war. Barret's examples of the power of cultural trends reminds

us to insert the dopamine hypothesis in a broader ideological movement and research program that reduces human experiences to the brain, and has roots that long precede this theory.

As noted, our research refers to the period between 1958-1965, sometimes described as period of transformation, it has been of interest for previous scholars. Continuities or discontinuities are alternatively valued, or overlooked, depending on the historiographical approach, as will be demonstrated here. Although overarching narratives diverge, depending on the aim of the individual studies, the following major works (outlined below) are generally referenced by those working on this period.

In the end of XXth century, Edward Shorter (1997) published a book that reshuffled expectations of the discipline. With it he retold or re-constructed a narrative that would become central to the way psychiatry saw itself. In the author's view from the 1950's to the 1990's a new biological psychiatry reaffirmed itself as an enormous success, dethroning psychoanalytic thought. This psychopharmacological *revolution* was presented by Shorter as reaffirming the primacy of the brain in a gloriously progressive manner.[3] His own historiographical approach mimics his central narrative, portraying himself in unequal combat with an iconoclastic tradition of psychiatric historiography. Its reception generated important discussions around psychiatry and its history. Barras (2001), for example, criticised the narratives hidden behind an appearance of neutral facts, as sources seem to be read simplistically and used uncritically. Beveridge (1997) criticised its manichaeism, and its use of historical work to justify present psychiatric practices. Others, like David Healy (1997), unabashedly applauded the strong positioning in the book. Nevertheless, despite its alleged thoroughness and breadth, *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* doesn't really delve into the dopamine hypothesis. It is referenced (p. 265, 267), but van Rossum's contribution is neglected.

Just one year later Elliot S. Valenstein (1998) published his book about neurochemical explanations, including the dopamine hypothesis for schizophrenia. An American professor of neuroscience, his interest stems from his scepticism about the sprawling identity between human lived experiences and neurochemistry, found in contemporary discourse. His book analyses what he calls the "shaky scientific foundations of these theoretical constructions". In

[3] As we will see, in our research, we found a much more nuanced transition in our sources, where psychoanalysis, neuroleptics, and other biological therapies, coexisted.

it, he thoroughly examines the "evidence" behind these hypotheses, and ponders the arguments used in the late 1990's to uphold them. In so doing, he finds them less than convincing. Another important part of the book analyses the way the pharmaceutical industry promoted this discourse as a way of marketing drugs. Valenstein interests himself less about how these hypotheses were created, and more about how they gained their relevance.

Again, shortly after, David Healy published *The creation of psychopharmacology* (2002). In it he portrays the rise of the pharmaceutical industry as stemming from the seminal moment of "chlorpromazine's discovery" that he considers one of the pivotal events of psychiatry's history. Healy sees this as having consequences ranging from the development of other drugs to more broad cultural tropes (like changing the way we experience ourselves) and societal conundrums (including behaviour control). He portrays this rise of biological explanations as instruments captured by the thriving new pharmaceutical corporations. Despite Healy's and Shorter's similar approaches, the overarching narratives in these specific books couldn't be more different. A mostly linear progressive way of seeing the history of psychiatry (that we can find in Shorter's work), is here clearly contested, as Healy keeps a pessimistic regard to (then) present practices and research.

The dopamine hypothesis is referenced and van Rossum's work is recognised by Healy, but the author is more interested in later developments, including Solomon Snyder's work of laboratorial "validation". Healy's description of van Rossum as an obscure figure is representative of the sparse biographical data concerning him in such studies. Even though the author directs an intensive criticism towards the pharmaceutical industry, the role of Janssen Pharmaceuticals seems overlooked.

Following roughly the same chronology seen in Healy's work, Joanna Moncrieff's (2013) *The bitterest pill,* has an even more critical outlook. Concentrating on the origins and current use of antipsychotics, she interests herself explicitly in the way they historically acquired their present disease specificity. She recognises the influence of the pharmaceutical industry in this process, extensively analysing drug side-effects that, in her view, psychiatry tried to hide, or denied persistently. She also criticises current drug trial organisation, from rating scales to the idea of randomised controlled trials. More than an exercise in history, it is a book of critical psychiatry, questioning today's knowledge and practice. Historical work, here, serves a clear purpose of reinforcing the principal narratives of psychiatry, with the

central idea being that what we now call antipsychotic drugs were really better described by the first clinicians as neuroleptics due to their capacity to slow and numb normal thoughts and feelings.

Jean Noel Missa's *Naissance de la psychiatrie biologique* (2006), also intersects with our chronology of interest (1920-1960). This study is enriched by several interviews with those he calls "pioneers", depicting multiple perspectives during the first use of new treatment approaches. It portrays the hesitations and doubts that accompanied biological therapies, subtle feelings that memories transport. His main argument returns to the empirical necessities of medicine as a discipline. A pragmatic approach had created first the biological treatments, but afterwards also the pathophysiological theories (including the dopamine hypothesis).

Judith Swazey's *Chlorpromazine in psychiatry: a study of therapeutic innovation* (1974) tells the story of chlorpromazine synthesis, and market introduction. Financed by the committee for brain science of the US national research council, Swazey was interested in understanding the processes behind therapeutic innovation. In the book, the author follows the biography of chlorpromazine from its conception as RP 4560, stemming from French pharmaceutical company Rhone Poulenc's research on anti-histamines. Swazey describes chlorpromazine as the result of different multidisciplinary research programs from organic chemistry to surgery. She contestes assumptions about the benefits of highly organised biomedical targeted applied research, as innovation also seems to come from the accumulation of knowledge by fundamental sciences (although she recognises this is an artificial dichotomy). Her books goes further, following the first trials and uses of chlorpromazine, addressing psychiatry's unequal response, as well as considering external factors, from political powers to the press.

Toine Pieters and Benoît Majerus (2011) paper interests itself with a more regional approach, being a comparison of chlorpromazine's introduction in both Belgian and Dutch markets. Elements of continuity with previous therapeutic interventions were highlighted, here and from their examples we can see how chlorpromazine (and later reserpine) was integrated in treatment in a slow and heterogenous manner. Further, this study addresses how standards of safety and therapeutic guidance were constructed in a relationship between clinicians and drug company sales representatives. In this paper, the neurochemical

hypothesis in general, and specifically the dopamine hypothesis, is placed firmly in the context of chlorpromazine's introduction, and the changes it implied.

Alan Baumeister and Jennifer Francis' (2002) paper reviews the "discoveries" that inspired the dopamine hypothesis. In a more internalist manner, concrete elements from two different lines of research are presented. One concerning neuroleptics, Parkinson disease, and brain dopamine. The other referring to psychostimulant research - van Rossum's principal interest. The main "intelectual antecedent" of the dopamine hypothesis is said to be reserpine's introduction and the following research about its mechanism of action. The laboratory work of Brodie, and later, Carlsson is described as a succession of "discoveries" progressing towards a more accurate understanding of events. Van Rossum's contribution is described and its "main lines of evidence" are pondered. The importance of Paul Janssen's work to van Rossum is referred to in a personal letter from van Rossum to Baumeister.

Kenneth Kendler published two successive articles about the dopamine hypothesis, the first published in *Philosophy, psychiatry and psychology* (Kendler and Schaffner, 2011), and the second one published in the edited volume *Philosophical issues in psychiatry III* (Kendler, 2014). The articles combine a short historic revision, with an empirical evaluation of recent experimental findings, and an analysis of the factors contributing to its success. Historical methods, again, are used superficially with the intention of clarifying the context of the main questions, those can arguably be said to be more clinical than historiographical. The 2011 article has allegedly found difficulty in being published in a mainstream psychiatric journal, requiring the choice of a more philosophically inclined journal (Parnas, 2014). This predicament is justified by the persistent unpopularity of questioning the dopamine hypothesis within the psychiatric discipline. Although the authors recognise van Rossum's key contributions in the 2011 article (this is not the case of the 2014 paper), their historical interest is posterior and concentrated almost exclusively after 1973. This is in stark contrast with our thesis project.

From our literature review we can see psychiatrists are often still the ones writing history of psychopharmacology. Maybe as a consequence many historiographical approaches have multiple presumptions, be it about the true nature of mental illness, or for example the continuity of biological signs over time. Historical discussions are frequently contaminated by more clinical questions like the effectiveness of psychiatric drugs, for example. In this

context, a careful historical analysis of the dopamine hypothesis for schizophrenia is still lacking. Other reasons for this lacuna may include the chronological proximity of these events, the persistent force or influence the hypothesis still holds over the discipline, its status as a sensitive issue where criticism is sometimes badly received. Finally, the polarisation it creates within psychiatry, between believers and detractors, may also contribute for the sparse amount of uncommitted literature produced.

1.2. An approach to the dopamine hypothesis

The dopamine hypothesis for schizophrenia is sometimes presented as a factual truth, hiding from criticism, an an-historical reality. Our main objective is to contribute to the understanding of this idea mostly through confining it to a location in time and space. Realising when, how and why it was created is the first step towards rescuing it from the natural world and placing the idea firmly in the center of the debate. Although we wish to contribute to the framing of this dispute, the debate in itself isn't part of our research. We aren't interested about the relation between the dopamine hypothesis and the truth of the phenomenon that it refers to. Again, we wish to contribute to the shaping of that discussion, not to the discussion itself. This is a critical distinction, a distinction that, as we've seen in our literature review, is often overlooked.

There is a gap between what the dopamine hypothesis represents in psychiatry and its historiography, where it is often reduced to a succession of "discoveries". As we've seen in chapter 1.1 we believe this should be overcome by paying attention to the multiple agents at play. Scientists, drugs and diagnostics are interwoven in the process of knowledge construction, and should be addressed collectively. Scientists have motives, personal ambitions and elective affinities that mark the direction of science. Drugs are seen as theory laden beings capable of transforming practice, and building new theory. Diagnostics are treated as theoretical constructs, changing lenses for a complex reality. Protagonists, artefacts and theory will thus be given proportional attention here, and their intersections, their interactions, will be carefully highlighted.

These relationships will be put in the broader context of the discipline, where we will search for changes and continuities. We will be particularly attentive to how psychiatrists meet, how they share theory and therapeutic technologies, and tensions between regional knowledge production and internationalisation.

Within the influences that can have an impact on our object of study, we will be vigilant about financial forces. How important is funding, be it private or state sponsored, in shaping the direction of research? How can financial aspects frame scientific debate?

One of the trends we also identified in our literature review is the discomfort with the generalisation of "brain talk", seen in the social sciences but also in important sectors of the psychiatric discipline. This reducing of human experience to neurochemistry has been amply

noted, and the identity between our sense of selves and our brains has even been described by some as *Brainhood* (Vidal, 2009), or *Sujet Cérébral* (Ehrenberg, 2004). Can we place the dopamine hypothesis within this ideological framing?

We wish to remain attentive to categories of gender, class and ethnicity throughout our research, and try to be aware, and highlight, institutional mechanisms of exclusion or subordination.

As we take these objectives in mind, several questions can be raised, including: what role did drugs, in general, and specifically haloperidol, have in the construction of the dopamine hypothesis? How was haloperidol constructed? Was it a serendipitous event or consequence of theoretically supported endeavour? How to differentiate between substance and drug? How were haloperidol's trials designed, and what was exactly being tested? How did the drug "travel", in the context of the internationalisation of biological therapies of the time? How was haloperidol's reception in the United States and Canada? Were clinical trials giving different results, if so why? What could be the significance of this divergence? How were side-effects perceived, and in what context did this perception arise? How did the concept of "neuroleptic" articulate side effects and therapeutic effects? How were state laboratories studying the new neuroleptics and why? What role did instruments play in this research? How did studies about neuroleptic's mechanism of action contribute to a new model of neurotransmission? Why did van Rossum propose the dopamine hypothesis? How did he combine knowledge from different fields? How do scientists organize their career choices, and how does that influence theory construction? What role do formal and informal relationships have in psychiatry? How did the discipline change in this chronology, and how did it remain the same?

To respond to these questions, an important part of our work is analysing psychiatric literature published at the time. This includes scientific papers published by specialty magazines, as well as books and manuals.

Medical journals from the 1950's and 60's as primary sources can seem initially simple and dry. Their consistently rigid structure, objective tone, and mostly short format, transmit a straightforward simplicity that natural sciences often entertain. This first impression is quickly overcome by the richness of information that can be deduced from such sources.

Our approach to a published paper included detailing its described methods and main results, but wasn't limited to them. The papers structure frequently reflected the conditions of its creation. Papers from clinical trials in continental Europe, at the beginning of our chronology, often come enriched by comprehensive clinical vignettes illustrating the results. This habit is progressively lost as we approach 1965, a tendency particularly felt in Anglo-Saxon countries. The degree of detail in methodology is also sometimes particularly expressive. New instruments, concepts or substances are often extensively detailed in order to facilitate comprehension and reproducibility. When a new technology stops being explained it may mean it is in the beginning of a process of being black-boxed. The paper's references were always extensively analysed, as a way to understand the authors interpretation of the literature and confront it with its own sources. This process enables us to establish relations between the paper's described research and other research programs. Author's affiliations are generally correctly noted, and we can use them as sources to locate individual workers in time and space as well as a way to recognise formal partnerships between different institutions. We were particularly attentive to footnotes describing funding or private support. This kind of disclosure, today is seen as an ethical imperative, was maybe less so in the 1950's, nevertheless many of the papers that we've seen frequently addressed these concerns.

But beyond what we can directly read, we were interested in what we could indirectly perceive. What was the theoretical frame underlying the article? Sometimes we can apprehend a conceptual frame from methodology – for example looking at criteria chosen to evaluate a drug, we can understand the way a certain diagnostic is understood. Sometimes the language chosen, namely the presence of psychodynamic concepts, can be a clear indication of a psychoanalytic frame. Sometimes answers come from positioning the source in the broader career and interests of the authors, other times from contextualising the study within the conditions of the institution where it took place. Finally, we wanted to understand why a certain paper was chosen for publication, and what can that tell us about editorial priorities.

Individual articles can represent examples, but we can't be sure of their significance, or their acceptance in mainstream science. Books and manuals published during our period of interest serve a purpose of portraying a broad contextual reality. There we can appreciate the prevailing ideas, analysing what was at the center of the discipline and what was in the

periphery. Although they also have a specific agenda or a theoretical framework, they are still useful in evaluating the impact value of individual papers.

Many of the actors behind the events described in our research are now dead. Professor van Rossum, for example, died February 27th, 2020. Nevertheless interviews were an important primary source for this study and during our research, we conducted three different in-person interviews: Dr. Fernand Goffioul, Dr. Christian Mormont and Dr. Douwe de Boer. These were three particularly pleasurable moments in my research. Interviews were thematic, but mostly structured around open questions. The first two men's descriptions of *la clinique psychiatrique de Liège* during the first days of the haloperidol trials, gave texture to our research and Dr. de Boer was a valuable asset in understanding van Rossum's personality and its impact in his career. Personal communications by email were used as means to elucidate specific details or when interviews weren't possible. Mary Seeman gracefully answered our questions by email.

Healy (1998a, 1998b; 2000) published *The psychopharmacologists*, an impressive volume of interviews he conducted himself. These are quite structured, framed by Healy's interests as well as his intelectual positioning. Nevertheless, they are often conducted with subtlety and charm, making room for the voice of the interviewee. They are never critical or confrontational, they accommodate the scientists narratives, mostly without contradiction. The resulting narratives bring a rich first person texture to the history of psychopharmacology. We can sometimes perceive these scientists believed they were taking stock on their careers, and the resulting narratives can feel rehearsed or self-aggrandising. Contrasting these accounts with other primary sources, like published scientific articles, but also other interviews was an important step in evaluating testimony for this research. But the rehearsed narrative itself is also telling, purporting to record the scientists main values and exposing his beliefs.

Jean Noel Missa (2006) work also rests upon interviews that he sometimes shares with the reader through generous transcriptions. Direct quotes were important primary sources.

Other media interviews were also of value even if they were often framed by an uncritical adulatory tone.

We also used photographs as sources. They allow us to confirm presences, to place encounters in time and space, but they can also be fructuous on more informal elements of meetings and events. From clothing to drinks, we can get a sense of a meeting's atmosphere.

Access to Janssen pharmaceuticals records was requested, but unfortunately this request remains unanswered. Access to the laboratory records as pertaining to haloperidol could shed direct light onto some of our questions. We hoped that we could find documents where the degree of disclosure was probably untroubled by considerations of making history (one of the problems with interviews), nor by worries of academic reception (one of the limitations of scientific papers). Its absence presents one of the most important constraints on our work.

2. Haloperidol - from Beerse to Liège

2.1. Constructing haloperidol

There may be a strange feeling in attaching the word ‘constructing’ to a drug, as we are more frequently used to hearing the word discovery in this context. I chose the term constructing, not because I wish to hinder the serendipitous component of the events described here, nor because I wish to promote a view of the phenomenon as an hierarchically led, and conceptually orientated, endeavour. Rather, I prefer to emphasise the prolonged continued process (as opposed to the fleeting moment of discovery), as well as the multiplicity of social forces, protagonists, theories and instruments, stories and lived experiences involved. As we will see compound synthesis, chemical identity and social meaning are inextricably tied to the process of constructing a new medication. This was a social process that goes from the patent certification to its everyday use in asylum wards, from financial interests to test tube experimentation and animal modelling.

“What’s new”, Paul Janssen said everyday entering his laboratory in the Belgian town of Beerse. As a young doctor he picked up his father’s drug import company, and transformed it into a pharmaceutical empire. Still, till his retirement, he was personally involved in the day to day development of new substances. He called himself the conductor of the orchestra. His rapidly growing team was inexpensive, most of them non-academic (Granger & Albu, 2005), many returning from colonial Africa (Lewi, 2008). At the end of his life, he would remember longingly these first years of his career, namely the freedom of science unconstrained by patients rights, or legal safeguards (Missa, 2008). A time of well meaning common sense, of ethical simplicity, a farmers world (Lewi, 2008)(Janssen, 2002) .

Although he was obviously the son of privilege, Janssen persistently painted himself (and was described), as understanding the value of hard work and necessity. At 22 years old, still waiting to graduate from medical school, he went to the United States visiting academics and pharmaceutical companies (including Searle with which he would later develop a close collaboration). Seeing himself in financial trouble to pay for his stay, he slept at the YMCA, and made enough cash to pay for his trips in the amateur chess competition at the Manhattan chess club (Schwartz, 1989, p. 21). The reader is obviously free to believe or mistrust these anecdotes, but shouldn’t be left with a misconstrued idea of the Janssen family’s financial capacity. Another story, in the same book, (possibly) gives us a more accurate understanding.

During the trip the young Paul phoned home, to his father Constance, excited by a new instrument he wanted his father to acquire. He was asking for a Beckman ultraviolet spectrometer (Schwartz, 1989, p. 22), an impressively expensive instrument (a Beckman spectrometer cost more than 700 dollars in the forties (Simoni, Hill, Vaughan, & Tabor, 2003)). His father bought it reluctantly, but it was left untouched during the next few years, until Paul returned from medical school.

His father's company (first NV Producten Richer company, afterwards Richter-Europharma) was doing well financially. Initially importing and repackaging Gedeon Richter's tonics and vitamines, and after the second world war, with the death of Richter,[4] producing the medications locally (López-Muñoz & Alamo, 2009). By 1949 the sprawling business had 80 employees - this included of course a high percentage of non-research personnel.[5] Nevertheless, at his medical school the young Janssen was mocked, and his father's company ridiculed for selling unproven medicines (Schwartz, 1989, pp. 18-20).

Janssen was also critical of his parents company, and in 1953, at 26 years old, his father loaned him 50 000 Belgian francs and a small space in the plant. From there the company grew quickly, producing thousands of compounds in just a few years (Schwartz, 1989, p. 22).

Haloperidol, R 1625, was developed in February 1958, in this new and rapidly growing business, in the small country of Belgium, and in the next few years would become one of the most important medications of the 20th century. The biochemical construction of haloperidol's molecule was such a complex undertaking that it can't be reduced to an unique narrative, remaining a combination of multiple perspectives.

> There are five, six, seven versions of people who have been witnesses and all of them, being quite honest, are trying to remember what has really happened. But the real story very often is very difficult to put together because so many seemingly unrelated events led to that particular moment. (Janssen, 1992)

---

[4] Gedeon Richter , a jewish pharmacist from Hungary, had developed an important pharmaceutical enterprise that, at its peak, was present internationally in more than a hundred countries. He would suffer with the second world war. In 1942, he was deprived of his role in his own company and was subsequently killed in 1944 along with 99 other jews, tragically shot in the Danube embankment (Hargittai & Hargittai, 2015, pp. 271-274; Pavan, 2021).

[5] For comparison in 1950 the Suisse Rhône Poulenc Vitry's laboratory had 80 researchers (Swazey, 1974, p. 89).

Was it a concept driven project or the result of unexpected serendipitous events? Are these two opposed narratives impossible to reconcile? In such a debate, the dynamics of discovery and construction are put against each other, the role of leadership comes into question, but ideas about reasoning in science also must be considered.

In his interview in David Healy's *the psychopharmacologists* Heinz Lehmann described the central key to haloperidol's enterprise as an acidental observation by a female technician of a strange behaviour in mice (1998a, p. 184). This narrative is compelling in many ways. First because while it underscores contingency, it transforms haloperidol's conception into a fleeting revelation. More than a determined and organised search from an initial strong idea, as science is sometimes purported, this brief commentary suggests a view of psychopharmacology, in its beginnings, as an open, or even anarchic, process of creating conditions for moments of chance. But Lehmann's description is also interesting in its allusion to gender roles, and their implications in the broader context of women in the dawn of psychopharmacology[6]. The anonymity reinforces the unexpected aspects of the discovery, but also curtails leadership influence. Finally, this simple explanation still emphasises the primacy of animal models.

Janssen's response in a 2002 interview in a ECNP Newsletter takes a different direction (Janssen, 2002). Here he seemed to describe a concept-driven process deriving from the central idea that amphetamine intoxication could be used as a model for paranoid schizophrenia. Janssen describes that anecdotes of similarities between the stereotypic behaviour of cyclists on amphetamine intoxication and schizophrenia were brought to his attention, from there animal models were developed to test products looking for amphetamine antagonism. So, in Janssen's 2002 description haloperidol's construction was from the beginning an iterative process with a clear aim, it was from the beginning the search for a treatment for schizophrenia. In this definition of psychopharmacology a clear idea defined the scope of research, and a clear objective gave it meaning, organising day to day work in a

[6] Hannah Steinberg describes the early days of psychopharmacology "At the time, when I started in psychopharmacology, I was probably the only woman who had any sort of established university position then Daphne Joyce went to Birkbeck. And later Elizabeth Sykes worked in Edinburgh and Bangor. More recently of course there have been several prominent women in this country, Sandra File, Sheila Handley and Susan Iversen. Nonetheless, women are still expected to be assistants and agony aunts rather than independent scientists, let alone heads of departments. I also think that some male research students may find it harder to be supervised by a woman, which is understandable, if not desirable."(Interview with Hannah Steinberg in Healy, 1998a, p. 235)

focused and rational way. In this description the fundamental role of Janssen's leadership is clear. The margin for chance disappears.

Amphetamine's importance in the history of psychopharmacology is indisputable. Its relevance is felt not only in the clinical world, in the day to day activity of doctors and their patients, but also, as we wish to show in this thesis, in the laboratory (with its role in the construction of neuroleptics) and in academics (influencing theory construction about schizophrenia).

The story of amphetamine's complex process to become a psychiatric medication is comprehensively told by Rasmussen (2006). Challenging some preconceived ideas about the history of psychiatry, and the start of the "new biological" era in the fifties, Rasmussen proposes that American psychiatry in the 30's and 40's was already much more eclectic than was previously thought, integrating both biological and talking technologies in a way that gave rise to the development and widespread use of the first "antidepressant" - amphetamine.

The place where the story starts, depends like all stories, on the choices of the narrator. It can start in China with the herb Ma Huang, Gordon Alles's laboratory or in Smith Kline and French marketing department. Ephedrine (the Chinese herb Ma Huang purified) was being commercialised by American pharmaceutical company Lilly for allergies and asthma, but supply was dependent on Chinese production. In search for a synthetic substitute for ephedrine, Gordon Alles, a South Californian biochemist, was looking at related molecules when he prepared the compound phenylisopropylamine. In April 1934 Alles sold his patent to Smith, Kline and French. This pharmaceutical company was recently under new, bold leadership and searched through a broad net of possible clinical uses, identifying a marketing opportunity in neuropsychiatry. In 1937, the American Medical Association council on pharmacy approved its use in narcolepsy, post-encephalitic Parkinson and depression. An extensive advertising campaign in specialised medical journals followed suit, and by 1945 one million pills under the trademark *Benzedrine* were being sold everyday (Rasmussen, 2006). In the next few decades Benzedrine would strongly influence wider American culture, from mathematics to poetry (Foer, 2005; Jacobs, 2012).

Amphetamine's story is a prime example of the long road a substance needs to follow in order to emerge as a medication. This process includes building an explanatory narrative and a social role, entering prescription habits and embedding in day to day use. Multiple

stakeholders with opposing, and sometimes changing, interests negotiate in a long and complex dynamic. Although the use of amphetamine was persistently expanding, risks to mental health namely abuse, craving and addiction were soon recognised ("Benzedrine sulfate- a warning," 1938).

One of the first descriptions of psychotic states induced by amphetamine came from the clinics of David Young and William Beecher Scoville. They describe two patients who developed psychotic symptoms after starting taking Benzedrine for narcoleptic states. A thirty-four year old became suspicious after starting benzedrine, three years later he became worse, was “hearing plots against his life”, “feared for the safety of his family” and “believed his house was wired”. Being forcibly admitted to the hospital where all medication was stopped, he quickly became better, being discharged after just five weeks. Another young man was taking benzedrine for three years and had developed hearing voices in the last few weeks before admission, unfortunately this patients hallucinations persisted even after discharge. The authors interpret these findings, underlining Benzedrine’s action on alertness, that in patients with previous vulnerability (“paranoid trends”) could precipitate psychotic states (Young & Scoville, 1938).

In Young and Scoville’s vivid descriptions we can start to see how complex the term psychosis was, and how contemporary views of the term could mislead us about its meaning in the thirties. Although the authors talk frequently of “paranoid psychosis”, and they consistently describe hallucinations and delusions, they never refer to schizophrenia or dementia praecox. Delusions and hallucinations primarily defined these paranoid states that could be provoked by drugs, in this case amphetamine, but the clinical picture was substantially different from what was then called schizophrenia. Hallucinations and delusions were only accessory symptoms of schizophrenia (Bleuler, 1937, p. 29), its fundamental characteristic was a much more complex global splitting of the psychic activity touching almost every aspect of human inner life. During this thesis, we will follow the way these nosological concepts were changing during the fifties and sixties, and explore how these changes relate to the new therapeutic technologies (specially haloperidol) (see chapter 2.6, and 3.2). Through this process, we will see how much the new schizophrenia will redefine itself, finding distance from the classical Bleuler and Kraepelin’s definitions, and forging similarities with these paranoid states as described by Young and Scoville.

William Beecher Scoville's personal history would later be marked by immense controversy. Scoville would become a neurosurgeon in Hartford hospital neurosurgery department. During his professional career he developed new modified techniques and special instruments used internationally. He was never in the fringe of the field, on the contrary, he was firmly a part of not only the clinical but also the academic elite, as emeritus clinical professor of neurosurgery at Yale ("William Beecher Scoville obituary.," 1984). As neurosurgery approaches to psychiatry became mainstream during the forties, Scoville performed the procedure (fractional lobotomies) in more than 300 patients that had been diagnosed with schizophrenia (Scoville & Milner, 1957). In order to maximize clinical benefit, he elaborated experimental surgeries stretching the cut from the frontal to the temporal cortex. This more extensive procedure was done in 30 patients, one of them was Henry Molaison who suffered from uncontrollable seizures. After the operation Molaison's memory became severely disturbed. He was unable to form new memories, although early childhood memories were conserved. He became stuck in the present unable to understand his past and future. His mother said he would complete the very same jigsaw puzzles everyday. He would never live an autonomous life, depending first on his parents and then on a nursing home in Connecticut. Molaison's memory was extensively studied by more than a hundred different investigators (Lichterman, 2009), most of them trying to relate his clear clinical picture with the lesions that had been inflicted to his brain, as the search to localize specific cognitive and behavioural functions in the brain persisted as one of neurosciences principal trends during the second part of the 20th century.

Scoville experimented with temporal cortex in the beginning of the fifties (Henry Molaison's surgery was in 1953), at the same time that the new neuroleptics were starting to be recognised (namely chlorpromazine and reserpine). His extensive use of fractional lobotomies in schizophrenia is sometimes interpreted in the context of therapeutic nihilism. As chemical intervention was seen as insufficient, physical interventions in the brain, namely neurosurgery, held the promise of progress for sometime.

The story of Scoville's interest in psychiatry is deeply personal and disturbing. It seems to have been his first wife's mental illness that brought his attention to psychiatry, and it is said she was also one of his patients. His grandson later alleged that Scoville may have performed one of his fractional lobotomies on his first wife (Zhang, 2016).

This brief biographical story reminds us that the history of psychiatry is, in a way, a history of institutional violence, where powerless patients were submitted to experimental and sometimes cruel treatments. Their lives and their choices were sometimes erased and their names forgotten. Henry Molaison is, in a sense, an exception, his name endured as a cautionary tale on unconstrained approaches to neurosurgery.

But this chapter is about haloperidol, and the role amphetamines may have had on its development. From Young and Scoville's work we can recognise that medical literature had already acknowledged the possibility of clinical psychotic features driven by amphetamine use. Janssen possibly knew about these descriptions. When Janssen (2002) describes the anecdotal evidence brought to his attention of stereotypical behaviour in cyclists using amphetamine to enhance performance, in a way he, again, centred his narrative in a real world, common sense context, a methodology that we know pleased him. Janssen was a great communicator and his narrative of a clear concept driven process of constructing haloperidol begins with this simple everyday event, that we can easily connect to and understand. Amphetamine antagonism may have probably played a role in haloperidol development but certainly wasn't the only idea behind the research.

In another interview, in 1986, Janssen offers us a narrative with hybrid elements. There seems to be an element of contingency "…we stumbled upon compounds that antagonised effects of amphetamine on rat behaviour" that opened up an opportunity for pursuing a concept driven process. "Since amphetamine poisoning in men produces symptoms which are also observed in paranoid schizophrenics, we did not overlook the idea of trying amphetamine antagonists in psychiatric patients" (Janssen, 1992). The importance of amphetamine antagonism is still highlighted, but loses its foundational character as in the earlier narrative.

As we will see, two other concepts seem to have been driving Janssen's laboratory research: one of them was the enhancing of opioid analgesics.

R 875, dextromoramide, is said to be Janssen's first great media success. Recognised as an analgesic more powerful than morphine, it placed the name of young Paul Janssen in multiple newspapers both in France and Belgium, and demonstrated the importance of the market for powerful synthetic analgesics. It is said that that's what brought Janssen to start working with pethidine derivatives (Schwartz, 1989, pp. 64,65).

Pethidine (more commonly known as meperidine in the United States and Canada) had been synthesised in 1930 by a german chemical manufacturer as an antispasmodic but it was only in 1939 that its analgesic effects were recognised (Eisleb & Schaumann, 1939). This apparently serendipitous revelation follows the process of pharmaceutical development most frequent at the time. Substances were synthesised many times pursuing a specific therapeutical function, but a sometimes surprising biological activity was only later identified/constructed in animal testing. Otto Eisleb synthesised the compound looking for an anticholinergic, but it was only 9 years later that Shaumann recognised a specific behaviour in mice suggestive of narcotic action (Sneader, 2005, p. 122). The substance was created in a two step process, first the construction of a chemical identity to which it was later attributed a behavioural effect, a function, a medical meaning. Identity and meaning defined the substance, and prepared it for integrating the medication concept and its social use.

But pethidine's importance in history isn't only as a comercial success, but as an inspiration for organic chemistry internationally, a percursor of numerous substances with important clinical effect (for example alphaprodine, or ketobemidone) and this seminal capacity was amply recognised since the 1940's (Eddy, 1957). In 1944, Macdonald and Woolfe from Manchester had developed a simple technique to test different compounds analgesic activity. Mice were placed on a metal plate warmed to 55ºC and the timespan till limb movement was measured. If after 30 seconds no limb movement was observed it was concluded the compounds were actively curtailing pain. This simple technique would later be progressively refined by Nathan Eddy at the National Institute of Health (for a brief history of the NIH see chapter 4.1.), and it became known as "Eddy's hot plate method" (May & Jacobson, 1989). Macdonald and Woolfe kept working with analgesics, and developed a special collaboration with the Swiss company Roche. Macdonald and Woolfe's work with Roche was published in 1946, in an extensive article on the potential analgesic action of pethidine by-products (Macdonald, Woolfe, Bergel, Morrison, & Rinderknecht, 1946). This was a popular line of research for the pharmaceutical industry at the time, pethidine derivatives being studied at least by Roche, Merck and Lilly.

With this background, it isn't surprising that in 1954 (eight years after Macdonald and Woolfe's article) Paul Janssen, eager to follow through his success with dextromoramide, recognised pethidine as a molecule simple to work with chemically, and started developing

pethidine derivatives looking for enhanced potency in analgesic action (López-Muñoz & Alamo, 2009). Both morphine and pethidine had in their chemical structure a piperidine ring, and in Janssen's laboratory the idea that there was something inherently active in this structure became widespread (Stanley, Egan, & Van Aken, 2008). It is even said that "the piperidine ring became the main theme in the early series of symphonic drug compositions" (Schwartz, 1989, p. 55).

For non chemists, calling this piperidine structure a ring may suggest this kind of biological (maybe even in a sexual sense) metaphor for the drug activity that seems to permeate Janssen's drug development process. It reinforces this idea that the drug's spacial conformation was to match a specific spacial identity within the body. The concept of drug-receptor interaction was old, introduced at the end of the nineteen century, but was still gaining gradual acceptance during the fifties (Prüll, Maehle, & Halliwell, 2009). Nevertheless this kind of reflection, coming from pharmacology, would be new when applied to the central nervous system (ideas about central neuro transmission were still mostly electrical in the beginnings of the fifties).

In his 1965 article Janssen give us a description of the compound sequence that followed:

> In 1954 we were studying an extensive series of 4-phenylpiperidines related to meperidine [also known as pethidine]. One of the ideas was to try to increase morphine-like potency by replacing the N-methyl group of meperidine by other chemical moieties. This turned out to be easy: a Mannich reaction with normeperidine and acetophenone yielded the propiophenone derivative, R 951 (Table 11), which was found to be about one hundred times more potent as a morphine-like drug than meperidine itself (Janssen et al., 1958, 1959b). This interesting result, contradicting the classical belief that the N-methyl group was "optimal" for morphine-like activity (Eddy, 1959; Janssen 1962a,b), led to further experiments in this newly opened chemical field. Lengthening the ethylene side chain of R951 to a propylene chain produced the butyrophenone derivative of normeperidine, R 1187 (Janssen et al, 1960a). The first screening results of the hot plate method clearly indicated that this compound possesses highly unusual properties, the induced effects being both morphine-like and chlorpromazine-like (Table I1). (Janssen, 1965)

This synthetic, sequential, rational enterprise is again something that we know pleased Janssen in its no nonsense approach, but seems simplistic in our eyes. We seem to go logically and almost directly from pethidine, to R951, to R1187. Of course we know that the process took three to four years and hundreds of substances. The R number reflects the

number of compounds synthesised by Janssen's laboratory (the R was still a reference to Gedeon Richter). Between R951- the potent analgesic and the R 1187, the promising butyrophenone, there were 236 substances that were newly synthesised and extensively animal tested. This 1965 narrative also encloses the research project in the laboratory. In its simplicity it separates the research from the complexities of the social world. Financial interests and constraints vanish. Intentions and protagonists disappear. But we know that the laboratory is part of the city, and within its walls social forces persist. We know, for example, that the role of competition, and the safety of patents was one of the moving forces in this compound sequence. R951 and derivatives resembled compounds synthesised by Merck and Lilly, making their protected patent, and comercial chances, risky (Granger & Albu, 2005). Possibly one of the reasons behind the lengthening of the ethylene lateral chain that made R 1187 was this competitive search for a safer patent.

After the second world war most of the pharmaceutical industry was working in a similar way. Chemical advances permitted the synthesis of hundreds of new compounds. Often the impetus behind the construction of new compounds were theoretical understandings about the activity of some chemical structure. These were then tested using standard animal methods (as Eddy's hot plate), sometimes with surprising results. As we have seen with the pethidine example, although the original theories were then frequently questioned or even abandoned, the new chemical entities created new theories of their own and gave place to new derivatives. This was an industrial undertaking with hundreds of compounds passing quickly between the test tubes and mice. Although simple logical accounts were written up *a posteriori*, most of the progress depended on chance (Gaunt, 1977). Theoretical considerations were part of the research, and we can even argue that they were in a sense indispensable to the whole endeavour, but they were possibly less stable, less coherent, less logical than they appear in *a posteriori* narratives.

Animal models were a fundamental piece in this process. They offered an easy, rapid and inexpensive screening of the developed products. These empirical techniques embedded in theory redefined the compound, gave it a new meaning. They were constructed, as we have seen with the case of "Eddy's hot plate" method, through a very theoretical approach of the concept. In the hot plate example, the concept of pain was explored through the notion of burning sensation. Subjective perceptions had to be translatable in observable behaviour, that

gave the test objectivity - in this case the mouse limb movement. Progressive technical sophistication permitted standardisation and reproducibility. Finally quantification (in this case timespan measurement) permitted the intensity of the compound's activity to be compared.

In his 1965 article, Janssen explains the most important animal tests used in the development of haloperidol and the butyrophenones. From its combination we can start to see a third conceptual approach to the butyrophenones development - that we would call chlorpromazine *pharmachomimesis*, a similar concept to what some called *pharmacological isomorphism* (Matthysse, 1986). So, in Janssen's article, a picture emerges of a concept driven process, but where the original concept seems not to be an animal model of psychosis (as the amphetamine concept suggest), or just the enhancing of analgesic activity, but a pharmacomimetic approach, where finding and enhancing chlorpromazine-like behavioural/ motor activity became the main aim.

Again in a 1985 article there is no mention of amphetamine, the first lead concept detailed is the enhancing of analgesic properties from pethidine, and with the unpredicted first observation of a chlorpromazine-like activity in one of the compounds, a new concept started leading the substance synthesis.

> […] describing the birth in 1958 of haloperidol, at that time a completely novel major tranquillizer. Thus, although the original objective was met - viz. the synthesis of a more potent analgesic by structural modification of a 'lead' compound - the prepared mind, free to speculate, spotted the unexpected and wandered along an untrodden path. (Janssen, 1985)

Janssen was working with butyrophenones, that had a very different chemical structure from chlorpromazine (that was chemically called a phenothiazine). Regardless of these diverging structures, Janssen starts trying to find, through animal models, those butyrophenones that could more closely resemble chlorpromazine in their actions and could consequently have neuroleptic comercial potential.

> Subsequent studies revealed the fact that it is possible by "molecular manipulation" of R 1187, to increase its chlorpromazine-like potency while decreasing the intensity of its morphine-like effects (…)(Janssen, 1965)

Although the capacity to play with the chemical structure in order to fine-tune its influence in behaviour seems to us surprisingly complex, this description impresses by its simple form. Again Janssen's communication style may be a factor here. His straightforward approach may be deliberately hiding a strenuous endeavour. Nevertheless, clearly, both in his

1965's version and in that of 1985, chlorpromazine's role in creating haloperidol is unequivocal. Certainly, to understand how and why haloperidol was created, we have to understand the reasons for success of its most known predecessor - chlorpromazine.

Chlorpromazine had been developed by Rhône Poulenc in December 1950, eight years before haloperidol, and started to be marketed in 1952 (Sneader, 2005). Animal testing played a crucial role in its development. Courvoisier used animal models testing the anti-histamine central effects - namely "potentiation of general anestesia, potentiation of analgesics and effects on conditioned-reflex behaviour" (Swazey, 1974, p. 91). In the latter test, the rats were previously taught how to climb a rope to a safe platform after hearing a bell. In the absence of climbing a painful stimulus was administered through the electrified floor. After the rats were given chlorpromazine, they started failing to climb the rope despite the bell sounding (Swazey, 1974, p. 93). Effects on conditioned-reflex behaviour would gain historical importance an an indication of the drugs most central effects (related to the brain), and also, as we will see in this chapter, as a proxy for more complex human behaviour.

In the next few years, while Delay and Deniker were demonstrating the importance of chlorpromazine in psychiatric patients and constructing the concept of neuroleptic, Baruk was experimenting with animals and inducing catalepsy (Healy, 2008, p. 420). Catalepsy was a mixture of muscle rigidity and posture fixity that had been associated with Parkinson's disease.[7] He was well positioned to do that, as he was interested in disturbances of movement in psychiatry well before the neuroleptics (De Jong & Baruk, 1930) and had been promoting animal studies as a way of understanding the basis for psychological data and treatment development (Bovet, 2012, p. 118). Biography, previous research and theoretical stances sometimes leave researchers in a privileged position to formulate theory from novel technological developments (for another related example see chapter 3.3).

By 1954, chlorpromazine was introduced to the American market accompanied by a tremendous marketing effort by Smith, Kline & French that included everything from political lobbying with state legislatures to televised sessions. As sales representatives were judged inadequate by the marketing department, a separate task force was created to work with lobbying groups and legislators. One member was assigned to each state capital. working with state governments at many levels. State Hospital administrators received

[7] The English doctor James Parkinson (1755–1824) had proposed in 1817 a condition affecting motility characterised mainly by muscle rigidity, akinesia, and tremor (Shorter, 2005).

extensive training from Smith, Kline & French including presentation techniques and number organisation so they could promote their treatment program. Quantity discounts and cheaper higher dose tablets were offered to mental hospitals. Smith, Kline & French sponsored international symposia, and published booklets for the family physician (Swazey, 1974, pp. 203-207). This enterprise was so impressive that 14 months after its introduction it was estimated that 4 million persons had been medicated with chlorpromazine (Valenstein, 1998, p. 169).

Janssen would later describe psychiatrists in the fifties as being mostly involved with psychotherapy and therefore resistant to psychopharmacology, that was, in his view, one of the major barriers to his work (Janssen, 1992). Indeed, some would say this may have played a part in the delayed introduction of haloperidol in the United States. Nevertheless, by the end of the fifties, chlorpromazine had shown the existence of a burgeoning profitable market for chlorpromazine-like compounds.

Also, during the fifties the profile of side effects of chlorpromazine was well studied: "generalized cogwheel rigidity, tremor, mask-like facies, and marked motor retardation" (Azima & Ogle, 1954) were described. These motor abnormalities closely resembled Parkinson's disease, and would also be called extrapyramidal side-effects (Steck, 1954) (see Chapter 3.3.).

Screening for these chlorpromazine-like characteristics (or phenothiazine like-characteristics) many animals methods were used, these included the hot plate method described above, but not exclusively. Let's look at the main animal tests described as being used in butyrophenones development (Janssen, 1965) :

- Hot plate method in mice - described above.
- Catalepsy-ptosis method in rats. Catalepsy is the same phenomenon that had been extensively studied by Baruk within his chlorpromazine's studies. A state of immobility with waxy flexibility that the researcher would try to objectively rate. Ptosis is a falling of the eyelid. Both gross behaviours were observed and quantified.
- Jumping box method in rats and dogs. Janssen adapted an apparatus, first proposed in 1932, for creating and then testing conditioned responses in animals, similar to the one used by Courvoisier. The animals were previously conditioned to jump when they heard a sound stimulus. Failure to jump would be punished with an electric stimulation.The test

screened drugs that interfered with learned conditioning, that delayed or stopped dogs jumping. Janssen extensively details the experience in the interest of reproducibility (Janssen, Jageneau, & Schellekens, 1960).

- Anti-amphetamine method in rats- Amphetamine was known to produce repeated stereotyped behaviours in high doses, and rats would show compulsory gnawing movements. The drug's dose necessary to block these movements was assessed.

- The anti-apomorphine method in rats. In a similar way, Janssen describes the apomorphine behavioural effect in rats as gnawing, and the capacity to block it was measured.

- The anti-apomorphine test in dogs. In dogs the apomorphine provokes vomiting, and the drug dose necessary to inhibit this vomit response was measured.

- **Δ**W-test in rats- The capacity to change the rats food consumptions was assessed.

- Open field test in rats - Rats were placed in a black painted arena, with a loud and persistent noise. The scientists noted the number of times the animal showed some specific behavioural phenomena as ambulation or defecation. The dose of drug necessary to curtail these events was measured.

- Anti-epinephrine and anti-norepinephrine test in rats - The capacity to block overdose effects of both catecholamines.

- Anti-tryptamine test in rats- Tryptamine in high doses would provoke clonic seizures of the forepaws. The dose administered able to block the seizures was measured.

- The Noble and Collip drumming procedure. Measured the drugs capacity of protecting dogs from the traumatic shock induced by the test.

This was not a simple process and encompassed quite an extensive battery of test subjects. Animals included mice (1), rats (9) and dogs (2). Tests were developed in a way to maximize objectivity, and quantification, so to maintain inter-rater reliability. This implicated complex standardisation of instruments, techniques and rating approaches. Everything was noted and published from room temperature during the open field tests for rats (Janssen et al., 1959), to the measurements and materials of the jumping dog boxes (Niemegeers & Janssen, 1960). Many other tests were developed and discarded (Janssen, 1965). The means necessary to develop the animal testing methods, and to accurately use them to screen hundreds of compounds were certainly considerable both in human and technical resources. Some tests

were trying to assess more complex behaviour, but the majority constituted a thorough assessment of the animals motor activity, looking for a certain way of interfering with that activity. A second group of animal testing included the drug antagonist tests, including, maybe specially, amphetamine but also catecholamines, apomorphine and tryptamine. Drug antagonist tests were interesting as they didn't have a clear theoretical layout (the concepts of receptors and neurotransmitters were incipient see chapter 4.), but helped characterise the substance.

From these mixture of tests a capacity emerged for screening changes in animal motor behaviour that closely resembled the drug-induced parkinsonism that had been described with chlorpromazine. And indeed some of these tests were very similar to what Courvoisier used to screen for chlorpromazine. Specifically the Jumping box method is reminiscent of the rope test she used to study interference with conditioned response. Antiemetic activity had also been studied in chlorpromazine by Couvoisier, also through the use of apomorphine in dogs. It was concluded that chlorpromazine was an important vomit supressor (Swazey, 1974, p. 96). Finally, amphetamine antagonism was also studied by Courvoisier in 1953. Chlorpromazine antagonised amphetamine (Dundee, 1954), in a similar way to Janssen's new butyrophenones.

The new R 1625 was chemically formed on the 11th February 1958. The researcher was Bert Hermans (Granger & Albu, 2005). Two days later it was being injected in mice and submitted to a battery of screening tests including Eddy's hot plate. In the complete screening assessment haloperidol showed to be 10 to 75 times more potent than chlorpromazine (Janssen, 1965) including no limb movement in Eddy's hot plate, long lasting catalepsy and no conditioned avoidance response in the jumping box method. During "Open field test in rats" haloperidol (similarly to chlorpromazine) decreased ambulation, rearing and defecation. Conclusion was the drug affected (like phenothiazines) the animal's capacity to react to environmental stress with exploratory behaviour (Janssen, Jageneau, & Schellekens, 1960).

As we have described, during the 1950s it was increasingly recognised that chlorpromazine, and the other neuroleptics, affected motility in a specific way. At the time, it was difficult to disentangle what were beneficial therapeutic effects of neuroleptics, from what were worrisome side-effects, they came entangled together and were mostly recognised as such. How important were these changes in motility that would be called extra-piramidal?

We will explore these questions and their multiple answers in chapter 3.3 and 3.5. Independently from the position he would later take on this discussion, Janssen knew how chlorpromazine performed in the animal tests, so in the hundreds of compounds that were going out of the test tubes he kept those that would most favourably compare with chlorpromazine's behaviour. Haloperidol was then recognised as the promising consequence of this complicated process.

> On the basis of the results obtained in this battery of screening tests (Table IV), it was concluded that haloperidol and trifluperidol possess a series of pharmacological properties that are quite comparable to the properties of several neuroleptics or major tranquillisers derived from phenothiazine. (Janssen, 1965)

The amphetamine thesis, this idea that amphetamine could provoke a similar state to schizophrenia in animals, was what is called by some a "symptom similarity animal model". These are difficult to develop, as animals lack the self described experiences that characterise most major psychiatric disorders (Geyer & Markou, 1995). Also, psychiatric disorders are so complex, touching most spheres of human activity, that finding animal behaviour that could serve as model for those experiences seems restrictive (Geyer & Moghaddam, 2002). The chlorpromazine idea, the search for a substance that would have chlorpromazine-like characteristics is sometimes called "pharmacological isomorphism",or pharmachomimesis (Matthysse, 1986). Although this is useful as a way of finding new drugs within the same medication class, this approach can be somewhat conservative and, is accused of being incapable of creating completely new compounds.. However, pharmacologic isomorphism, besides being quite productive in psychiatry, has a sometimes surprising quality, it gives us ideas, gives us ways of thinking about mechanisms of therapeutic action - from there hypotheses for mechanisms of illness may follow. If two medications have the same pharmacological effect, then there's something in common between the two medications that pushes them to act in a similar way. In searching for commonalities between the compounds, one may find keys to understanding their effect.

So compounds were synthesised in big numbers, and were tested garnering those that changed animal motor behaviour in the ways described. Accordingly, haloperidol and other neuroleptics, namely butyrophenones, were developed screening for the exact same changes in posture and movement that were already provoked by chlorpromazine and other phenothiazines. Phenothiazines and butyrophenones didn't share a chemical proximity, but

their effects in motor behaviour were similar, both specifically promoting drug induced parkinsonism (extrapyramidal side-effects).

> All neuroleptic agents except the depleting agents reserpine and tetrabenazine are potent antagonists of amphetamine with respect to the induced compulsory gnawing effect (23) and spontaneous locomotor activity (35). Amphetamine antagonism occurs at largely the same doses as the blockade of conditioned avoidance behaviour (23). (van Rossum, 1966a)

When van Rossum underlines this common action of both butyrophenones and phenothiazines in his line of argument in favor of the dopamine hypothesis for schizophrenia 8 years after the creation of haloperidol, we should remind ourselves that anti-amphetamine activity was a factor in their laboratorial construction. Pharmacological isomorphism has unintended consequences, commonalities gain significance because they are commonalities, minimising the fact that some of these commonalities exist by design. After what seems to have been a very empirical construction searching for the same characteristics, the theoretical stance tries to form an explanation for the result, exactly from this characteristics. Interestingly, in van Rossum's example, as discussed in the above quotation, the dose needed to act as an amphetamine antagonist being the same that the one needed to block conditioned avoidance behaviour is a very effective argument. Here we see why the jumping box and similar testing were important. As the example showed, they were viewed as the closest thing to therapeutic antipsychotic action. The drugs capacity to make the dog (or the rat in Courvoisier's work) wait passively for punishment, instead of using learned behaviour to escape it, became, in a way, a proxy for therapeutical neuroleptic action in humans. This idea that neuroleptic activity should encompass a profound indifference to exterior stimuli was still very present in the fifties and sixties, and would only slowly change as neuroleptics (or Major tranquillisers) transform themselves into antipsychotics (we look at the beginnings of these transformations in chapter 2.6.). In van Rossum's quote the neuroleptic dose for both curtailing learned avoidance responses and anti-amphetamine activity being the same, reinforces the idea that the mechanism of therapeutic action (supposedly responsible for the first) was possibly the same as the mechanism for the anti-amphetamine activity.

The word chosen in this quote by van Rossum for this minimising of the conditioned behaviour - blockade, is quite telling about the inner reasoning of the scientist as we will explore further in Chapter 5.

Interestingly we end this first chapter with the text that will interest us most in the last chapter of this work. The moment where van Rossum, so many years later, will propose the dopamine hypothesis for schizophrenia, is also the moment where he looks back to the moment we are describing now- haloperidol synthesis and animal testing, citing Janssen's work. This is why this thesis starts here and ends with van Rossum, as those moments are inextricably connected:

> Indeed a number of the classical screening tests, including catalepsy and reversal of apomorphine induced gnawing, are now generally considered to be models for extrapyramidal side effects rather than for antipsychotic potential. (Ellenbroek & Cools, 2003)

Since the eighties some defend these common features of the first two major families of neuroleptics, namely extrapyramidal motor side-effects, require dopamine antagonism in the striatum. If so, these screening tests were already, in some sense, laying the ground for the dopamine hypothesis for schizophrenia.

> The key element of all of these tests is now evident - they require a striatal dopamine blockade, possibly combined with an inhibition of psychomotor initiative in the limbic system.(…) Indeed, that neuroleptic agents antagonise at striatal dopamine receptors reflects their undoubted ability to induce extrapyramidal side effects - dystonias, parkinsonism, tardive dyskinesias. (Costall, Domeney, Kelly, & Naylor, 1991)

As we will see in this research, dopamine antagonism would later be proposed as the biological basis for the therapeutic action of neuroleptics, but some can argue that dopamine antagonism unites neuroleptics just because neuroleptic development depended on animal models that selected exactly for that (specifically D2 antagonism). But let us not get ahead of ourselves, it was 1958, central nervous transmission was thought to be mostly electrical, receptors were hypothetical, and the dopamine hypothesis hasn't even been proposed at this point in the historical timeline.

As here, during this thesis we will frequently hesitate before judging the past. As, in a sense, intentions stayed with the actors (mostly dead now), and actions existed in the historical context, modulated by biographies, social forces, instruments, theoretical stances, and so forth. Nevertheless, injustices shouldn't be forgotten, and actions that hurt our retrospective perspective should be clearly addressed. Animal testing, a key feature of pharmacologic research, was at the time, as we have seen, unlimited and unregulated. This wasn't restricted to Janssen's laboratory but widespread in the industry's day to day activity. From mice to dogs, how many animals were hurt in the development of these screening

batteries? How were they born and how did they die? What kind of life did they live in Janssen's laboratory? As they were repeatedly burned at 55 ºc (as in Eddy's hot plate), or electrocuted in the jumping box method, did they receive any kind of care?

Haloperidol's construction starts with this complicated story, where elements of conceptual research, vision and leadership, combine with chance and serendipitous events. This wasn't so unusual at the time. As we have seen, three concepts dominate the narratives later told about the compound's synthesis. Amphetamine antagonism, enhancing opioid activity, and searching for chlorpromazine-like characteristics.The latter arguably being the one with more explanatory power, but the first one having strong implication in theory construction.

Regardless, constructing haloperidol wasn't only about the chemical structure of the butyrophenones, or the biological effects in animal models. For the substance to become an active drug, it had to define and promote social uses and consequences, it had to gain significance. From the laboratory, haloperidol exits already embedded in chlorpromazine's significance, as Janssen pushed the substance to find a role as a neuroleptic. But neuroleptics were at the time a very spacious concept, imprecise and equivocal. They didn't yet have a clear indication of use, neither a definite mechanism of action. To build its symbolic power as a medication, and its comercial success, haloperidol had to reconstruct a net of meanings, from the disorder itself to the reasons for its therapeutical activity.

Concentrating on the action of one man, or a few men, in this discussion can be seen as silencing or at least underestimating potent social forces, and consequently isolating Janssen's actions from their historical, cultural, and geographical context. We shouldn't forget that Janssen's ability to influence this complex, international, process stems from the unique position of power he was in, and this relates primary to his multilayered identity. Janssen was a European in the center of a declining colonial empire (Janssen Pharmaceuticals benefited directly from the falling African empire). He was a Belgian, born at the linguistic frontier and was specially able to create bridges between Germanic and French scientific traditions. He was a man in a world where women weren't taken seriously. He was the son of a rich man – who financed the start of his company. He was a researcher unconstricted from animal rights concerns. He was a pharmacologist in a world where patients rights weren't recognised, at least to the extent they are today. As it sets out to construct the history of the dopamine

hypothesis, this thesis acknowledges that social identities, in their diversity, impact knowledge construction.

2.2. Regulatory context

Between 1957 and 1962, processes for the introduction of new drugs, and their governmental control, were irreversible transformed. Thalidomide market introduction began in 1957, and the legislative reform that institutionalised the oversight practices of the American drug agency took place in 1962.

Haloperidol was created on February 11, 1958 (Granger & Albu, 2005), in the midst of this overhaul. As we will see over the next few pages, the methodology used in haloperidol's trials, the clinical indications and the safety profile around the drug underwent important changes in these early years of the substance. It is important to note that those changes reflect other broader social transformations. After the laboratory development of R 1625, the social construction of haloperidol, as a drug with therapeutic action, was based on empirical data from the first clinical trials, but also on negotiated interests and perspectives of the various stakeholders. Tensions between safety and efficacy, between scope and specificity of therapeutic action, between individual clinical observation and randomised controlled trials were, as we will see, being negotiated between all the various protagonists with a voice in this process.

The first administrations of haloperidol to humans took place less than two months after its laboratory synthesis, more precisely five weeks later (Granger & Albu, 2005).This speed, impressive to our contemporary gaze, while implying the easy transition of newly synthesised compounds between the pharmaceutical industry and the clinical world, possibly also reflects the absence of institutionalised safeguard measures. Could it be ethical to start clinical trials so early? Was it?

Other questions around the release of haloperidol to humans include: how well known were the risks associated with the introduction of a new drug? Even if hypothetical risks were known, how present could they be in the decision making process of Janssen Pharmaceuticals?

Judging history and its protagonists is a complex task of dubious value, yet medical history cannot scotomize injustices or abuses. A possible approach would compel us to be aware of the *horizon* as seen by the actors. Reflecting on the ethical aspects of the early introduction of haloperidol by Jansen Pharmaceuticals, implies an attempt to understand their point of view globally, acknowledging the diversity of options available at the time, exploring

the perception they had of possible consequences, and questioning what was and what could have been valued in the decision-making process. A large part of this reflection is beyond the scope of this research, nevertheless if we are interested in the way that medical knowledge was constructed, we cannot forget the risks that were taken in this construction, especially when these risks are taken by people who were unaware of them, and whose consent had not often been obtained.

The medical term phocomelia describes a significant decrease in the size of the arms or legs due to the absence of long bones, but keeping the proportion of the hand and fingers. The severity of phocomelia ranges from the complete disappearance of long bones, leaving the fingers attached directly to the trunk, to less severe forms of diminished limbs. Phocomelia of the upper limbs would become the stereotypical image of thalidomide, but birth defects were not limited to limbs and were also described in the face, eyes, ears, genitals, heart, kidney, and gastrointestinal tract (Vargesson, 2015).

Grunenthal started testing thalidomide in early 1954 (Lenz, 1988), and was introduced to commercial markets in 1957, 4 months before haloperidol's creation. The swift start of human experiments after laboratory synthesis, and the insufficient professionalisation of these trials (although common practice), was not consensual, even at the time. An article in the *Der Spiegel* published in 1962, references Professor Wolfgang Heubner, deceased in 1957, as expressing a clear critique of these unsupervised procedures.

> Daß ein Stationsarzt ein neues Mittel verabreichen läßt und nach einem halben Jahr über die günstigen' Ergebnisse in einer medizinischen Wochenschrift berichtet, genügt wirklich nicht. (Heubner W., cited in"Gefahr im Verzuge," 1962)[8]

In 1957, a drug's market introduction was a simple, easy, inexpensive procedure, mostly grounded in the good faith and reputation of industry and clinicians. The same informality that had led to thalidomide was believed to continue with haloperidol, or that was the initial expectation.

Grunenthal introduced thalidomide under the name Contergan in West Germany, recommending it for a wide range of indications from insomnia to morning sickness in the first few weeks of pregnancy. The areas of clinical practice were so broad and unspecific that

---

[8] The present, all-too-typical approach, whereby a practicing physician gives out a new drug and then reports on the "favourable" results in a medical journal a half year later simply does not suffice (translation in Daemmrich, 2002).

Grunenthal associated the use of thalidomide with images of a peaceful nature, promoting thalidomide as a break from the busy life (Daemmrich, 2002). Such wide indications are similar to the socio-cultural perspective on neuroleptics in the 1950's, specially chlorpromazine, as will be shown in our research.

Between 1957 and 1961, when a large number of children were born with birth defects including, but not exclusively, phocomelia, the teratogenic etiology wasn't immediately recognised. It was only in 1961, four years after its introduction on the market, that the relationship between the epidemic of congenital alterations and thalidomide was established. Interestingly, this link was identified almost concurrently by two clinicians working in two opposite parts of the world: Widukind Lenz in West Germany and William McBride in Australia (Vargesson, 2015).

In hindsight it is difficult to understand whether this relationship could have been established earlier. It is difficult to determine if the non-recognition by industry and institutional supervisors stemmed from gross negligence or tragic ignorance, and hard to ascertain if the consequences of such a calamity could be foreseen as a possibility before the event occurred.

Widukind Lenz argued that a drug's potential risk to the foetus was already recognised in the late 1950s (1988). Lenz references, among other authors, Ancel, who had carried out an extensive review into this at the beginning of the decade (Ancel, 1950), along with calls in the literature for a more methodical study of the effects of drugs on early development (Willis, 1958).

In haloperidol's path to become a drug, there's a peculiarity with important consequences. The way in which its reception diverged on both sides of the Atlantic created differences in the practice and theory of psychiatry, between Europe and the United States. The history of thalidomide shows us that haloperidol was not a unique case

In September 1960, the American firm Richardson-Merrell submitted thalidomide, under the name Kevadon, for FDA approval. At the time, the FDA had only 11 medical officers, 4 of them part-time (Daemmrich, 2002).To reinforce this small team, Frances Kelsey was hired that same autumn, and the thalidomide/Kevadon dossier ended up in her hands. It was Kelsey, who after a long and complicated process, rejected thalidomide's application for the American market. The various reasons proposed for this rejection ranged from concern

about an increased risk of damage to the peripheral nervous system, an intuition about the teratogenic potential and, perhaps above all, a feeling of distrust towards the promoter (Carpenter, 2014, p. 222). We can read in her notes from a meeting with Richardson-Merrell representatives, held in March, 1961, the importance that Kelsey attached to respectability and trust.

> I had the feeling throughout the day that they were at no time being wholly frank with me and that this attitude has obtained in all our conferences etc. regarding this drug. (Kelsey,1961 cited in Carpenter, 2014, p. 221)

The rejection of thalidomide's application to the US market reflects not only the increasing inflexibility of a progressively professionalized FDA, more demanding in terms of the complexity and extent of empirical data, but also the importance of reputation. The way a promoter of a drug had behaved in the past was scrutinised from an ethical point of view. The degree of availability and honesty in the disclosure of clinical data seems to be paramount at this point in history.

At the same time a congressional process in the United States, resulted in the 1962's "Kefauver-Harris Amendment". The legislative change required the inclusion of extensive data, not only on safety but also on the effectiveness of drugs, before a market entry could be granted. Several protections of the rights and interests of patients were legally recognised, namely in relation to the exposure of pregnant women to substances with teratogenic potential.

A new, powerful FDA, whose practices had been legitimised by the legislature, emerged and became the model for international supervision. In several other nations, including England and France, government control of the pharmaceutical market quickly became more formal (Carpenter, 2014, p. 264).

Understanding comprehensive historical transformations often ends in a tension between events and protagonists of abrupt transformations, on the one hand, and the identification of less visible but more pervasive processes, on the other. These processes, without clear protagonists, often derive from subtle affinities or hidden conflicts between the interests at play. Although the change in pharmaceutical oversight practices is often attributed to the thalidomide scandal and the Kefauver hearings, others prefer to focus on earlier changes in the organisational practices of the FDA – both approaches have merit in assessing such shifts. Since the Second World War, the supervising body had been developing a

growing concern about the safety, therapeutic value and regulation of clinical trials (Carpenter, 2014, p. 119). Those that see the abrupt transformations of these years as the result of a process of bureaucratisation and progressive professionalisation of the supervising institutions, point to the frustration of the pharmaceutical industry (namely Smith, Kline & French) with FDA rigidity and delays, predating thalidomide's disgrace (Carpenter, 2014, p. 119).

Regardless of the drivers of change, haloperidol was born at the center of this transformative moment. The pharmaceutical industry in which it was created in 1958 was not the same almost a decade later when it was finally introduced into the North American market.

The professionalisation of clinical trials lead to the construction of a new device, at the intersection between the clinical, academic and industrial worlds. This thriving scientific field was built to answer simple questions on efficacy and safety, but was less invested in questions about disease mechanisms. Thalidomide's failure, associated with broader historical processes, contributed to the emergence of this new order. The nation state found a new role through its regulatory entities, but maybe more importantly there seemed to be a triumph of empiricism (Pignarre, 1997, p. 34).

Paul Janssen would later regret the transformations of supervisory bodies that had emerged from concern for patients' safety and rights. During this research, his initial resistance to randomisation, and to double-blind trials became increasingly clear. Such professionalisation clashed with his bold and simple vision of clinical efficacy. Another important reason for this opposition was the financial cost that the new rules required. If what he calls "bureaucratic requirements" were already in place in the 1950s, the creation of haloperidol may had been impossible (Janssen, 1992).

> In 1953 the cost of research and development of a new chemical entity was a few tens of thousands of dollars approximately. Fortunately for me because that is all I had. in the case of haloperidol probably even less - maybe 20,000 -30,000 everything included, which in those days was considered an enormous amount of money. (Interview with Paul Janssen cited in Healy, 1998b)

In 1958, when the clinical trials of haloperidol began, the young pharmaceutical company created by Janssen already had some products on the market. Lomotil, for example, marketed in partnership with Searle in the United States, was the source of an important

financial income (Interview with Paul Janssen cited in Healy, 1998b). But the industrial and clinical relevance of Janssen Pharmaceuticals was still far from the position it would attain in the following decades, so Janssen's concern with the costs of development and market introduction are unsurprising, from his particular perspective, at that precise moment of Janssen's development and history. Much of the firm's future commercial and scientific success was gained precisely at the expense of this then newly synthesised substance - R 1625.

2.3. Choosing Bobon

Some say the secret for Janssen Pharmaceuticals' impressive rise came from Paul Jansen's management style, and the close relationship he developed with his team members (Lewi & Smith, 2007). Still, Janssen described himself as having little pleasure in human contact, and did not yet have a network of clinicians to facilitate a rapid transfer of products between the laboratory and the clinical setting. Andre Mullie, said to be a friend from his time in medical school, was chosen to serve as a bridge, being responsible for clinical trials and bringing together a group of psychiatrists who were both interested in and capable of testing haloperidol. Janssen continued to closely monitor the testing of his products and a few weeks after the development of haloperidol, Janssen visited the psychiatrist Jean Bobon in Liège, a city just over 100 km from Janssen's headquarters at Beerse (Missa, 2010).

Some authors remind us that the selection of lead researchers is one of the main ways that the pharmaceutical industry influences clinical research (Valenstein, 1998). Nevertheless, we don't know much about the specific reasons that led to Liège being chosen to carry out the first trials of haloperidol, or about the precise qualities that Mullie and Janssen were looking for in a researcher. It is likely we will never know precisely which characteristics in Bobon's path and personality led Mullie to suggest his name to Janssen, or why Liège University was selected for the clinical trials.

Jean Bobon was born in Thun (on the French side, but close to the Belgian border) and studied Medicine at the University of Liège (Mertens, 1992). Curious, spirited and open-minded, he had founded the student magazine "Le carabin" in college, where he published several psychoanalytical papers and was the reason for a brief correspondence with Sigmund Freud in 1936. Before the Second World War, he started his internship in psychiatry at the "clinique de Glain" (one of the first institutions in Belgium without involuntary commitment) and he also introduced electroconvulsive therapy in Belgium (Mormont & Englebert, 2019).

Bobon's real interest was the psychopathology of expression. "Expression" here referred to the way thoughts and feelings found concrete form in the material world. It was not limited to psychopathology of verbal language, of the word, but it also included graphic creativity like drawing and painting (Bobon, 1962, p. 3). Bobon wasn't only interested in language in mental illness, in its strictest sense, but also, and perhaps above all, in the visual arts. He assembled a vast collection of works, among anonymous and recognised authors, and

built a wide network of elective affinities that spanned from Gaston Ferdière, the eccentric psychiatrist of Antonin Artaud, to Salvador Dali whom he met in 1956.[9]

Maybe because he had these numerous areas of interest, we see Bobon repeatedly described as an optimistic young psychiatrist open to change(Missa, 2010; Mormont & Englebert, 2019). Interested in technology and novelty in general, he even built a lie detector, and is said to have been the first in Europe to install video surveillance cameras in his wards. He believed a cure for schizophrenia was possible and represented a fundamental change from previous generations, more influenced by German psychiatric skepticism, of which Divry was an example. Paul Divry emerges from contemporary descriptions as a counterpoint to Bobon, as a figure more interested in pathological anatomy than in the clinical encounter, and an "austere", "cold", "meticulous" man (Mormont & Englebert, 2019).[10]

> Well Divry was the professor of psychiatry in Liège and he was super-sceptical. He would practically never use the word schizophrenia. I remember that he once told me: don't believe Bobon: I am telling you, young man, nobody will ever cure schizophrenia. What he really meant was chronic hebephrenia because only patients with a very low IQ who were chronically ill were in his opinion probably suffering from schizophrenia. All others were doubtful and he was not interested. He was constantly looking at slides of brains and he was more interested in the shape of the brain of a human being than in psychiatry. He was a strange man and he played no role at all in the development of haloperidol. (Interview with Paul Janssen cited in Healy, 1998b, p. 51)

In the descriptions of Bobon and Divry, we see how their differing characteristics and personalities gather with their perspectives of psychiatry and their general attitudes towards scientific research. Together, they seem to form contrasting positions in an almost stereotyped manner. While one was dynamic the other was austere, while one was open to novelty the other was skeptical. Bobon was interested in words, in the expression, and invested in the construction of collaborative networks, Divry was interested in brain morphology, dedicating his life to the laboratory's solitary work.

---

[9] Jean Bobon returned from this meeting with Salvador Dali with the following curious note "Pour mon ami/ Le Docteur Bobon/ 50 secretos « magicos » PARA PINTAR/Vive la/ GALADésoxyribonucléoporotéide" (Mormont & Englebert, 2019).

[10] Christian Mormont recounts that, after Divry's death, an impressive collection of histological samples, post-mortem sections of his patients' brains, would be discovered. Having no interested parties, they were donated to L. Van Bogaer (Anvers)(2019).

These postures, tendencies or attitudes are materialised in the concept of schizophrenia that the authors subscribe to. If Bobon seems to believe in a broad concept of schizophrenia with diverse prognosis and responding to therapeutic interventions, Divry seems to have a view of schizophrenia more influenced by the concept of degeneration, reserving the diagnosis for patients with very low functionality and poor prognosis.

Through these extreme positions, we can see how the concept of schizophrenia was increasingly divided in the late 1950s. From the vast (even vague) construct that Bleuler and Kraepelin had constructed a few decades earlier, a new schizophrenia was emerging at the time of the first haloperidol trials, which was represented above all in the work of Kurt Schneider (more on this in chapter 2.6). The divergence between Divry's and Bobon's views seems to reflect this tension, which was probably also generational.

For Janssen, it was seemingly easy to take a position on this spectrum. Schizophrenia as linked to poor cognitive functioning and an inevitably poor prognosis didn't interest him. On the one hand, the classic schizophrenia that Divry subscribed to was in fundamental opposition to the animal and experimental model of amphetamine psychosis that seemed to be important to Janssen (see chapter 2.1). On the other hand, it would certainly be more difficult to intervene pharmacologically in an illness where functions were so persistently compromised that the prognosis was seen as dreadful. More acute cases, with better previous social functioning, certainly offered a more fruitful possibility of drug response, placing him more in line with Bobon's ideas.

In addition to his open attitude to novelty and technology, and his perspective on schizophrenia, closer to that of Janssen, there was another characteristic of Bobon that could be seen as a convenient advantage in leading a new clinical trial - his personal ambitions. Bobon had enemies within the university department, and succeeding Divry, as he had always wanted, would not be easy (interview with Christian Mormont, Liège, February 27, 2019).

Publishing positive results from the haloperidol studies could help climb the medical hierarchy (Missa, 2010), a desire recognised by Janssen himself:

> But Jean Bobon who was his first assistant, was eager of course to get Divry's job because Divry was approaching retirement. He was eager to publish something because he had never published and that played a role. I had never been in contact with psychiatrists and I was very pleased that there was at least somebody who was willing to look at haloperidol. (Interview with Paul Janssen cited in Healy, 1998b, p. 51)

In Janssen's quote, and in the pleasure he seemed to feel in meeting Bobon, we can foresee the impact that their first meeting would have on their (long) subsequent relationship.

In addition to the figure of Bobon, the university clinic in Liège met a set of conditions that may have promoted its choice. In our interview with Mormont, he depicted the story of the " clinique de Glain", where the university had its patients:

> Notre-dame, à Glain, n'était pas, à l'origine, destinée aux soins des malades mentaux. C'était une clinique, notamment obstétrique. Daniel Bobon [fils de Jean Bobon] y est né, son père y faisant une espèce d'internat. Toutefois, Divry, dès 1928, a participé au projet, mis en oeuvre à Glain, de soigner des malades mentaux ailleurs que dans un asile et sans collocation. Ce projet pionnier a sans doute assuré la position de Divry à Glain, ce qui a permis que là se constitue plus tard une partie du service universitaire de psychiatrie, localisée dans une clinique privée. C'est, à ma connaissance, après la guerre, que la clinique a pris une orientation plus spécifique, toujours sous l'influence du Pr. Divry. A cette époque, et jusque dans les années 60 [1964?], le service appelé "Clinique psychiatrique" désignait un enseignement, non un lieu. Quand je suis entré dans ce service, il n'y avait aucune possibilité d'hospitalisation organisée par l'université ou la faculté de médecine. L'accès aux malades, nécessaire pour l'apprentissage de la clinique, était le fruit d'un arrangement avec l'Assistance publique qui donnait accès aux malades de ses deux hôpitaux: Volière et Sainte-Agathe. Toutefois, si les "universitaires" avait le droit d'examiner ces malades, le professeur de psychiatrie n'y avait pas de "lits". Ceux dont disposait le Pr Divry (les lits Divry, puis Bobon) étaient à la clinique de Glain. Ces lits ont acquis un statut de service universitaire puisqu'il n'y avait pas d'autres possibilités offertes par la faculté de médecine. Les candidats psychiatres faisaient un internat ou une partie de leur formation dans ce cadre.
>
> La collocation était à l'origine de la plupart des internements à l'asile, et en l'absence de traitements efficaces, l'internement était souvent très long ou définitif. J'ignore le régime financier des colloqués. Je pense que s'ils avaient des biens, l'Assistance publique récupéraient les dépenses faites à l'asile. Pour les indigents, je suppose que l'Assistance publique prenaient les soins en charge. A Glain, l'hospitalisation était payante. Je ne dirais pas que la population y était généralement nantie. Ce n'était pas une clinique de luxe!! Mais les familles pouvaient assumer les frais. (Interview with Christian Mormont, Liège, February 27, 2019)

In this description of the "Clinique de Glain", I would highlight two characteristics of interest to anyone planning to carry out a clinical drug trial. On the one hand, it was a clinic where people were admitted voluntarily (it was actually one of the few places in Belgium at the time where the mentally ill were admitted mostly voluntarily). On the other hand, it was a private clinic where, in most cases, the expenses were borne by families. Together, these two

characteristics conditioned a higher pressure for therapeutic results. Quite possibly the cases selected for Glain (as opposed to the large asylum institutions) were thus oriented as they were likely to have a good prognosis from the start. It was crucial to have therapeutic results good enough to allow early discharges and a high turnover (interview with Ferdinand Goffioul, Liège, March 01, 2019).

The psychiatrist Georges Lanteri-Laura has shown how, in psychiatry, the conditions of observation are central to the subsequent theoretical construction. The rules of private establishments, where alienists, like Esquirol, were working in the first half of the 19th century, led to a social and economic selection. This process favoured the admission of patients whose social contexts were advantageous and whose clinical picture seemed more treatable. It is from these conditions of observation that the main theoretical body of psychiatry, in the first half of the 19th, century was built. These favourable conditions of observation would be the main reason for the therapeutic optimism of the founding authors of French psychiatry, before the pessimism of Morel's *démence précoce* (Lanteri-Laura, 1972).

As stated, "La Clinique de Glain" was a health unit with chosen patients, both from a more strictly clinical point of view, but also from a social and economic point of view. Moreover, there was a strong pressure for short stays and high turnover. Together these conditions allowed for greater therapeutic optimism and thus enabled promising results for a clinical trial. Janssen would, most probably, have been aware of this when he chose Liège. If Janssen intended to move away from the concept of dementia praecox, then it is natural that he would avoid the asylum context where this concept thrived. At Glain, he found observation conditions linked to a much less pessimistic view of mental illness.

One final reason for Janssen to cross the Belgian language border and choose Bobon and Liège was offered by Christian Mormont. Other regions were perhaps less interested in participating in clinical-pharmacological experimentation. Not only because of a resistance to drug therapy in psychiatry, but also because the first clinical trials were often censored in ethical terms (Interview with Christian Mormont, Liège, February 27, 2019).

The proximity between the pharmaceutical industry and the clinical and academic world benefited both sides. Bobon and Janssen's first meeting (and the subsequent relationship that blossomed between them) clearly symbolises this union of perspectives and interests. If publications were seen as ammunition in climbing clinical and academic

hierarchical structures, and journals published (publish) preferentially positive results from clinical trials, the conditions were created for the establishment of privileged, and perhaps unhealthy, affinities between these two apparently distant worlds.

Throughout our research we repeatedly highlight how the construction of the current psychopharmacological industrial and academic complex was grounded on the creation of privileged relationships between its protagonists. In this example we see that, in addition to overlapping views on schizophrenia, and the sharing of a similar therapeutic optimism, there was a fundamental coincidence of practical interests. We can see this proximity materialised in the French expression "connivence" used by L. Botte, then just a young intern in psychiatry at the university clinic, to describe the relationship between our two protagonists: "Il y avait une connivence entre Paul Janssen et Jean Bobon." (Missa, 2010)

But what does the term "connivence" mean in this context? It might convey moral ambiguity or at least a secret convergence of interests. It certainly suggests a relationship of privileged intimacy. Janssen and Bobon seemed to share intentions, and both would benefit from a possible success of haloperidol.

Was this complicity supported by direct financial exchanges? Janssen, in his interview with Healy, addresses this issue directly:

> In the 1950's and 1960's I was so afraid of being misled by clinicians that I refused to work with clinicians who were asking for money. If they were not interested scientifically, I told them to forget it. But in those days, it was relatively simple to find clinicians who were willing to do whatever was required simply for the sake of their patients and because they were interested. Jean Delay or Jean Bobon, for instance, never asked me for a dime. What was not uncommon was that you would then do clinical investigators a favour after they had done their job. That was a question of being polite and grateful. But to discuss money was simply not done, it was even considered very impolite. Jean Delay I am sure would have been angry if somebody had raised the subject with him. (Interview with Paul Janssen cited in Healy, 1998b, p. 65)

Here, Janssen emphasises altruistic motivations, namely with patients well being. We can understand his argument, in that he purports interests in knowing the product he has conceived before making important investments in its production, marketing and distribution. A direct financial exchange, if it implied distorting the empirical data produced, as Janssen assumed, could jeopardise the company's own ability to devise a successful commercial strategy. Nevertheless, it is also reasonable to think that concerns about respectability were

extremely important in a growing, young pharmaceutical firm. As we have seen, underlying the FDA's 1961 refusal to license the commercial sale of thalidomide was a fundamental idea of a lack of trust in its promoter (Carpenter, 2014). Respectability was (is) a capital value in the context of the pharmaceutical industry, and this and other statements by Janssen have to be read in this context. Wrapped in the mantle of respectability, financial exchanges took place, but they would not be directly requested.

The first visit by Janssen to Bobon in Liège, was in the winter of 1958, a few weeks after the creation of haloperidol. That moment was the beginning of a personal and institutional relationship that would last decades, and profoundly change psychiatry.

2.4. The beginning

> Ceci dit on n'avait pas de protocole de recherche, c'était dit par le médecin comme dans la clinique en générale, je vous donnerai bien ceci on va un peu voir (Interview with Ferdinand Goffioul, Liège, 01 de Março de 2019).

For any incident, or moment in history, several versions of the same events are unavoidable. Events are lived differently, in different bodies, from diverse perspectives, but events will also be reconstructed in memory in a different manner. When, several years later, a coherent narrative is rebuilt, the storyteller transforms into an actor, again. His words, shaping the past, impact the present and the future. Most narrators know their power. Different stances are opportunities, through their contrasting descriptions we can grasp information that may elude us otherwise. We can perceive the storyteller's perspective as he looks back, but also his view of the present and maybe even his agenda for the future.

As we approach Janssen's narrative of haloperidol's first clinical administration, we are particularly interested in details that may shed light on his understandings of schizophrenia and his use of consent. In the background to this moment, there is an inescapable reflection on the broader ethical crossroads of drug experimentation in psychiatry.

Janssen's version of haloperidol's first clinical administration is surprising. It's depicted in at least two in-depth interviews, the first in March, 1996, with David Healy, and the second in May, 2002 (a year before his death), with Jean-Noel Missa. Due to its revealing details, we transcribe the complete version relayed to Missa below (2006):[11]

> C'est là qu'André Pinchard, un médecin travaillant dans le service de Bobon, administra pour la première fois de l'halopéridol à un fils de médecin qui avait développé des symptômes psychotiques. Son histoire mérite d'être contée. Certes, il ne s'agissait que d'un cas. Mais c'est ce cas-là qui me convainquit que j'étais sur la bonne voie. Un jeune homme d'une quinzaine d'années avait été transféré à l'hôpital psychiatrique de Glain (Liège), où Pinchard était de garde, avec des symptômes de schizophrénie paranoïde ou de bouffée délirante.
>
> Pinchard avait le choix entre la camisole de force ou une piqûre d'Haldol®. Il lui fit une injection intraveineuse de dix milligrammes d'Haldol®. En quelques minutes, le malade se calma.

[11] This account is very similar to the one that appears in Healy's work (1998b).

> Pinchard m'appela. Je me rendis à Liège de bon matin. Je vis un garçon qui dormait dans son lit. Pinchard essaya de convaincre le service qu'il s'agissait d'un syndrome de schizophrénie paranoïde. Les dix milligrammes d'Haldol® avaient apparemment eu un effet monstre. Nous eûmes alors une discussion avec le père, un médecin urologue. Le fils avait eu des prodromes avant la crise. Si on n'agissait pas, le malade risquait de faire une rechute. On décida alors de lui donner un milligramme d'Haldol® par jour. Dix milligrammes, c'était énorme, mais un milligramme, ce n'était quand même pas beaucoup. La mère lui mit les gouttes nécessaires dans de l'eau, le soir.
>
> Pendant des années, ce jeune homme reçut un milligramme d'halopéridol par jour. Son père nous invitait chaque année, avec Bobon, Pinchard et d'autres, pour discuter du cas de son fils. Son fils ne présentait plus de symptômes. Il termina des études d'architecte, il se maria et eut deux enfants. Les symptômes avaient disparu. Que fallait-il faire ? Continuer le traitement ou l'arrêter? Après tout, le malade n'avait peut-être eu qu'une bouffée délirante? Pendant huit ans on maintint le traitement. Puis le père entendit parler des terribles effets secondaires potentiels du traitement, les dyskinésies. Il prit alors la décision d'arrêter le traitement. Trois semaines après, le jeune homme eut une rechute. C'est ce cas qui me persuada de l'efficacité de l'halopéridol. Un cas. (Interview with Paul Janssen cited in Missa, 2006, p. 240)

Andre Pinchard, then a young intern at the "Clinique Universitaire de Liège", would start working for the Janssen corporation in the next few years. Throughout the 1960s and 1970s, he continued to work in Liège, but a few days a week Pinchard was in Beerse, paid by Janssen. His work was to advance the partnership between Liège University and Janssen Pharmaceuticals (Interview with Christian Mormont, Liège, February 27, 2019). His career, shared between industry and academia, demonstrates the need for progressive professionalisation of drug trials in psychiatry, and the complex clinical and scientific collaboration that these would increasingly demand. Pinchard's professional path is thus also the first materialisation of a very close relationship, not only between the two institutions - Janssen Pharmaceuticals and "Clinique Universitaire de Liège"- but also, as we have seen, between its two leaders - Janssen and Bobon. In this context, we can better understand that Janssen proposed Pinchard for the role of haloperidol's pioneer in both 1996 and 2002, even if Pinchard's name doesn't appear in the authors' list of the first published paper on haloperidol.[12]

---

[12] The absence of Pinchard's name from the list of authors doesn't, by itself, disprove Jansen's narrative. Louis Botte, a psychiatric intern at Glain at the same time as Pinchard, and also participating in the first haloperidol trials, explains "Divry, Bobon et Collard furent les premiers à tester l'halopéridol. Ils ont eu la gentillesse de ne pas nous mentionner dans l'article. C'est nous, en tant qu'internes, qui administrions l'Haldol aux patients." (Missa, 2006, p. 244).

However, the significant aspects of this account, told by Janssen, are not limited to the medical protagonist, the first patient to be injected with haloperidol is also, in many ways, paradigmatic. His place in the social hierarchy - the son of a doctor - sets him apart from the image of a forgotten, marginalised, victim, abandoned to pharmacological experimentation. On the contrary, its entry into the R 1625's clinical trial is not framed as a risk to be taken, but as an opportunity, a benefit hitherto denied to those that only had the straitjacket option.

"Pinchard avait le choix entre la camisole de force ou une piqûre d'Haldol®" (Interview with Paul Janssen cited in Missa, 2006, p. 240). Janssen simplistically reduced the therapeutic possibilities existing in the clinic at the time. Chemical restraint was already widely used before haloperidol and there were several different psychopharmacological interventions used to control agitation. Contrasting haloperidol with the straitjacket is an effective way of conveying the drug's importance in setting free the mentally ill, reinforcing the popular, but contested, thesis that neuroleptics liberated the asylum.

Nevertheless, in 1958, Pinchard had other choices. The first neuroleptic - chlorpromazine - was already increasingly used in clinic as a first-line treatment. Other sedative drug options included barbiturates, namely phenobarbital (Bayer's Luminal) and amobarbital (Amytal marketed by Ili Lilly). Both were widely used in Belgium before the introduction of neuroleptics, and even after. As an example, in that same year, 1958, at the "Institut de psychiatrie" in Brussels, 1000 doses of amobarbital were ordered every month (Majerus, 2013, p. 219).

Dr Paquay, who had also been Divry's intern at Glain, would later describe the different chemical restraint strategies already in place even before the Second World War:

> Jusqu'en 1940, à Glain, il n'y avait pas de cure de Sakel. Pour la schizophrénie, on n'avait pas de traitement, juste la sédation. Le pharmacien de Liège montait à Glain tous les jours une quinzaine de bouteilles qui contenaient du bromure, des barbituriques et de l'opium. C'était le traitement classique. Les gens étaient mis en cure sédative, en cure de repos. L'essentiel du traitement avant l'insuline, c'était la sédation. C'était d'ailleurs souvent à cause de leur agitation, de leur agressivité que les patients étaient placés en collocation à Volière l'Institut psychiatrique pour hommes de Liège ou en service libre à Glain. (Interview with Joseph Paquay cited in Missa, 2006, p. 216)

Continuing to reflect upon Janssen's account around haloperidol's debut, we should also pay attention to the way a certain representation of schizophrenia is deployed. In this narrative, schizophrenia is still firmly defined as a chronic illness (at least as a disease that

required persistent treatment) but with a, more or less, acute onset where hallucinations and delusional ideas predominate. When Janssen referred to the existence of prodromal symptoms, he was alerting us to a process that was already taking place prior to the acute episode, suggesting a temporal persistence that would reinforce chronicity characteristics. In practice, the reference to prodromal symptoms worked to exclude the possibility of spontaneous remission, and uphold the drug's role in improving the clinical picture.

Even when these chronicity characteristics were emphasised, Janssen was also comparing the young man's clinical picture to the French concept of *bouffée délirante,* the latter being theoretically, and by definition, an episode without prodromal symptoms. The concept of *bouffée délirante* was first constructed at the end of the 19th century by the alienist Valentin Magnan and his disciples Saury and Legrain. Strongly influenced by Morel's theory of degeneration, the *bouffée délirante des dégénérés* represented a transient psychotic episode, characterised by an acute and exuberant onset, disorganised delusions, perceptual changes, decreased clarity of consciousness and rapid and complete remission (Pichot, 1986). Maybe not surprisingly, we can verify how much this symptomatological constellation and its natural course are similar to the picture classically associated with amphetamine intoxication, that Janssen considered the paradigmatic model of schizophrenia.

Creating a link between these two concepts (schizophrenia and *bouffée délirante*), Janssen intended to reconstruct and redefine, a particular schizophrenia. This schizophrenia, that would emerge progressively in the next few years, is outlined in this brief narrative. It combines a course of progressive installation with pre-morbid symptoms, with the cardinal symptoms hitherto more usually described in acute episodes. Furthermore, when including the flowery characteristics of the *bouffée délirante* in his descriptions, Janssen highlighted a certain condition as a privileged indication for his product. This clinical picture was similar to his model of amphetamine intoxication but also, and maybe more importantly for the trial's success, was already classically associated with a good prognosis.

This young man did not have side effects, his clinical condition remitted completely and without residual symptoms, the course usually described in cases of *bouffée délirante*. Unfortunately, years later, the same young man, as in a moral fable, fell ill again three weeks after stopping treatment. Rumours about the risks of movement disorders associated with

haloperidol, tardive dyskinesia (see chapter 3.4), had lead to the drug's suspension.[13] The therapeutic path of this young man is paralleled by the historical path of haloperidol itself, as we will see in more detail in the following chapters. Thus, as with our patient, after great initial enthusiasm, particularly in continental Europe, the progressive recognition of movement disorders strongly threatened haloperidol's commercial success. Tardive dyskinesia would become an existential threat to haloperidol, and similarly, in Janssen's story, it became the main obstacle to our patient's otherwise successful treatment. The descriptions of tardive dyskinesia are the main villain of Janssen's clinical vignette but curiously they were also, in this story, a crucial element in the clarification of haloperidol's role. In fact, it is in the relapse, after treatment suspension, that Janssen demonstrates haloperidol's responsibility in keeping the patient asymptomatic throughout all those years.

It is difficult for us to believe in all the details of Janssen's narrative, perhaps because it is full of symbolic elements, sometimes seeming to closely resemble a parable of haloperidol's commercial course. But our disbelief is mainly due to the anachronistic vision of haloperidol that we find in his account. As this research will show, the idea of haloperidol as an anti-schizophrenic, that emerges from the account of Pinchard's first administration, would only slowly build up in the months or years that followed (the contemporary concept of antipsychotic formed over the following decades). Even if we accept that this idea was perhaps already an intuition of Janssen's, it was certainly not the predominant view in the Clinique Universitaire de Liège in 1958. This vision of a specific and chronic drug, the idea of a maintenance treatment, was not necessarily the way the first neuroleptics were seen. On the contrary, this point of view was developed over the following decades, with costs and resistance, as we will see in the following chapters. The haloperidol in Janssen's recollection is much closer to the substance we know today, after all its social construction, than to the substance that existed at the time - fresh out of the laboratory.

In 2005, after the death of Paul Janssen (2003), Bernard Granger and Simona Albu published a very different narrative based on the correspondence between Andre Mullie (director of clinical trials at Janssen Pharmaceuticals) and Jackie Collard (from the clinique universitaire de Liège and one of the authors of the first published paper on haloperidol).

---

[13] The expression "tardive dyskinesia" refers to a delayed onset and irreversible movement disorder believed to be associated with long-term use of neuroleptic therapy (Shorter, 2005).

The first psychiatrist to administer haloperidol would have been Claude Bloch, in Brussels. At the end of March, 1958, five weeks after the synthesis of R 1625, samples of haloperidol were sent to Bloch, who had been asked to test the safety of the product. He injected 2mg of haloperidol intravenously to several patients with delirium tremens.[14]

This indication is perhaps not too surprising, as the first neuroleptics, namely chlorpromazine, were already common in the treatment of alcohol withdrawal (Majerus, 2013, p. 239). On April 4, 1958 Andre Mullie wrote to Jackie Collard " The study of Dr. Bloch shows that there are neither sedative effects after an intravenous injection of 2mg of R 1625 nor adverse reactions, leaving aside a slightly and temporary blood pressure decrease" (in Granger & Albu, 2005). Bloch's work, for some reason, was never published and his name doesn't appear in any publication concerning haloperidol.

On April 16, Collard sent a letter to Mullie explaining the first administration in Liège:

> Yesterday I made the first clinical test with R 1625 under the supervision of Pr Divry. The patient was a young woman of 25 years old with a good physical condition who presented an emotional crisis (hypermotricity). A slow injection of 1ml was immediately followed by a slight sedation and three minutes later by drowsiness. Three hours later, the sedative reaction was still present, but to a lesser extent. Her blood pressure decreased from 120/70 to 95/70 mmHg while her heartbeat went from 25X4 (excitation) to 19x4 (sedation). (Correspondance from Jackie Collard 1958, in Granger & Albu, 2005)

This correspondence tells a different story, specially in some revealing details. The patient was a 25-year-old woman, gender and age were more in line with the profile of patients studied at Glain's clinic, who were mostly women (83%). The clinical indication "emotional crisis (hypermotricity)" is also closer to those found in the first haloperidol trials, where patients were selected by Bobon mainly because of the agitation they presented, more than for any symptomatological constellation. Only 2 of the 18 patients, included in the published first trial results, presented symptoms similar to the paranoid condition described by Janssen: "une psychose hallucinatoire aigue endogène agitè" and "un delire d'interpretation avec agitation"(Divry, Bobon, & Collard, 1958).

---

[14] Delirium Tremens was an expression proposed in 1813 by Thomas Sutton, nowadays mostly used to designate confusion in the context of alcohol withdrawal. It's an acute state that includes tremor, hallucinations and psychomotor agitation (Shorter, 2005).

Whatever the context of the first haloperidol prescriptions - a young man admitted acutely to Glain's clinic, patients with alcohol withdrawal symptoms in Brussels or a 25-year-old woman chosen for her exuberant psychomotor agitation - the simplicity of the research protocol stands out.

As Goffioul emphasised during our interview, reflected in this chapter's opening paragraph, and as is clear in the official narrative repeatedly offered by Janssen, the first clinical trials with haloperidol were carried out without informed consent. Sometimes, the narrative even suggests that some patients had no knowledge that a substance was being administered (in Janssen's example the mother would insert medication in the patient's water).

Today, in the highly regulated practices of current clinical trials, consent is indispensable, not only in the sense of being voluntary, but also ensuring, on the one hand, the competence for autonomous choice, and on the other hand, the clear disclosure of possible risks and benefits. It is therefore of interest here to reflect on how decision makers, in both the University of Liège and Janssen Pharmaceuticals, assembled ethical considerations in order to justify the total absence of consent. This detour is important, as cruel experimentation without consent is of the most recurring critiques of psychiatry, an image it still struggles to shred today.

Looking back, the absence of a precise protocol, and the lack of consent, seems a threat to patients' rights specially when they are in a position of fundamental fragility. But, again, in order to analyse choices and procedures from an ethical point of view, we need to access the decision-making rationale of those responsible at the time, and we need to understand the possible choices and the capacity for self-reflection they had on their own actions. It is therefore an exercise in history, as well as ethics.

Medical research has always existed in a delicate balance of values. On the one hand, there is the principle of autonomy - a fundamental concept of modern political philosophy, which has been increasingly imposed in the medico-legal discourses of the West, on the other hand, there is the tradition of beneficence, which has influenced medical action since the Hippocratic Oath (Fulford, Thornton, & Graham, 2006, pp. 499-508).

Fundamental freedoms in choice and action have often, and probably progressively in recent decades, been regarded as an essential condition for human dignity. The principle of

autonomy easily extends to the ability to decide whether or not to take substances potentially capable of acting on our bodies, and perhaps more importantly, on our minds.[15] Throughout its brief history psychiatry has often promoted this interference without consent. In the first psychotropic drug trials, including those relating to haloperidol, a direct contradiction to the principle of autonomy seems to be still in play. Since the 1960s, this idea of hidden drug experimentation has appeared repeatedly in the critical imagery of psychiatry as a discipline.

Understanding psychiatry's conventionally accepted ability to repeatedly overcome the usually voluntary nature of individual choice is a complex endeavour. We should recognise the various possible limits to the autonomy principle, but also the frequent ethical juggling that psychiatry, both as practice and research, performs in the face of challenging borderline cases. Against this complex background, psychiatry frequently sees itself following a tradition of beneficence, characteristic of medical activity in general. Treating the disease would be the doctor's superior duty. Treating the disease becomes an imperative and the patient's expression of will is often seen as invalidated, as weakened, by his own position as a patient. In psychiatry, even more than in other medical branches, doubts about the decision-making competence of patients have often favoured these paternalistic approaches. Was this kind of ethical reflection, that ponders autonomy and beneficence, accessible to the authors of the first haloperidol trials in 1958?

Surprisingly atrocious medical research during the Nazi regime in Germany originated in a particularly well educated medical class and took place in a context of extreme power asymmetry, with subjects chosen from among concentration camp residents. This research was later criticised for the violence and cruelty of the suffering inflicted, contrasting disproportionately with the uselessness of the acquired knowledge. Powerless research subjects were considered incapable of decision-making, disrespecting the value of autonomy in direct relationship with phenomena of dehumanisation linked to the extermination projects. In the same sense, the traditional medical duties of beneficence weren't pondered, leading to a complete absence of concern for present and future health of the patients. A particularly relevant criticism highlights the hollowness of the acquired knowledge, namely, that this research had no intent to contribute to the health of the victims, neither at that moment, nor in

[15]The principle of autonomy, despite being increasingly reflected in Western medico-legal discourses, can be accused of Eurocentrism, and may lose validity in cultural contexts that value the role of broader social entities in defining one's will (Okasha, 2000).

the future (Faden, Beauchamp, & King, 1986, p. 154). With the fall of the Nazi regime, in the aftermath of the Holocaust, doctors and hospital administrators were brought to trial in the Nuremberg courts. In 1946, the Nuremberg code transformed consent into an essential part of medical research, defining four characteristics: voluntary, competent, informed and complete (Minor, 2015).

In 1958, when haloperidol's trial began in Liège, 12 years had passed since the Nuremberg code had been drawn up. The risk of violence and cruelty associated with extreme power differential was known. Experimentation with haloperidol at Glain's clinic could reproduce these fundamental inequalities, with Bobon and Divry's knowledge and social capita contrasting with the deprivation of liberty of the trial patients. Following the Nuremberg code, informed consent was proposed to rebalance these asymmetries of power, and its absence in this research favoured the persistence of important and troubling disparities.

The recent memories of the holocaust, and the subsequent general context of criticism about medical experimentation, may help explain the lack of interest, from other Belgian clinics, in participating in the Haloperidol trials (Interview with Christian Mormont, Liège, 27 February 2019).

In the early 1960s, the Declaration of Helsinki was already being drawn up, and in 1964 it would once again uphold informed consent as the centrepiece of medical research (Minor, 2015). But Helsinki also favoured an important distinction - the difference between therapeutic and non-therapeutic oriented research. The potential therapeutic value for the subject may become so important that informed consent may be waived if it is not "consistent with the patient's psychology" (Faden et al., 1986, p. 156).

In haloperidol's trials, researchers justify the absence of consent, or protocol, by a risk-benefit analysis. They highlight the potential therapeutic value for the patient, emphasizing the principle of beneficence. Several stakeholders referred to the absence of effective alternative strategies and the serious medical and social circumstances they were faced with. It is in this light that we can read the phrase, which is perhaps somewhat misleading, by Janssen:

> Pinchard avait le choix entre la camisole de force ou une piqûre d'Haldol®. Il lui fit une injection intraveineuse de dix milligrammes d'Haldol®. En quelques minutes, le malade se calma. (Interview with Paul Janssen cited in Missa, 2006, p. 240)

In more contemporary views of schizophrenia, the disease is not seen as completely obliterating patients' decision-making capacity. The research of the last decades favours a heterogeneity between the various persons with this diagnosis, but also between different moments of their biographical paths (Roberts, Geppert, & Brody, 2001). But before the 1980s people diagnosed with schizophrenia were often seen as mostly or even totally incompetent for treatment choice (Dunn, Candilis, & Roberts, 2006). This recent change in perspective reflects a profound transformation in the schizophrenia construct, still moving away from the more degenerative classical connotations. Arguably, this transformation also stems from haloperidol's social path as a drug. In the last few decades, the concept of consent, in itself, has also been reframed, from static and homogeneous to dynamic and plastic.

In the late 1950s and early 1960s, both the "Clinique Universitaire de Liège" and Janssen possibly maintained an idea of schizophrenia as impairing consent, and an idea of consent as a closed, binary concept. In this context, autonomy as a principle might lose importance as the clinical setting justified non-consented pharmacological interventions in a long tradition of concern for the well-being and superior interests of those they considered sick. Nevertheless, the freshness of the holocaust experience, and the subsequent Nuremberg code, frame a particular background to their experiments, which were, already at the time, subjected to criticism.

2.5. Silence and tranquility

> Un médecin qui s appelait Paquay, médecin directeur d'un hôpital psychiatrique, qui a fait une très longue carrière, qui a commencé a travailler avant la découverte des neuroleptiques, avant meme la chlorpromazine, et qui m'a dit, c'est un homme extrêmement sympathique et humain, et qui m'a dit, la premiere chose que les neuroleptiques ont apporté c'est le silence, dans l'hôpital. C'est quelque chose qu'on n'imagine plus très bien, mais si vous avez un hôpital avec mil psychotiques, débiles, etc, c'est un bruit infernal, ça criait, ça gémissait. C'est intéressant de voir que la première effet des neuroleptiques c'est le silence, le calme, c'est pour ça que le côté agitation était très sensible, parce-que parfois si on a un schizophrène halluciné tranquillement dans son coin, bof. (Interview with Christian Mormont, Liège, February 27, 2019)

Silence is a prevalent element in the introductory narratives of the first neuroleptics. Silence and tranquility were presented as a value in themselves, but also as signs of a profound transformation that was to come. In this sense, descriptions of haloperidol's introduction are very similar to those that emerged during chlorpromazine's onset, 6 years earlier.

> At Ste. Anne's, the windows facing the street were opened in the spring and summer, and the clamor of patients would normally be audible along the rue d'Alésia in the fourteenth arrondissement. After June 1952, the local merchants began pulling aside Jean Thuillier, one of Delay's assistants, and asking him with wonder: 'Doctor, what are you doing with the patients up there? We don't hear them anymore.'(Shorter & Healy, 2007, p. 166)

When the haloperidol trials started, the "Notre Damme des Anges" clinic (Clinique de Glain), which served as the university's medical center, frequently received patients diagnosed with schizophrenia. Some had childhood onset, and were often placed there by the justice ministry. These young adults were described as difficult, and distributed in large rooms with thirty to forty patients. Daily life was described as strenuous, existing between screams and moans. With existing treatments, the risk of toxicity was important and silence sometimes felt beyond reach (Interview with Ferdinand Goffioul, Liège, March 1, 2019).

Although Glain, as noted in the previous section, had pressure for a high turn-over (still according to Goffioul) and wasn't, in that sense, an asylum institution, the expression of human suffering was described as so intense that it seemed to obstruct communication, and fundamentally disrupt psychotherapeutic intervention. The silence offered by the first

neuroleptics was described as a fertile silence, allowing the return of a humanised routine, re-emerging dialogue, and the revival of the institution's therapeutic function.

Silence becomes not only the main descriptive element around neuroleptics, but also the concrete demonstration of their effectiveness. To become a drug, a product has to find within itself the promise of transformation. Efficacy is measured by this ability to create change, indicating that the therapeutic process is underway. For the first neuroleptics, this transformation, this ability to act, materialised in the pacifying of patients (and so of institutions). This serenity, this calm, this silence, is seen as both overt and objective. It doesn't need mediating elements, quantitative instruments or scales. This notion of a clear tranquillising action is critical to understanding the first clinical trials with haloperidol, and their subsequent success. As we will see, haloperidol was repeatedly defined as evidently "effective", as "potent", and its potency didn't require, at least initially, any interaction with the patient's internal narratives. It was beyond subjectivity.

A primary reason for this centrality of silence in the haloperidol narrative derives from the psychopharmacological tradition present at the time. If nosological classifications were thought to be specially heterogeneous, influenced by authorial traditions, or inserted in philosophical movements that are often difficult to export, the truth is that the reality of somatic therapies had, on the contrary, always been unspecific. Precise strategies targeting each nosological category had not been developed. The treatment of the most disruptive mental illness included sedatives - barbiturates, and the new neuroleptics were initially interpreted in the same way, as sedative agents. The possibility of developing a specific antipsychotic action would face strong resistance (Lehmann, 1993).

When, in 1956, 2 years before the haloperidol trials, Heinz Lehman introduced the term antipsychotic, he did so in a more metaphorical than concrete sense. He considered neuroleptics more psychotostatic than antipsychotics. Their therapeutic capacity resided in creating the conditions for a new inner reorganisation by the mind itself. Within this conceptual framework, it is not surprising that silence was chosen as the main trial outcome. Silence, while pacifying mental activity, allowed a deeper recovery of the mind.

Perspectives like this one reveal the hybrid discourses used in the process of somatisation of mental illnesses during the 1950s (but also in the following decades). Concepts of psychoanalytic origin not only coexist, but interact with elements of somatic

therapies, undermining simplistic narratives of radical opposition between psychoanalysis and psychopharmacology.

In another example, Nathan Kline and Mortimer Ostow built an explanatory model of neuroleptic action that highlighted their ability to reduce intrapsychic tension, allowing the reemergence of unconscious contents that were previously inaccessible to the conscious, and promoting a new balance between the Ego and the Id (Ramos, 2013). As in Lehman, the central idea was that neuroleptics created the necessary conditions for renewed psychoanalytic work.

We will rediscover this theoretical blend throughout the first published papers on haloperidol, and the discussions that arose around them, which, it seems, played an essential part in the process of legitimising pharmacological therapies. In order to penetrate a clinical practice strongly influenced by psychoanalysis, psychopharmacological approaches, especially at the beginning, did not present themselves as competitive or incompatible interventions, on the contrary, they were grounded on the most prevalent psychodynamic explanations of the time.

The dynamics between specific treatment, directed at certain categories of disease, and comprehensive treatment, directed at symptoms or conditions, was reflected in the confrontation between Janssen and Divry. Janssen's project, later described as seeking to develop a specific treatment for a specific pathology (see chapter 2.1.), was quickly confronted with Divry's skepticism, that emerges in these narratives as the representative of the medical hierarchy and traditional psychiatric practices. Goffioul described this first meeting in our interview (Janssen's similar version is depicted in his interview with David Healy (1998b, p. 51)).

> Janssen presente le médicament comme anti-agitation, mais parlait déjà de schizophrénie. Divry était le patron et il était sceptique. Paul Janssen avait a ce moment lá une petite quarantaine d'années, si je me rappelle bien… Divry lui disait en regardant au dessus de ces lunettes: 'jeune homme, ce n'est pas votre produit qui guérira la schizophrénie', et Janssen est parti accablé. Divry a mis la molecule en experimentation, et d'abord uniquement en injection en cas d'agitation. (Interview with Ferdinand Goffioul, Liège, March 01, 2019)

Another reason for the central role of tranquillising action in the first haloperidol trials can be found in the methodological difficulties that psychopharmacological research encountered at the time. The incipient professionalisation made it difficult to make ambitious

scientific statements. The number of patients was small and the lack of instruments for measuring psychopathological phenomena (or what was seen as an inadequacy of the existing instruments - such as the Rorschach test) was said to hinder clinical objectivity, and favor inter-observer variability. Psychopathology assessment scales, moving away from psychoanalytic theory, were developed in the second half of the 1950s, namely Wittenborn, 1955, and Lorr and Rubinstein, 1956, and took a long time to find a privileged place in clinical research (Norton, 1967). Silence went beyond the subjectivity inherent to the most subtle psychopathological phenomena, and could be affirmed as an objective experience of daily life in psychiatric wards.

In 1958, randomisation and placebo were already well known, especially in the United States and England. Four years earlier, the Elkes couple had used, in Birmingham, sophisticated methodologies that included placebo control in a chlorpromazine's trial (Elkes & Elkes, 1954). However for various reasons (ethical, practical and academic), these techniques had difficulty in penetrating psychiatric research in general, and continental psychiatry in particular. The development and universal implementation of the sophisticated psychopharmacological research designs, that we are used to today, was slow and fraught with resistance.

Linford Rees recounts that amongst the 150 studies presented in the 1955 conference on chlorpromazine, Rees's studies were the only three double blind placebo trials,"It may be a little unfair but the French favoured a more 'impressionist' approach" (Interview with Linford Rees in Healy, 1998b, p. 172). Janssen himself would remain skeptical throughout his life.

> From that day on I have always been very sceptical when it comes to double-blind trials because the same risks exists everywhere. I don't know of any learned professor or any good observer who takes the trouble of doing what the protocols require in terms of observing. Certainly not in psychiatry. But what is the reliability of a psychiatric observation if it is done by somebody who does not know anything about psychiatry? I am not talking about theoretical psychiatry, I am talking about someone who knows how to observe psychiatric patients. (Interview with Paul Janssen in Healy, 1998b, p. 50)

Thus Janssen suggests that the double blind characteristics of placebo trials, in which neither investigators nor patients know who is given the placebo and who is given the test substance, may hamper the ability to cross check results, and irremediably hinder data quality. This kind of statement is in line with Janssen's *no nonsense* approach to psychiatry (see chapter 2.1).

At the Clinique Notre Damme des Anges, haloperidol's trial wasn't randomised nor placebo controlled, on the contrary, patients were handpicked, assessing the intensity of the psychomotor agitation and previous resistance to known drug treatments.

> C'est une anecdote: en plein tour de salle, où le patron se trouve avec les assistants, une jeune délinquante qui était au même temps une délirante mais agité avait saisit une bouteille d'eau mineral, et l'avait jeté, que avait explosé et ça avait provoqué a ce moment la, pas toute une rébellion mais, enfin, un mouvement. Et on lui a fait une injection de haloperidol qui a eu un effet extraordinaire, parce que a la fin du tour de salle la patiente était en isolement, elle était éveillé, elle répondait et parfaitement calme. C'était puissant cet affaire la! (Interview with Ferdinand Goffioul, Liège, March 1, 2019)

As noted, the first neuroleptics did not just transform the behaviour of patients, they acted on the asylum's social experiences. They changed its power relations, its interdictions, its rituals of punishment and the way discipline was enforced. Silence, as a measure of effectiveness, scotomizes all these more subtle changes that form the daily life of psychiatric wards. Haloperidol, like chlorpromazine before it, introduced new elements that this simplistic view, centred on effective tranquillisation, minimizes.

The existence of safe, injectable drugs, easily handled by medical and nursing teams, gives caregivers a new ability to intervene, and fundamentally alters the balance of powers.

In Goffioul's example, the powerful medical hierarchy sees its ritual of analysis and classification, materialised in the *ward round* ("tour de salle"), dramatically interrupted. In the subsequent explosion of a water bottle we can vividly imagine a violent clash of perspectives. Our young "delinquent", by creating a riot, demonstrates her ability to defy medical hierarchy, to subvert its ritualised activity. This turmoil is, however, extinguished in a single gesture - an injection of haloperidol. Medical power displays its ability to act on the girl's body, but also on her mind. In minutes, the patient is stripped of her clastic capacity, incapable of contestation, unable to continue creating chaos. Her menace of destroying the internal hierarchy of the asylum is silenced. This is the almost magical quality that the first trial descriptions attribute to haloperidol. The substance gains the power of quickly restoring order and hierarchy, of renewing a docile dialogue, and reinstating the psychotherapeutic project.

Silence in the asylum was understood, by some, as suppressing the voice of those condemned to life there. Silence implied shifting the expression of suffering from a public sphere to an internal space. In this sense it risked being seen as a disempowerment of the

patient's voice, the erasure of their capacity to protest, the transformation of the mentally ill from threatening to docile. These ideas germinated within the anti-establishment protesting movements that flourished throughout the 1960s, David Cooper, for example, would call psychiatric drugs "abortifacients of the spirit", and accused them of having a "mind colonising power" (Cooper, 1974, pp 16, 19) .

Whether or not silence is fertile ground for psychotherapeutic transformation, the opening of the asylum doors, and the beginning of deinstitutionalisation or, on the contrary, the censoring of the rebelling voices of change, it nevertheless becomes an essential factor of the asylum experience and measure of the effectiveness of the first neuroleptics.

The first published article on haloperidol reflects all these trends. "Le "R 1625": nouvelle thérapeutique symptomatique de l'agitation psychomotrice" was sent for publication on October 28, 1958. Haloperidol had been synthesised in February 1958 and first administered in Liège before April 16 (Granger & Albu, 2005). This first publication is therefore the result of 5 or 6 months of clinical experimentation. Divry, Bobon and Collard signed the article, which doesn't include the name of what was, according to Janssen, the first to administer haloperidol, the young intern Andre Pinchard. Janssen summarises this first article as follows:

> His [Bobon's] first paper describes the effect of haloperidol on psychomotor agitation, not on schizophrenia. It simply states that the intra venous administration of 5mg of haloperidol is quite active in calming down acutely agitated patients - that's all. (Interview with Paul Janssen in Healy, 1998b)

Contrary to the simplicity suggested here by Janssen, it seems to me this paper is full of tensions and ambivalences. Although true that, mostly following Divry's perspective, the Liège clinic focused on haloperidol's sedative capacity, the authors also suggest a different therapeutic action - although unspecific.

> Notre experience actuelle du "R 1625" étant encore limitée nous nous bornons a le qualifier de "sédatif" de l'agitation. S'il nous apparait déjà comme un "psycholeptique" seule l'administration continue et prolongée nous apprendra s'il mérite d'être qualifié de "neuroleptique".
>
> Il semble un sédatif manifestement très actif dans l'agitation psychomotrice, puissant a des doses minimes, maniable et apparement très bien toléré. Toutefois, son intérêt ne nous parait pas devoir se limiter a la seule agitation ni au seul mode d'administration par voie intraveineuse. Des etudes pour determiner son action dans le traitement de fond des nevroses

et des psychoses, en administration continue et surtout orale, sont en cours. (Divry et al., 1958)

In these first paragraphs, the authors link the substance to two principal characteristics that were extremely influential in the history of haloperidol - potency and ease of use or safety. These two concepts may seem conflicting, in the sense that we could assume that a more potent drug could be judged more dangerous, less well tolerated or more difficult to administer. Regardless, these recurring descriptions will be frequently referenced throughout the drug's history.

This article describes behavioural responses to intravenous administration. Injection was the possible route in very agitated patients, probably refusing care, judged incapable of consent, and requiring a coercive mode of administration. Choosing the most agitated patients would make it possible to observe the most robust responses, as well as the most noticeable, most evident behavioural changes. But intravenously was also quite possibly a mode of administration where greater rapidity of action could facilitate data collection. Given the lack of sophistication of these first protocols, namely the absence of placebo control, the temporal proximity between administration and therapeutic response could be seen as helpful in identifying drug effectiveness.

Liège's team didn’t claim that haloperidol was psychotherapeutic in itself, but the first suggestions emerged that the drug favoured or facilitated psychotherapeutic contact. Again, discourses of somatic therapies and psychoanalysis weren’t in opposition, and we find mixed elements in abundance in the literature of the time.

Selected patients had a wide range of diagnoses, ranging from large groups of endogenous psychoses to neurotic disorders. It is interesting to see how some of these diagnoses seem exotic to us today, signs of the transformation of nomenclatures and diagnostic manuals:

A. Treize psychoses

Trois manies (2 hypomanes et 1 manie “ au long cours”), 5 mélancolies (2 anxieuses et délirantes, 1 stuporeuse avec agitation occasionnelle, 1 anxieuse), 2 psychoses délirantes (1 hallucinatoire, 1 d’interpretation), 1 confusion organique senile, 1 épilepsie , 1 cas de schizoïdie.

B. Trois nevroses

Une névrose avec agitation continue, 1 psychonévrose avec crises motrices hystériques, 1 confusion hystérique.

C. Deux psychopathies (dont 1 hérédosyphilitique). (Divry et al., 1958)

This short paragraph reflects two of the main tensions in the history of psychiatry. From a nosology point of view between discrete entities and spectra, and also from a treatment point of view between specificity and scope. These dynamics exist since the notion of unitary psychosis,[16] and are still reflected in current psychiatric practice and theory.

The construction of the therapeutic effect of a drug during a clinical trial begins with patient selection. By limiting the field of clinical indications, an outline of the drug's action emerges. In this sense, haloperidol's example is similar to the substances that preceded it. The first neuroleptics launched without a specific indication, and their use even transcended the classical barrier in psychiatric nosology between psychosis and neurosis. Chlorpromazine was marketed under the name Largatil, and some argue that this name derives from the desire to assert this large scope of action.[17]

Historian Benoit Majerus analysed references to chlorpromazine in *Acta Neurologica et Psychiatrica Belgica*. Largatil presented itself, in these first advertisements, more as a "symptomatic therapy" than aimed at a "pathogenic specificity". Even with the passing of the years, chlorpromazine's indications remained vast during the 1950's and 1960's, from psychomotor agitation, to depression or obsessive syndromes (Majerus, 2013, p. 238).

In a similar way, Joanna Moncrieff examines advertisements in the Journal of Mental Science (which would later become British Journal of Psychiatry) between 1955 and 1960, to note, in parallel with Majerus, the absence of specific diagnostic categories. On the contrary, she highlights the wide scope of application being marketed (Moncrieff, 2013).

Nevertheless, despite this, the young Janssen seems to have had a different vision for his product. From the beginning, Janssen seems to have believed in a specific action of haloperidol on schizophrenia. When faced with Divry's skepticism, he went to Dave's asylum where he met the psychiatrist Joseph Pacquay, and conveyed his theory of R 1625 as an anti-schizophrenic. The story is told in two voices – and so we finish this chapter by reading Paquay's account and start the next chapter with Janssen's words.

---

16 The historian German Berrios defines *unitary psychosis* as a heterogeneous set of doctrines that in common share the belief in the existence of only one major psychosis, whose different clinical presentations derive from secondary factors (Berrios & Beer, 1994).

17 "There was no doubt about the efficacy of chlorpromazine or about its wide range of pharmacological and clinical action - that's why they called it Largatil." (Interview with Linford Rees cited in Healy, 1998b, p. 177).

Mais Janssen avait le sentiment que le R 1625 était plus qu'un simple sédatif. Il me dit : "Docteur, je suis fort perplexe. J'ai un médicament qui est un excellent sédatif, mais je suis persuadé qu'il y a autre chose dedans. J'aimerais qu'on l'étudie un peu mieux. Il faudrait beaucoup de schizophrènes, et du temps pour tester le produit (interview with Joseph Paquay, in Dave, 2003, in Missa, 2006, p. 247).

2.6. Building specificity

> Paquay knowing of this case [Pinchard's patient], said - well, haloperidol is obviously very potent against hallucinations and delusions - I am going to try it in chronic cases. He tried low doses - 1-7mg daily. The objective was clear - to make hallucinations and delusions disappear, to control the agitation if necessary and to re-establish normal human contact. These were considered the core symptoms of schizophrenia. (Interview with Paul Janssen cited in Healy, 1998b, p. 43)

The last paragraph of our previous chapter, and the first paragraph of this chapter, seem to refer to the same event - a meeting between Janssen and Paquay. In the previous chapter, Paquay's words describe a proposition for an exciting hypothesis to be tested, outlining the possibility of something new. Did haloperidol possess any therapeutic activity beyond the sedative elements already described by Bobon? This chapter's version of the meeting seems more conclusive. In Janssen's words, there *was* a "clear", concrete and well-defined project.

In Paquay's interview the idea of the essay is ascribed to Janssen. In Janssen's interview the trial project is credited to Paquay. This mutual attribution is not surprising in itself, and we can understand it today as an elegant and humble chivalry. Nevertheless, other crucial diferences remain between the two displayed narratives. Changing from one quote to the other, we can not only see the clinical trial project being materialised, but also the first crucial steps regarding a reconstruction process of the whole theoretical framework, namely redefining schizophrenia itself.

Drug building doesn't end after the laboratorial synthesis of its chemical structure. Substance construction, creating a new medicine, implies formulating its clinical efficacy. This process, called a drug trial, includes selection of participating individuals, and devising data that allows analysis of the drugs effect (results). In haloperidol's case, as we have recognised from the outset of this research, the drug's social manufacture required a redefinition of the medical illness itself, a reconstruction of the symptomatological constellation that characterised schizophrenia.

Saint-Martin's asylum in Dave is located on the outskirts of Namur, just over 60 km west of Liège. It is still Wallonia, French-speaking Belgium. Built in 1901, Joseph Paquay started working there in 1947.

Prior to working at Dave, Pacquay, like Bobon, had been Divry's intern at Glain. Saint Martin's asylum was very different from the Notre Damme des Anges clinic. Both belonged to religious orders, but while in Glain the clinic was private and oriented towards short stays, in Dave the asylum was devised for long periods of seclusion. In the 1950s, the Saint-Martin's asylum was the second largest psychiatric institution in Belgium, and had about 900 institutionalised men, distributed through 4 buildings, with large wards of 60 men each. For these 900 men, there were only 3 doctors - Dr Focquet, Dr Arnould and Dr Pacquay, and three dozen nurses - members of the religious congregation "frères de la charité" (Missa, 2006, p. 245)

Most hospital admissions were compulsory, against the patients' will. This medico-legal process is called "collocation" in Belgium. Hospitalisations were often long or even permanent. In 1950's, at Dave, most patients had been there for a long time and would stay there for a long time (Interview with Christian Mormont, Liège, February 27, 2019).

The most common somatic treatments were insulin therapy, electroconvulsive therapy, and leucotomy. Leucotomies were performed by an external physician, Dr Ectors, with no specific nosological indication, with the objective of agitation control above all. This was seen as necessary, even if some decrease in intellectual capacity was noted (Missa, 2006, p. 246).

If in chapter 2.3 the contrast between Divry and Bobon was highlighted, here we find parallel differences between Divry's and Pacquay's personalities and professional paths. While Divry is recurrently described as serious, skeptical, and mainly concerned with his academic and scientific career, Paquay is often described as warm, playful, interested mainly in his patients and without any academic ambitions (Interview with Christian Mormont, Liège, February 27, 2019). Bobon and Pacquay were the new generation of practitioners, promising a fresh approach.

At this time, Janssen was expanding the haloperidol trials, searching for a diversity of settings in different countries. He had a vision for R 1625 that clashed with Divry's skepticism, and was received by Pacquay with availability and openness. The number of patients at Dave's permitted a large trial. The long periods of hospitalisation allowed for more accurate longitudinal diagnoses and a longer clinical trial. Thus, a confluence of perspectives, and interests brought Paquay and Janssen together over haloperidol.

Three months after receiving the first samples of haloperidol, Pacquay published his first paper in *Acta Neurologica et Psychiatrica Belga* "Étude clinique de l'action du R 1625 a doses moderées en psychiatrie" (Paquay, Arnould, & Burton, 1959). Most of the patients included in the trial had a schizophrenia diagnosis, but there were still cases with other nosological categories (namely two intelectual disabilities, one "manic-depressive in a manic episode", and one agitation in the context of an acute confusional episode). The desire to present haloperidol as a privileged intervention in schizophrenia was not yet reflected in this diagnostic heterogeneity. On the contrary, the article still maintained the sedative action on agitation as its central therapeutic objective. Main trial objectives included studying an oral route of administering the drug (intravenous administration had been preferentially used in Glain's trial), defining therapeutic windows and elaborating dosage recommendations.

"À l'agitation habituelle a succédé le calme; c'est une sidération, comme si 'l'ange du silence les avait frappés de sa baguette" (Paquay et al., 1959) Haloperidol's almost magical ability to bring about silence and tranquility was already the Liège's team main conclusion and this persisted in Paquay's interpretation of the results. Chlorpromazine was still seen through a broad action profile, more tranquillising than healing. In this light, the first patients studied didn't really fit Janssen's description of a specific treatment intervention trial. The idea of studying haloperidol's anti-hallucinatory and anti-delusional activity probably grew more slowly. It took at least a few months for Paquay to present, a new innovative perspective for haloperidol,[18] at the 57th session of the "Congrès de psychiatrie et de neurologie d'expression française", in Tours.

Comparing the first results published in *Acta Neurológica et Psychiatrica Belga* (first presented on January 31, 1959) and the data presented in Tours (June 8-13, 1959), 5 months later, a new surprising frame of reference emerges.

The clinical trial design, as presented in Tours, was summarised in the paper "Experimentation clinique du haloperidol" (Paquay, Arnould, & Burton, 1960). It was a simple approach. There was no sophisticated quantitative testing and the nursing team's qualitative assessment was crucial. 70 patients diagnosed with schizophrenia were chosen among the 900 men that lived in Dave. Selection criteria besides diagnostics weren't

---

[18] Paquay would later describe this moment in his interview with Jean-Noel Missa «À ce congrès de Tours, en 1959,® j'étais le seul à parler de l'Haldol®. Au colloque suivant, en 1960, à Lille, nous étions vingt L'Haldol® était lancé. Janssen nous fut toujours reconnaissant du travail qu'on avait fait»(Missa, 2006, p. 248).

described. Doses used were relatively low compared to those used in Glain, starting at 0.5 mg/day and increasing to 7mg/day (rarely more).

In his 2003 interview with Missa, Dr Paquay describes his memories of this essay:

> On avait d'abord lancé l'Haldol® sur tout le monde, les 90 patients, provoquant ainsi la sédation profonde de tout l'établissement. Ensuite, on réserva l'Haldol® aux schizophrènes pour étudier ses effets. Il y avait une trentaine de patients. C'était une expérimentation. Quand on voit à l'heure actuelle, ce qui est exigé pour entamer un essai clinique! À l'époque, les choses étaient plus simples. On avait chacun sa petite fiche. Un examen général était réalisé par le médecin interniste. Et alors, tous les jours, on observait les malades et on recevait aussi les notes et commentaires des infirmiers et des surveillants. Au bout d'un peu de temps, nous commençâmes à voir le délire s'atténuer, les hallucinations s'estomper, le patient redevenir normal. Ce fut un miracle, vraiment. Lorsqu'on vit le premier schizophrène retrouver son état normal, c'était extraordinaire. À cette époque, cinq ou six schizophrènes purent quitter l'asile alors que nous pensions que leur destin, c'était de rester toute leur vie à Dave. (Interview with Joseph Pacquay cited in Missa, 2006, p. 248)

The number of patients mentioned in Missa's interview (30), is about half the number presented in the published paper (70), an understandable discrepancy taking into account that 40 years had passed between the trials and these statements. There was no placebo control and there was no randomisation. On the contrary, the patients were chosen from a wider group that had already been subjected to a previous exposure to haloperidol assessing its sedative activity. Such parameters prompt questions including: how many of these patients were among the 25 patients described in the article "Etude clinique de l'action du R 1625 à doses modérées en psychiatrie"? What exactly was the clinical profile of these patients? How many of them had already been, for example, subjected to surgical treatments (leucotomies)?

In this trial, the therapeutic response was documented comprehensively. The control of psychomotor agitation continued to be a highlighted factor in the presentation of results, but most importantly, Janssen's intuitions were confirmed, haloperidol seemed to have a specific action against delusions and hallucinations. According to Paquay's article, in half of the men treated with haloperidol, hallucinations and delusions disappeared. In 75% of the patients, "sociability" had improved. Half returned to some type of work activity, and 16% were discharged with reintegration into the family.[19]

---

[19] Although 16% discharge can be seen as a phenomenal result for those liberated patients and their families, bringing optimism and hope, numbers of this magnitude cannot explain, by themselves, the fall in institutionalisation observed in Europe and North America.

The team at the Saint Martin asylum in Dave, as Divry and Bobon had done before, and several other authors would go on to do, introduced haloperidol into the set of therapeutic technologies accepted at the time. It didn't present the new drug as an exclusive or competitive strategy but as a complement to the practices used. Throughout the article "Experimentation clinique avec l'haloperidol" (1960), Paquay frequently defends the role of psychotherapy, the importance of robust social integration projects, and occupational projects. Treatment could blend haloperidol with psychotherapeutic approaches but could also combine haloperidol with other somatic technologies available at the time. Despite defending the efficacy of haloperidol, the authors also state that it was still inferior to insulin therapy,[20] especially in the treatment of new cases of schizophrenia. The combination of haloperidol and insulin therapy, however, opened up new therapeutic possibilities.

The idea of haloperidol as a drug aimed at a specific nosological category emerged in Dave's clinical trial. In "Experimentation clinique du haloperidol" (Paquay et al., 1959) the idea of an anti-schizophrenic drug was present both in patient selection, with a sample composed exclusively of patients diagnosed with schizophrenia, but also in the results assessing process, particularly the attention given to complex psychopathological phenomena such as hallucinations and delusions. Constructed along these lines, haloperidol's marketing strategy departed from the approach followed by its main predecessors. Chlorpromazine, the first neuroleptic, had been defined by its wide application, surpassing the barriers of nosological categories. Neuroleptics' strategy had often emphasised their ability to create a neurological change, neurolepsis, which could then favour other more specific therapeutic interventions (Moncrieff, 2013). Early on, at Dave, Haloperidol begins to present itself quite differently. Its great advantage didn't come from the creation of an altered neurological state, but on the contrary, came from its ability to remove the cardinal symptoms of a specific disease.

At Dave, the blueprint for the contemporary concept of the antipsychotic begins to be drawn. This new layout involved the deconstruction and reframing of schizophrenia itself. To understand this paradigm shift, we need to return to the history of schizophrenia, when the concept begins to be sketched, at the intersection of the works of Kraepelin and Bleuler.

---

[20] Insulin coma therapy was proposed by Austrian born doctor Manfred Sakel in 1927. It used insulin to provoke hypoglycaemic coma in patients with a schizophrenia diagnosis (Shorter, 2005, pp. 142-144).

Kreapelin and Bleuler viewed schizophrenia from two fundamentally different perspectives. This wasn't limited to the cultural memes where the diagnosis would thrive (degeneration Vs splitting), but included an even deeper and apparently incompatible stance on the phenomenon (natural explanation vs human understanding).

The concept of "dégénération" entered scientific thought during the eighteenth century with Georges-Louis Leclerc (1707-1788), Comte de Buffon. Buffon presented a creationist thesis of natural history, where God created perfect prototypes, but successive generations had degenerated in nature's diversity. With time, races variated from the ideal model into different adaptations. From the beginning, degeneration was a Eurocentric idea of white race superiority, marked by colonialism, wherein other races were seen as degenerations from the caucasian ideal. Nevertheless, Buffon believed these physiological changes didn't fundamentally transform the core ontology of the species (Mason, 2010).

Before studying psychiatry with Falret at the Salpêtrière, Benedict Morel was at the seminary of Saint Dé. Morel's appropriation of Buffon's concept became a moral tale. Morel, strongly influenced by theological principles, saw ambiental and moral elements, from alcoholism to work conditions, as key factors producing physical and mental decline. It was an hereditary process, with health decreasing with every new generation, ending in sterility. Catholicism is the core of Morel's theory, original sin being the first moral transgression deviating man from the original healthy creation. Degeneration's dreadful prognosis had an optimistic outlook, as inexorable decline would ultimately protect humanity from the sinful misdeeds of some (Barrett, 1998a). Morel's theory offers a unified explanatory model for mental illness, even if it was still seen as multifactorial and, above all, multidimensional. Disorders of the soul could have "moral causes" but also physically affected the brain. (Liégeois, 1991).[21]

Morel's *démence précoce* was proposed in 1860, in his *Traité des maladies mentales* But his influence in Kraepelin's nosology is strongly contested. Some argue that Morel's *démence précoce* was more descriptive than categorial, and as such shouldn't be considered

[21] *Dégéneration*'s popularity in Germany, and its subsequent influence in Nazi ideology shouldn't be neglected.

Kraepelin's direct predecessor (Berrios, Luque, & Villagrán, 2003).[22] Other's look for schizophrenia's conception only in Kraepelin's fourth edition in 1893 (Meduna & McCulloch, 1945).

However in *Traité des maladies mentales* (Morel, 1860), *démence précoce* can be found at multiple instances (119, 279, 516, 526, 566). Its frequent use seems coherent, mostly referring to the end-stage of the aforementioned degenerative process. Throughout the book it was sometimes defined more theoretically, other times used in the context of clinical vignettes, but kept a uniform meaning. Although it was more a stage than a disease, it affected mood, social function, intellectual faculties and had delusional manifestations. Minkowski summarises Morel's *démence précoce* in three main traits - patients age, quick evolution, and dementia as a final stage (Minkowski, 1925). Mis-understandings about Morel contributions originate, maybe, from the concept itself being ill-defined. Morel's treatise had been written for the "medicine de la vie pratique" (general practitioner), and as the demented were mostly confined to the asylum, Morel feared that extensive characterisations could bore its audience. However Morel's influence over Magnan's nosology and European psychiatry in general has been strongly emphasised (Huertas, 1992).

Although there are secondary sources placing "dementia praecox" as first appearing in Kreapelin's textbook's fifth edition, in 1896 (Berrios et al., 2003), the fourth edition we consulted, published in 1893 already contained a description of "dementia praecox".[23] Included in the group "Die psychischen entartungsprocess" (Processes of mental degeneration) were three different categories, namely "die dementia praecox" (here clinically similar to Hecker's hebephrenia), "die katatonic" and "die dementia paranoides" (Kraepelin, 1893, p. 435). As a nosological category "dementia praecox" would expand, from its inception, into broader scope (Minkowski, 1925). In the textbook's sixth edition it had already replaced "Die psychischen entartungsprocess", and absorbed its three subtypes (catatonic subtype, paranoid and hebephrenic) (Kendler, 2020).

---

[22] Although Minkowski famously said " Un abime sépare, semble-t-il, la démence précoce de Morel de la démence précoce de Kreapelin", he didn't contest Morel's role in the concept origin, one being the stream, and the other the flood. "le ruisseau s'est transformé en torrent puissant qui, oubliant ses origines modestes, menace de tout submerger sur sa route"(1925).

[23] After Morel's work, and before kraepelin's use, the latim expression "dementia praecox" was used by Heinrich Schule (1840-1916), and Arnold Pick(1851-1924) (Noll, 2012).

Dementia praecox as a nosological category is said to have been constructed mainly longitudinally by observing a natural history of disease that included an insidious onset and a chronic course associated with the idea of progressive deterioration of functioning. Some authors highlight Kraepelin's ambivalent relationship to *dégéneration,* although he undoubtedly used degeneration theory at least as a broad theoretical framework (Hoff, 2008).

In the 1893 edition of his textbook, Kraepelin didn't recognise Morel's role in the creation of the expression "dementia praecox", but he did thoroughly explain the main principles of Morel's treatise when discussing hereditary predispositions (Kraepelin, 1893, p. 63). Regardless of Morel's influence, "dementia praecox" was defined as a process of decline in a frail minded state, with a quick progress to a mostly irreversible mental impairment, recognisable from the outset.

Kraepelin's nosology was based on clinical and demographic data he extensively collected and organised through subjective interpretation. The frailty of this method has been highlighted elsewhere (Shepherd, 1995). The result was firmly influenced by his views on masculinity, embedded in a reductive dichotomy of strong will versus feeblemindedness (to which women, children and primitives were inclined) (Barrett, 1998a). Eastern Jews, for example, were inclined to degenerative and hysterical features, and women were prone to extremes of excitement due to their lack of self control (Kraepelin, 1992/1920). More than a hundred years later, Kreapelin's eurocentrism parallels Buffon's original thesis.

Bleuler's formulation, *schizophrenia,* follows a different trend. Influenced by Romanticism, German academics since Griesinger identified a failure of inner unity, a divided person, as the culmination of mental illness. For some authors (Barrett, 1998b), Bleuler proposed *associative splitting* as the primary core pathology to schizophrenia following these XIXth century cultural tropes.

His term schizophrenias (die Schizophrenien), introduced in 1908, was an explicit reference to Kraepelin's dementia praecox.[24] Even so, schizophrenia departed from dementia praecox's more fatalistic course, and their diagnostic core was firmly based on the fragmentation of psychic functioning. From Dementia praecox to die Schizophrenien there are two notable linguistic changes. From singular to plural, and from a Latin term to a Greek

[24] Some argue that there is very little conceptual continuity between Morel, Kraepelin, Bleuler and Schneider (Berrios et al., 2003)

neologism. These alterations are telling. They are symbolic of a deep transformation in perspective, forming contrasts that have been comprehensively portrayed. Kreapelin's objective longitudinal observation sees diagnosis as a dynamic process, where the passing of time is crucial, but Bleuler's work introduces a more interpersonal transversal observation, with a more static diagnostic procedure. Differences between Kraepelin's strong interest in somatic/biological aetiologies and Bleuler's interest in psychological approaches has also been highlighted, as well as the distinction between a more deductive approach of Kraepelin with a more inductive approach from Bleuler. This transformation from latin to greek symbolises this shift from a natural understanding (Wesensverständnis), in Kreapelin's work, to a human comprehension (Menschenverständnis), in Bleuler's stance (Kuhn, 2004; Moskowitz & Heim, 2011).

A key concept in the definition of schizophrenia, and perhaps a guiding principle in Bleulerian psychopathology in general, was the distinction between fundamental and accessory symptoms, as can be read in the following quote:

> Bei manchen Krankheiten hat es einen Wert, unter den Symptomen Grundsymptome und akzessorische zu unterscheiden. Die ersteren kommen in jedem dieser Fälle vor, sobald die Krankheit eine gewisse Höhe erreicht hat; man muß also annehmen, daß sie in nice auch da vorhanden seien, wo wir sie noch nicht sehen können; sie hätten dann nur die diagnostische Schwelle wegen ungenügender Intensität noch nicht überschritten. Dahin gehören der "organische Symptomenkomplex" bei den Organischen oder die Assoziations- und Affektstörung bei den Schizophrenen. Die akzessorischen Symptome, wie z. B. die Halluzinationen und Wahnideen können bei diesen Krankheiten fehlen oder zu beliebigen Zeiten und in beliebigen Kombinationen auftreten und verschwinden. (Bleuler, 1937, p. 29)

Bleuler's fundamental symptoms (Grundsymptome) of schizophrenia include associative splitting and affective changes. These were always, and invariably, present even when we couldn't yet identify them clearly. Hallucinations and delusional ideas, on the contrary, although they may sometimes be present, never had specificity nor persistence. In Bleuler's definition, grundsymptome value is not only in diagnosis, they became, more than symptoms, crucial parts of the process of the disease.

For Bleuler, *loosening of associations* was not just a formal thought disorder, or its bizarre expression in discourse, as it is often considered today, but a broader concept that included several spheres of psychological activity - including memory, perception, and affect. Associations were not only the permanent connections created between diverse psychic

elements, they were the active process in which these connections are formed. Loosening is an interruption in the combinations of psychic elements, leading to pervasive fragmentation of the psyche. Bleuler argues that it is in these primordial disturbances that we can find the origin of secondary symptomatological constellations (Moskowitz & Heim, 2011).

> Alle einzelnen Symptome sind aber nirgends so sehr wie bei der Schizophrenie von ihrer ganzen psychischen Umgebung aus zu beurteilen. (Bleuler, 1937, p. 313)

In this quote we can see how far contemporary diagnostic procedures, mostly viewed today as a sum of multiple individual symptoms, have travelled from the original approaches of beginning of the XXth century. The clinical picture was seen as a global transformation of the self, especially so in schizophrenia.

Perhaps surprisingly to many considering themselves neo-Kraepelinians, Kraepelin was generally in agreement with this analysis. Kraepelin accepted this classification between fundamental and accessory as particularly convincing (unlike other divisions between primary and secondary).

> The distinction made by bleuler of fundamental disorders and accompanying phenomena of the disease is to be judged essentially otherwise. The former constitute the real characteristic of the clinical state and can be demonstrated in each individual case more or less distinctly; the latter may be present but may also be absent; they are not caused by the caracter of the morbid process but by circumstances which are in loose connections with it.(…) From this point of view the weakening of judgement, of mental activity and of creative ability the dulling of emotional interest and the lost of energy, lastly, the loosening of the inner unity of the psychic life would have to be reckoned among the fundamental disorders of dementia praecox, while all the remaining morbid symptoms, especially hallucinations and delusions, but also the states of excitement, depression and stupor, further the manifold disorders of volition, negativism, automatic obedience, stereotypy, mannerisms, impulsive action, would be regarded more as secondary accompanying phenomena. (Kraepelin, 1919, p. 248)

Schizophrenia was thus born, at the beginning of the 20th century, from this strange conceptual intersection between two profoundly different works, in a hybrid language between human and natural understanding, between deductive and inductive reasoning, between empiricism and theory. However, since its foundation, in this conjunction between Kraepelin's and Bleuler's work, schizophrenia has been predominantly considered as a global disorder of functioning deriving from the fragmentation of the inner unity of psychic life. Hallucinations and delusions were, both for Bleuler and Kraepelin, accessory symptoms and their presence, albeit sometimes helpful in diagnosing schizophrenia, wasn't decisive.

This schizophrenia, so defined, would lend itself with difficultly to pharmacological research. A global change in the functioning of the self was a complex concept to operationalise leading to low rates of agreement between examiners, and extremely heterogeneous clinical pictures. Also, a definition based on a longitudinal evaluation with a mostly pessimistic natural history of the disease, complicated not only the elaboration of effective strategies to modify the prognosis, but also the evaluation of these strategies.

Schizophrenia, as a diagnostic category, was constructed through this meeting between Kraepelin's and Bleuler's works, but would later have its limits and contours challenged. Especially from the 1950s onwards, when Kurt Schneider's first-rank symptoms gained influence. Psychopharmacological research played an important role in this process, and the Dave's trials are at the very center of this shift. In 1978, influential American neuroscientist Seymour Kety recalled this transformation, of which the first haloperidol trials were a part. He highlighted its economic advantages, specially for the pharmaceutical industry.

> Schneider, 50 years later (1959), (after Bleuler) gave renewed support to those who preferred to think of schizophrenia as a benign process by simply redefining schizophrenia to make it so. Features regarded by both Kraepelin and Bleuler as fundamental and characteristic (impoverishment of affect, disturbances in personal contact and rapport, ambivalence, lack of motivation, depersonalisation, and stereotypes) were specifically rejected and the new criteria were restricted to particular types of hallucinations and delusions which Bleuler had regarded as accessory symptoms. Schneider established a new syndrome with features that are more easily perceived and described, and which therefore show a higher degree of inter-rater reliability, features which are economically put into check lists and fed into computers. That syndrome may be more prevalent, have a more favourable outcome, and be more responsive to a wide variety of treatments, but it is not schizophrenia. (Kety, 1980)

The German psychiatrist and phenomenologist Kurt Schneider had originally proposed his first-rank symptoms in a brochure for general practitioners published in 1939 (Katschnig, 2018). Diagnosing subtypes within the endogenous psychosis was important for prognosis, therapy and description. The specific symptoms that gained power as diagnostic probes, concerned, not the illness experience itself, but the way it was lived. For Schneider the contents of the experience are interesting in a biographical sense but are useless in diagnostics:

> If I find withdrawal of thoughts, this is important for me as a way of experiencing and diagnostic evidence, but it does not interest me diagnostically whether the devil or the beloved or a political leader is withdrawing the thoughts. (Schneider, 2009/1956, p. 445)

This elegant distinction was present in Karl Jasper's work, having been drawn from Immanuel Kant's philosophy (Walker, 2013).

The list of seven symptoms included delusional perception (Wahnwahrnehmungen), thought-echo (Gedankenlautwerden), voices arguing among themselves (Stimmen in der Form von Rede und Gegenrede), hearing remarks commenting on the individual's actions (Begleitung des eigenen Tuns mit halluzinierten Bemerkungen), being influenced by somatic, or sexual, organs (körperliche, insbesondere sexuelle Beeinflussungen), thought withdrawal and insertion (Gedankenentzug und Gedankenbeeinflussung), and attributing feelings, motivations, and wills to others (thought diffusion was added in a later edition). Although Schneider himself viewed the presence of first rank symptoms as indicative of schizophrenia, their absence didn't exclude the illness (Shorter, 2005, p. 247). Differential diagnosis wasn't absolute, transitions and border-line cases existed (Schneider, 2009/1956).

Schneider's first english translation was published in 1959, concurrent with the Dave's trials, and would have an immediate impact on European psychiatry (Katschnig, 2018). Swiss psychiatrist Christian Muller would later say: "If I had to make a choice . . . and say who around the year 1960 most authoritatively influenced European psychiatry, I would certainly name for Germany Kurt Schneider, for England Aubrey Lewis, and for France Henri Ey" (Christian Muller cited in Shorter, 2005, p 102).[25] Schneider's growing influence in British psychiatry is also easily documented(Mellor, 1970). His reception in the United States was seen as a major contribution to challenge the psychoanalytic framework then sometimes described as dominant (Hoyt, 1962).

Two major trends characterise schizophrenia's transformation. On the one hand, an effort to divide into a list of symptoms what was once seen as a global difference in the experience of the self. On the other hand, the tendency to convert a diagnosis that implied a long follow-up, with sequential observations throughout the patient's life history, into a diagnosis that could be made in a single observation, in a single moment.

---

[25] Henry Ey's work and influence will be briefly explored in chapter 3.4

This shift, as suggested by Kety, served the interests not only of the pharmaceutical industry itself, but also of the emerging academic-industrial complex formed to create, evaluate and promote biological research in psychiatry. An increasingly relevant example is the intimate relationship that was gradually being built between Janssen and the Liège team. This complicity was one of the first stones in the construction of this complex.[26] The reconfiguration of schizophrenia that was promoted here would enable the entire process of the professionalisation of clinical trials in the coming decades. Drug trials would become the economic and financial heart of the relationship between industry and universities.

Now, we see more clearly how a substance can transform theory, and at the same time begin the process of reshaping itself. Haloperidol, in this model, becomes transformed and transformative. In Glain, R 1625 is formed as a sedative, a tranquilliser, in Dave haloperidol becomes psychotherapeutic. It is important to analyse the different conditions within these clinical trials, and how they may have contributed to the construction of such disparate drugs, from the same chemical substance. Some contrasts between them have already been highlighted in this chapter, from the personality of the study's leader, to the medico-legal conditions of Glain's and Dave's hospitalisations. Another important difference includes the gender of the participants, while in Glain the vast majority were women, in Dave they were all men. This is important because psychiatry in general, and the concept of schizophrenia in particular, was impregnated with gender references from the beginning.

Kraepelin's dementia praecox was more frequent in males (Kraepelin, 1919, p. 230), and that continued during the following years, as we can see for example in Alfred Gordon's extensive review in 1917 (Hirshbein, 2010).[27]

Gender identity, and the experiences associated with it, are a core structure of psychoanalytic approaches, and therefore maintained their influence throughout the first half of the twentieth century, while psychoanalysis dominated the theoretical framework. Even after the fall of psychoanalysis, the impact of gender on schizophrenia studies persisted, to the point that an entire issue of the Schizophrenia Bulletin (Vol. 16, No. 2, 1990) was devoted to this topic. It has continued to be widely reported, especially since the 1990s, that women have a later age of onset, better pre-morbid adjustment, adhere more easily to treatment and

---

[26] The founding of this complicity is detailed in chapter 2.3

[27] Bleuler didn't find these gender differences in his series (Bleuler, 1937, p. 317).

are less subject to forced hospitalisations (Walker & Lewine, 1993). These conceptions persist, as we can see in a very recent review by Mary Seeman (2019). Paquay's work, and the Dave's trial, reinforced this idea of Schizophrenia as a preferentially male disease.

Other salient differences between the Glain's and Dave's trials include mode of administration, oral in Dave as opposed to intravenous administration in Glain, and doses used, Dave's dosages of 1 to 7mg per day were much less than those implemented in Glain. This medical strategy, gentler in the asylum than the private clinic, may seem inconsistent. Yet in Dave, the patients lived there for long periods, turnover was incipient and the discharge expectations were low. In chronic settings, risking lower doses might perhaps be seen as more reasonable than in an acute ward.

In the results section of the published paper of the Dave trial, we can further clarify the concept of schizophrenia that Paquay used, and helped build. As we have identified in our research, medical articles may appear mostly empirical, specially when concerning drug essays. But the results section may be telling, revealing the therapeutic hypothesis that presided trial design, and the theoretical framework that encompasses it.

> On obtient:
> 1º une remarquable sédation des troubles psychomoteurs y compris de l'impulsion;
> 2º une reduction des hallucinations et, parfois, des délires dans environ 50% des cas;
> 3º une normalisation de l'émotivité, de l'affectivité et de la sociabilité chez 75% des schizophrènes. (Paquay et al., 1960)

Joseph Paquay, like Paul Janssen, or Kurt Schneider, understood schizophrenia as a set of symptoms arising in specific areas of human experience namely hallucinations, delusional ideas, psychomotor agitation, and contact or sociability. Global or broad concepts such as fragmentation of the self were not addressed here, and fundamental symptoms, once seen as part of disease process, like associative splitting, were also absent. This new schizophrenia could then be seen as stripped of theory, becoming a symptom inventory, easy and useful.

This schizophrenia, unsurprisingly, was also much more similar to the experimental models of psychosis.

Psychosis produced in the context of amphetamine intoxication was mainly characterised by exactly these inner experiences of delusions and hallucinations. If haloperidol had been developed as an amphetamine antagonist, then it would be normal for

Janssen to try to test it in clinical cases similar to the amphetamine intoxication model. Both industry and academics would gain from a schizophrenia closer to experimental models. This process, sometimes called paranoidization, benefitted drug development, drug testing, and clinical trials. If the model the lab used to simulate or provoke psychosis wasn't similar to schizophrenia, schizophrenia transformed itself as to resemble the experimental psychosis.

Both before and after the development of haloperidol, the diagnosis of schizophrenia was a way of articulating the heterogeneous individual narratives of those who had been diagnosed ill into a comprehensive category that made it possible to make sense of individualised experiences. The diagnosis of schizophrenia was, as it usually is in medicine, a way of locating the suffering of a given person within archetypes or comprehensive synthetic categories, able to carry answers, therapeutic procedures, to that specific situation. Haloperidol does not substantially change schizophrenia's role as a medical diagnosis. But what we see outlined in these first trials, and will observe in the subsequent theoretical construction, is that, gaining therapeutic specificity, the diagnosis of schizophrenia changes its contours, or resets its limits, obtaining *definitional specificity*.[28] During the next chapters, we will be able to observe the consequences of these transformations that begin here.

The somatisation processes of mind and behaviour, ongoing throughout the 20th century, found, in the creation of a delimited treatment, an antidote for schizophrenia, one more confirmation of the corporeal and cerebral materialisation of the mind. But the idea that a drug has the ability to modify thought contents, more precisely that an agent has the ability to shatter delusions, emerged in the face of a series of resistances.

> The second barrier, in those days, was that psychiatry was not ready for the concept of a pill which was capable of changing the human mind. They, the psychiatrists, were all involved with psychotherapy and so on. And the idea of such a pill was revolutionary to many. (Interview with Paul Janssen in Stanley, 1992)

There were always voices within psychiatry, from psychoanalysis to psychopharmacology, that opposed this process of mutual definition between illness and treatment, critics of this progressively narrow relationship between schizophrenia and neuroleptics.

---

[28] I've borrowed the expression definitional specificity from Charles Rosenberg "Particular ills have often been given a definitional specificity through the specificity of their response to therapeutics. Pernicious anemia, for example, was defined in the 1920s as the part of the spectrum of anemias that responded to liver extracts" (2002)

> The idea that disease is due to a specific agent which can be counteracted by a specific substance which eliminates toxic features. On the basis which is really Claude Bernard's basis for experimental medicine, the whole of the natural science approach to medicine, is constructed and it's quite wrong, not in itself but because it's so limited. It cuts out the non-specific factors which are in fact at least 50% and probably more in the aetiology of disease and of treatment and among them is placebo and the nocebo, both of which are extremely powerful. (Interview with Michael Shepherd in Healy, 1998b, p. 241)

Michael Shepherd, one of the first to develop professionalized methods in clinical trials in psychiatry (Shepherd & Watt, 1956), questioned the way in which, superficially following natural sciences models, psychiatry erased subjectivities, artificially simplifying the way the mind works.

Science is also built by polemics and disagreements. Haloperidol itself was marked by contradictory studies, divergent empirical results and plural theoretical interpretations. But the path of antipsychotic and schizophrenia mutual specification would advance inexorably, firmly implanted in an increasingly powerful academic-industrial complex.

2.7. Building international support

On organisa un symposium à Beerse. Mon raisonnement était le suivant. Il faut se méfier des psychiatres. Ce sont des gens un peu… Comment savoir s'ils racontent la vérité? Je m'étais mis en tête de donner l'halopéridol à huit psychiatres différents, dans huit pays différents, sans dire à l'un qu'il faisait la même chose que l'autre. Il y avait Delay à Paris, Lopez-Ibor en Espagne. On donnait le produit à tester, avec un protocole simple sans double insu, en gouttes et en ampoules. Après neuf mois, on demanda à ces psychiatres de venir à Beerse pour nous dire ce qu'ils pensaient du nouveau produit. À ma grande surprise, ils racontaient tous la même chose. Pour moi, c'était la preuve de l'efficacité du produit. Ils disaient tous qu'il ne fallait pas dépasser trois milligrammes par jour. Ils prétendaient tous que les hallucinations disparaissaient, avec les délires et l'agitation psychomotrice. Ils affirmaient tous que le contact humain s'améliorait. Cela m'étonnait que huit psychiatres puissent être d'accord (rires). Pour moi, c'était la fin de la phase expérimentale. J'étais convaincu, et eux aussi, que le produit était hautement actif et qu'il fallait le mettre dans le commerce le plus rapidement possible, en ampoules pour les grands agités et en gouttes. Tout ce qu'on sait sur l'halopéridol date de cette époque. Tout est dans le petit livre, les actes du colloque de Beerse de 1959. Les études en double insu, réalisées par la suite, n'apportèrent rien de plus. C'est une très simple histoire. (Interview with Paul Janssen cited in Missa, 2010)

2.7.1. Acta Neurologica et Psychiatrica Belgica

The history of medicine, as other forms of knowledge, has seen the periodic emergence of tensions between localised forms of knowledge and more broad or globalised transfers of epistemologies. Throughout the twentieth century, successive phases of this history have been sketched, distinguishing the predominance of one trend or another, according to different authors. In this precarious balance of forces, multiple financial, cultural, social and epistemological factors intervene, whose global analysis is beyond the scope of this thesis. However, it is important to understand the path taken by the dopaminergic hypothesis of schizophrenia, from a localised idea, born in a narrow geographical triangle at the center of the European continent (between Beerse, Liège and Utrecht), towards one of the most crucial concepts of international psychiatry, throughout the last decades of the twentieth century.

Our research shows that in order to understand this path of expansion we must follow a very similar path taken by a therapeutical technology (haloperidol), which preceded, and determined, the construction and internationalisation of the dopaminergic hypothesis.

According to John Burnham (2011), the inter-war period was geared towards the national production of medical knowledge, but from the 1950s onwards, the transfer and transnational communication of medical science would increase considerably.

In psychiatry, another process ran parallel. As noted, psychopathological traditions, namely descriptive psychopathology and nosology, were developed within linguistic communities and specific philosophical foundations, sometimes being judged incompatible, or incommensurable with each other (e.g. Kroll, 1979; Pichot, 1984). These regional forms of psychiatric knowledge and practice were confronted, especially from the 1950s onwards, with a growing desire for transnational implementation of more specific technologies - namely psychopharmacological therapeutic interventions. The technologies that had preceded them were of wider application, namely insulin therapy, electroconvulsive therapy or leucotomy. These technologies, because of their broad scope of indications could perhaps more easily tolerate local diagnostic heterogeneity. Uniformly applied to many psychiatric diagnosis, or psychopathological conditions, shock therapies perhaps did not demand the

same international homogenisation of diagnostic practices, that drug therapies would later entail.

Medical Journals were preponderant at the time, and perhaps still are, in the production and transfer of this technological knowledge. Janssen's firm shared this strategy of a specific but internationally homogeneous application.

During the 1930s, Paul Janssen's father, Jan Constant Janssen, had acquired the rights to distribute Richter company's drugs, in Belgium, the Belgian Congo and the Netherlands. Janssen had grown up within a transnational family business and we can assume, with reasonable certainty, that Paul Janssen knew well the dynamics of the European drug market. In particular, we can assume that Janssen was well acquainted with the difficulties and possibilities of cross-border drug transfers, as well as with strategies to penetrate national markets. While developing his compounds in the laboratory of this small growing firm, Janssen looked well beyond the fledgling Belgian market to the broader European continent. The early international expansion of haloperidol's clinical trials conveyed this desire of global affirmation.

During the first half of 1959, Janssen rapidly and effectively expanded the haloperidol trials, searching across Europe for available clinicians with whom he might find common interests and a similar frame of reference.

In this process, Jean Delay was an indispensable aid. The Paris team, founder of the neuroleptic concept, also received haloperidol and developed a clinical trial. As we will see, its results would be remarkable, but Delay's contribution was vaster. Delay recommended like-minded clinicians to the young Paul Janssen, helping him find eight of the most distinguished European psychiatrists (Interview with Paul Janssen in Healy, 1998b, p. 47). Still according to Janssen, each team worked alone, unable to contact other teams and without knowledge of concurrent clinical trials. Haloperidol was sent deprived of protocol, with no recommended dosage and lacking therapeutic indications. On September 15, 1959, head researchers were brought back to Beerse to present results during the first international haloperidol symposium. Articles were published in *Acta Neurologica et Psychiatrica Belgica* (Granger & Albu, 2005).

This seems an amazing strategy from a marketing perspective. Reference to clinicians nationalities and to local trials was a very efficient manner of promoting a drug (Hemminki,

1977). Choosing respected clinicians from all over Europe thus opened up local markets. Abandoning protocols meant the possibility of finding new indications and expanding the use. Not restricting dose levels could obviously favor higher quantities being used. Bringing physicians back to Beerse meant keeping a certain control over results. The massive quantity of published articles can be seen as serving the marketing needs of the company, and the academic ambitions of the clinicians.

This internationalisation effort was paradoxically materialised in a national magazine, *Acta Neurologica et Psychiatrica Belgica*, reflecting a tension between the desire for expansion and the need for local affirmation, and reinforcing the focus on the European continental market. *Acta Neurologica et Psychiatrica Belgica* was the chosen journal to publish the articles emerging from the international symposium on haloperidol. It was a Belgian magazine, mostly written in French, specific to psychiatry and neurology (the clear divorce between the two disciplines was a slow and heterogenous process).

The written language of the haloperidol papers is illustrative of this continental frame - sixteen were in French and one in German. The English language was relegated to a summary at the end of each article. This was not uncommon and reflected a transition period for the *Acta Neurologica et Psychiatrica Belgica.* In the early 1950s, 2/3 of the articles had no references from outside the French-speaking community, but, in 1967, 78% of the articles already had international references (Burnham, 2011). This data may reflect the importance of the French speaking world in this new configuration of psychopharmacology, and its subsequent decline.[29]

The published language of the haloperidol papers also helps to shed light on the scientific and commercial promotion priorities of Janssen Pharmaceuticals. First of all Belgium, then the wider French-speaking and German-speaking European linguistic space, and finally peripheral continental Europe. Excluded from this strategy seem to have been the English-speaking countries. In fact, none of the clinical trials reported at this first Haloperidol symposium took place in an English-speaking country, and of the 57 symposium guests only 3 came from the United States and England: Thomas H. Hayes, Chicago Illinois (EUA), I. C. Winter, Chicago Illinois (EUA) and G. R. Venning, High Wycombe (England).

---

[29] This transition may also be associated with broad linguistic trends in Belgium during the second half of the 20th century, namely the initial cultural predominance and subsequent decline of the French language.

The relationship between Janssen and Searle had been cemented in the lomotil (dyphenoxylate) distribution agreement in 1956, three years before the first international symposium on haloperidol in Beerse. This partnership included a pledge on the "right of first refusal" in exchange for 250,000 dollars a year, which had been indispensable for the expansion of Janssen's research team (Schwartz, 1989, p. 31). Hayes, Winter and Venning all belonged to the Searle firm. The following year, Hayes would be responsible for supplying haloperidol samples to the first American clinical trial (Denber, Rajotte, & Kauffman, 1959). Winter was Searle's director of biological research in Chicago, and Venning was Searle's medical director in England. Their presence suggests that negotiations for haloperidol's distribution in the United States and England were already well under way.[30] This difference in approach is noteworthy: from continental Europe, the most respected clinicians were invited to present their experience with haloperidol, while only representatives of the industry came from the United States and England, in preliminary negotiations on a future distribution. Perhaps in these strategic differences lie some of the reasons for the subsequent divide, concerning haloperidol's reception, between continental Europe and the United States.

The editorial space attributed to haloperidol by the editors of *Acta Neurologica et Psychiatrica Belgica* is perhaps surprising. The publication includes the totality of the 17 presentations (although they were heterogeneous in pertinence, methodology and results), as well as a summary of the discussion, and a brief bibliography. This abundant amount of articles dedicated to a new product, still in preliminary clinical trials, suggests an important proximity between the journal's editorial project and haloperidol's validation needs. The journal thus seems to sponsor haloperidol's launch. Also, Jean Titeca, secretary of the *Société de Médicine Mentale de Belgique*, and a member of the magazine's editorial committee, was included on the symposium's guest list. Such evidence suggests that specialty journals were crossroads between academic construction and commercial interests. The *Acta Neurologica et Psychiatrica Belgica* presents, among the articles of the first international symposium on haloperidol, advertising for various psychotropic drugs of interest to psychiatrists and neurologists (e.g. Largatil), as well as advertising for nursing homes in Switzerland.[31]

---

[30] These negotiations would ultimately fail in the following years (chapter 3.1)

[31] p.e. Les Rives de Prangins, at Nyon "toutes les affections du système nerveux" - "psychothérapie, cures de désintoxication et de sommeil, méthodes de choc, régimes."

The *Acta Neurologica et Psychiatrica Belgica* covers (in full) an event organised by the Janssen pharmaceutical company, held at the company's headquarters and dedicated to the commercial launch of a drug. Among the guests at this event were outstanding representatives of the academic world such as Jean Delay, clinicians with responsibility for a large number of patients such as Paquay, representatives of the pharmaceutical industry such as Venning and members of the editorial committee of an important academic journal such as Jean Titeca.

These men, who originally came from disparate biographical paths, and who each had different perspectives, met in Beerse, under the sponsorship of a commercial project. They exchanged, as we will see, scientific data, including quantitative results, and therapeutic and pathophysiological insights around haloperidol. They created points of agreement, and opposition, found common ground, and developed personal privileged relationships.

For clinicians such as the Portuguese Seabra Dinis, receiving the invitation to Beerse represented an opportunity to find themselves at the center of the academic and industrial world of the time, a useful contribution in climbing the medical hierarchy. For academics like Bobon, the invitation to Beerse and the articles that came out of the meeting represented the international recognition of their capacity for scientific production. For industry players such as Venning, the invitation represented an opportunity to meet the big names in the continental clinical and academic world and to understand the commercial possibilities of the new psychopharmacological developments.

The journal materialised these privileged relationships that were unabashedly built between the pharmaceutical, clinical and academic worlds. In the following years, medical journals would continue to function as important links in the construction of the industrial-academic complex that supported and developed psychopharmacological research. In this edition of *Acta Neurologica et Psychiatrica Belgica* we can start to identify the main elements of this construction. Its description of the first international symposium on haloperidol is our main primary source for the next chapter.

2.7.2. Symposium international sur le haloperidol

It is difficult to exactly reconstruct the atmosphere at the first international symposium on haloperidol, September 15, 1959. We can imagine a general sense of excitement with the launch of a new, said to be, transformative drug. International meetings were uncommon for the standards of the day. Janssen personally knew at least some of those present, others were invited through Jean Delay. This chapter intends to synthesise the main interventions that arose from this meeting, and its published proceedings. Of the 16 papers published in *Acta Neurologica et Psychiatrica Belgica*, 13 corresponded to clinical trials, and among those, 6 were developed abroad – in France, Sweden, Denmark, Germany, Italy and Portugal.

The French clinical trial by the Clinique Des Maladies Mentales et de L'encéphale, composed of Jean Delay, Pierre Pichot, Thérèse Lempérière and Elissalde from the Sainte Anne hospital was the meeting's principal presentation. They had been the first to use chlorpromazine as monotherapy in psychiatry, and Jean Delay brought the prestige of being considered the inventor of neuroleptics to the gathering.

While Deniker had been granted chlorpromazine, haloperidol was officially offered to Pichot, although Lempérière seems to have been the person responsible for running the trial. According to Janssen "When I wanted to know something about the clinical effects of haloperidol, after a short period of time I realised that the most effective way of knowing was to talk to Mme Lempérière" (Interview with Paul Janssen in Healy, 1998b, p. 49)

Janssen and Lempérière already knew each other from previous meetings and this probably facilitated their collaboration during the haloperidol trial (Interview with Thérèse Lemperière in Healy, 1998b, p. 8).

Despite being as Janssen says, the lead actor in conducting the clinical trial, Lempérière, wasn't present at the first international meeting on haloperidol. This absence may reflect issues related to medical hierarchy, the institution's internal logistics of praise, and the international recognition that the meeting might have provided. As described in chapter 2.4, although Andre Pinchard might have been among the first to administer haloperidol, his name too was absent from the first haloperidol paper. In the case of

Lempérière, we cannot exclude that issues related to gender might have influenced her exclusion, being one of the few women among the pioneers of psychopharmacology.

The Paris team recognised haloperidol as a member of the neuroleptic *family,* despite its chemical distinctions to the phenothiazines.[32] On the one hand, this language of kinship between substances studied by the authors reinforces the authorial role of Delay and the Paris clinic in the construction of the neuroleptic concept, but on the other hand it also reaffirms haloperidol as a legitimate therapeutic alternative to chlorpromazine, opening the doors to a whole set of therapeutic indications. Comparing haloperidol with the main representatives of the neuroleptic *family*- chlorpromazine and reserpine - would become a recurring theme at Beerse, and Delay had, of course, particular authority in this regard.

There are references to comparative efficacy trials (head-to-head trials) long preceding the introduction of haloperidol, even in psychiatry. For example, between 1952 and 1953, Louis Lasagna had already done an efficacy study comparing three different hypnotics and placebos (Shorter, 2011).

The knowledge necessary for designing a complex clinical trial was available, and in Paris a more formal confrontation between haloperidol, chlorpromazine and reserpine could have been developed. However, the clinical trial in Paris maintained an essentially qualitative approach, with no method of patient selection, no randomisation, no comparative elements (with placebo or with other drugs), almost without quantitative elements. The authors advocated the use of the Wittenborn psychiatric rating scale, which had been proposed three years earlier (Wittenborn, 1986), but did not disclose this data in Beerse. Results were set forth in brief clinical notes (of four lines for each of the clinical cases studied), differentiating between the great diversity of diagnoses used. This heterogeneity of admission criteria, nowadays outlawed, most likely conditioned the doses used, which varied greatly, from 2 to 24 mg/day (Delay, Pichot, Lemperiere, & Elissalde, 1960). Notably, this dosage variability wasn't unique within the studies presented in Beerse (see table 1, Appendix A).

Continental resistance to new clinical trial technologies probably derived from fundamental theoretical opposition, as well as from the complexity and cost they required. There was a critical stance toward randomisation and blind treatment, and ethical concerns to such practices were sometimes also cited. In the words of Linford Rees, French-speaking

[32] The phenothiazines, a pharmacological group that had emerged with chlorpromazine, were then the major class of neuroleptics,.

psychiatry preferred a more "impressionist" strategy (Interview with Linford Rees in Healy, 1998b, p. 172).

Despite the fact that there was no formal head-to-head trial, the main element of the Paris team's paper was haloperidol's comparison to chlorpromazine, the first among the neuroleptics. The Paris team declared haloperidol as qualitatively similar to chlorpromazine but quantitatively more potent. In this sense, potency seems to be the ability to cause direct changes in the patient, and the ability to provoke the desired behavioural or psychopathological reaction. Similarly, Delay uses the concept "activity": haloperidol, he says, would be more "active" than other neuroleptics in psychosis. Psychosis was used as a broad and comprehensive concept, and haloperidol was given multiple therapeutic actions in several heterogeneous psychopathological areas - namely anti-manic, anti-delusional and anti-hallucinatory. For the Paris team, haloperidol's potency was more than the ability to sedate, it was also the ability to "treat". In this way, Delay, the father of chlorpromazine, or at least of its application to psychiatry, recognised haloperidol as superior, as more potent, as more active than chlorpromazine – a powerful statement.

These conclusions marked the cementing of the history of haloperidol. The financial value they represented for Paul Janssen is incalculable: the legitimisation of haloperidol by the father of neuroleptics opened the door to the international market. Consequently, the international audience at the symposium was justified, specially the presence of Searle's representatives, with whom negotiations for haloperidol's distribution in the United States and England would soon begin.

From reading the papers presented at the first congress on haloperidol, we can try to guess the institutional context where researchers imagined its use. We know the role that would later be attributed to neuroleptics during the transition in the 1960's from asylum psychiatry to community psychiatry, but the impression we get from reading the articles in *Acta Neurologica et Psychiatrica Belgica* is that these first clinicians, pioneers of the first neuroleptics, did not yet foresee the role that will later be assigned to them. And, despite the safety of haloperidol being repeatedly stressed, the preferred background for its use appears to be the hospital setting.

In Delay's words:

> [...] le haloperidol nous parait avoir une efficacité remarquable à condition d'être administré avec précaution, sous surveillance médicale constante et attentive, et en adaptant la posologie aux réactions du malade. (Delay et al., 1960)

And, the same idea, more explicitly expressed by the Liège's team:

> Son application doit être l'objet d'une surveillance médicale constante que l'on conçoit mal dehors du milieu hospitalier. (Divry, Bobon, & Collard, 1960)

In this context, Waelkens' article is very enlightening as the first example of systematic out-of-hospital use in Rekem, on the border between Belgium and the Netherlands, halfway between Liège and Beerse (Waelkens, 1960).

Both the Paris and Liège teams advised the use of haloperidol under intense supervision, suggesting an exclusive intra-hospital use. Waelkens, on the contrary, tested haloperidol's performance in community treatment. That might be one of the reasons why Waelkens' article contrasted with the meeting's overall optimism. Presenting results with a very high number of participants (with about 160 patients, it was by far the largest clinical trial presented at the meeting), examples of therapeutic failure abound.

Waelkens used significantly lower doses in Rekem than those proposed by the other articles presented at Beerse (1.5 to 3 mg per day, see appendix A, table 1),[33] and described the higher doses as unendurable due to fatigue and neuromuscular side effects. This prompts the question of how to interpret this decrease in the therapeutic margin, especially when we contrast it with the other data presented.

Perhaps the behavioural changes and the clinical states that Waelkens was confronted with in an outpatient setting were qualitatively different, and perhaps quite possibly quantitatively less severe, since they were compatible with life in society and would not have required forced hospitalisation. Less complex clinical states, less severe behavioural changes, perhaps recommend lower doses. Behind this idea remains the hypothesis that the substance's activity, its transformative capacity, can be differentiated depending on the dose used. This quantitative view of the drug's action – where higher doses would be necessary in more severe clinical conditions - would be somewhat reinforced by the dopamine hypothesis of schizophrenia, which led to the megadose treatment sometimes seen in 1970's and 1980's.

The outpatient setting entailed different expectations. Being in the community perhaps involved changes even in the disease process, but certainly altered the way in which the

---

[33] For comparison Bobon was using 7.5 to 30mg a day (Divry et al., 1960).

illness was lived by the patient, and in a similarly way its impact in the patient-doctor relationship. Outside the rigid hospital hierarchy, a redistribution of power took place. Consent gained importance. Contrary to the asylum, in an outpatient clinic, therapeutic choice was almost always possible. Waelkens' identification of dose-dependent side effects, and the importance of minimising them in the context of a greater ability to oppose treatment, probably favoured the use of lower doses.

That being so, a major contraindication is outlined in Waelkens' presentation: “les états dépressifs et névrotiques dans toutes leurs formes” (1960). This proposition is important and revealing. It builds upon psychiatry's foundational schism between neurosis and psychosis, between outpatient and asylum, between private and public, and firmly places haloperidol on the second side of this barricade.

Another riveting presentation came from a young psychiatrist called Emile Meurice. Meurice was 33, trained in Medicine at Liège’s University, and had not yet completed his internship in psychiatry. He was working in Lierneux, where he would later become *médecin-chef* between 1970 and 1991. At the haloperidol meeting, Meurice didn’t present a clinical trial, but a captivating theory about neuroleptics and their therapeutic mechanism. He proposed that neuroleptics trigger a diffuse neurological state, with a global change in understanding, modifying the reaction to direct threats to the Self. Meurice saw neuroleptic action as unconditional and unspecific, that is, as independent from the patient’s diagnosis. This condition of greater indifference, of less discernment of danger, would prove to be particularly useful in psychosis.

Meurice didn’t consider the possibility of a differentiated therapeutic mechanism acting on the pathophysiology of psychosis. He didn’t see neuroleptics as acting on biological changes in the brain caused by the disease. On the contrary, neuroleptics created, through their biological activity, a unique neurological state (different from both normality and disease). If psychotic states were seen as hyper-focused on delusional contents, a nonspecific state of impaired judgment brought on by neuroleptics, could, somewhat incidentally, become particularly useful.

> Toute notre experience confirme que le R1625, comme les autres neuroleptiques, - et souvent avec plus de force - a comme première et principale action de diminuer *l’état d’hyperfocalisation* du malade vis-à-vis de ses préoccupations délirantes. Bien entendu, ce n’est lá qu’une conséquence particulière d’une diminution de l’acuité générale avec laquelle

> le sujet ressent les dangers que menacent sa personnalité. Le cercle vicieux de l'angoisse étant rompu, il n'est plus nécessaire de recourir à des défenses d'un niveau aussi mauvais que le délire, et le malade peut réorganiser progressivement sa personnalité. (Meurice, 1960)

This explanation of neuroleptic action maintains two main features that reflect the spirit of the time. On the one hand, a discourse mixing semantic elements with origins both in biology and psychoanalysis and, on the other hand, a view of neuroleptic treatment as unspecific. This exploration of the interaction between psychological, or psychoanalytic, traditions and somatic interventions may appear exotic to our contemporary gaze. In Meurice's case, the bridge between the two explanatory levels, the point of union between the somatic and psychological dimensions, was an altered state of discernment. The following paragraph clearly illustrates the psychoanalytic influence that remains remarkable:

> Il ne faut pas oublier que la psychose est la solution - la mauvaise solution! - par laquelle la personnalité essaie de compenser son incapacité d'intégrer de façon harmonieuse toutes les exigences auxquelles elle devrait faire face. Quand les neuroleptiques ont atténué l'état d'extrême angoisse qui avait fait recourir à la solution psychotique, ils n'ont pas résolu pour autant des problèmes fondamentaux de la personnalité. (Meurice, 1960)

This hybrid discourse was not surprising or unusual during the 1950's, we can find similar arguments present in the first published paper on haloperidol by the Liège team (Divry et al., 1958), but also in many of the presentations at the haloperidol's symposium (e.g.Gerle, 1960; Seabra-Dinis & da Silva, 1960). Influential scholars like Nathan Kline and Mortimor Ostow also subscribed to similar theories (see chapter 2.5). Neuroleptics were able to reduce intrapsychic tension, allowing the reemergence of unconscious contents that were previously inaccessible and favouring a new balance between the Ego and the Id. (Ramos, 2013).

In order to penetrate traditional clinical practice the new psychotropic drugs first allied themselves with a priori transnational technologies, including psychoanalysis, but also neurosurgical procedures and shock therapies. Different methods weren't seen as conflicting, on the contrary, they were mostly viewed as complementary. Authors such as Andrew Lakof argue that the introduction of new psychopharmacological interventions in the 1950s led to the strong development of group therapies, and a new expansion of psychoanalytic approaches to psychosis (2006, p. 8).

Another important idea shaped Emile Meurice's theory, as presented in Beerse, namely the therapeutic action of neuroleptics being seen as being without specific activity.

Psychiatrist Joanna Moncrieff argues that this representation was hegemonic throughout the 1950s and 1960s. Moncrieff describes early theories about neuroleptic action as drug-centred, only later theories would acquire a more disease-centred perspective (2013). The first neuroleptics (as Meurice explains) were capable of creating an altered state of consciousness, or at least a marked change in the way we feel or react to intense stimulus. This altered state helped control or mask the symptoms of mental illness. Over the next two decades, as the industrial and academic complex that supports biological psychiatry was being built, the concept of neuroleptics would be progressively transformed, patched up, and reconfigured into another term - antipsychotic. In the last chapters, our research showed some of the first crucial steps in that direction, as Paquay's and Janssen's work favoured a specific anti-schizophrenic activity.

During the following decades Emile Meurice would remain close both to the University of Liège and Janssen Pharmaceuticals. In the appendix B, figure 1, we can see a photograph of Meurice and Janssen at the inauguration of a series of seminars on the rehabilitation of schizophrenics, at the University of Liège. The academic meetings were called Paul Janssen's seminar (Cycle de séminaires Paul Janssen), and Emile Meurice was the leading scholar. This collaboration peeked with the book *Le traitement a long terme et la réhabilitation des schizophrènes*, sponsored by Janssen Pharmaceuticals and published posthumously after Janssen's death (Meurice, 2005).

Meurice is one example, among many, of the networks of personal and professional proximity that Janssen created between clinic, university and industry. Nevertheless, this (and othersuch) relationship reveals several delicate subtleties that those networks possessed. Although the young Émile's perspective was almost the opposite of the industrialist's view of his drug, Janssen invited him to present his point of view in Beerse. Although Meurice, throughout his life, remained close to these initial insights on the action of neuroleptics, rowing against the growing definition of substances as antipsychotics, Janssen maintained his support (including financial sponsorship of his book). This idea, that Janssen's support to academic activities didn't depend on, nor condition, scientific production, that may seem naïve, is recurrent throughout our research (for example in our interview with Christian Mormont, Liège, February 27, 2019), and finds support in this example. That the young Émile Meurice, who was not yet a psychiatrist, was invited to present his intuitions at Beerse,

even if they were the opposite of Janssen's own views, is significant. It suggests that an uninterested attitude towards scientific content, a resistance to exercise clear control over scientific directions, or maybe even an acceptance of a plurality of perspectives were important parts of Janssen's activity, not only in the establishment of the relationship between Janssen and Liège university, but above all in its durability and influence.

Alongside these examples, it is important to note that in the symposium's discussion section Dr Evrad of the Sanatorium pour maladies mentales, *Volière*, also in Liège, explained, another interesting theory for the therapeutic mechanisms of haloperidol (1960). For Evrad, painful and motor side effects associated R1625 diverted the patient's attention from his delusional concerns towards the body. Attached to the body, thought would not be able to surrender to delusional constructions. Here was a vision of psychological energy as something that was transported and transformed between the delusion and the body. This quasi-hydraulic view of human attention is reminiscent of psychoanalysis (Winograd & Davidovich, 2014). It was, again, an explanatory theory without specificity, based on broad indications, centring on a drug-centred mechanism (as proposed by Moncrieff (2013)), similar in this sense to Meurice's theories, and capturing the zeitgeist of the moment.

The Portuguese team's presentation was another example of a strong interaction between psychoanalysis and psychopharmacology. Seabra Dinis framed, from the outset, the use of R 1625 in a process of humanisation of care that involved the introduction of new psychotherapeutic and psychopharmacological techniques. Haloperidol was presented within a moral narrative with a progressive bent, where medical care was seen as increasingly well-intentioned and effective. This optimistic narrative, so prevalent in the history of psychiatry, contrasted with the tough reality of mental patients. For example, in Seabra Dinis haloperidol's trial 15% of patients had previously undergone leucotomy.

But, more than the therapeutic effects on the patient's individual symptoms, the Lisbon team highlighted the consequences of haloperidol in the institution itself: "le profond changement dans le climat des pavillons". So, silence and tranquility returned as important indicators of a drug's effectiveness:

> La drogue nous faisant ensuite défaut, nous avons dû interrompre le traitement chez la plupart de ces 39 malades, au grand regret des infirmières. Et cette situation a aussitôt fait dire, d'une manière ironique, que le nouveau médicament était au moins aussi utile aux infirmières qu'aux malades […] C'est pourquoi on a pu dire ironiquement que le R 1625 met les malades

> dans un tel état d'asthénie qu'ils ne sont plus capables de rien faire, ce qui allège beaucoup le travail de surveillance des infirmières. (Seabra-Dinis & da Silva, 1960)

This quote illustrates that even as therapeutic effects on specific symptoms started to be sketched, changes in the asylum's daily life continued to be a key factor in haloperidol's success. Those institutional transformations included a profound shift in the ward's power relations, a newfound ability to maintain order and a growing capacity to ensure collaboration.

Bo Gerle's presentation of the Swedish trials used the same hybrid discourse. The drug's action wasn't seen as psychotherapeutic in itself, but capable of creating conditions that allowed the use of other, more truly, psychotherapeutic instruments:

> The agent also proved beneficial in a specially selected case with a long history of autism and dementia at St. Lars Sjukhus, in which a definite improvement led to readier communication with the patient and a decrease in her personal carelessness; this may render her accessible to environmental and occupational therapy, and continued amelioration. (Gerle, 1960)

In the first international meeting on haloperidol secondary side-effects, namely extra-piramidal, or parkinsonian, side effects were gaining attention. Specifically a possible therapeutic role of motor changes was recurrently discussed.

Meurice, for example, dedicated a large part of his presentation to a reflection on the contours of this relationship, even if he concluded in favor of the independence of motor and psychotherapeutic effects (Meurice, 1960). The symposium's concluding discussion was mostly preoccupied with the same questions (1960). Bobon (representing Liège) asked Pichot (representing Paris) if he saw a temporal proximity between parkinsonian symptoms and neuroleptic therapeutic activity. As we will see in the chapter 3.5, this was the influential thesis of the German physician Hans Joachim Haase, and would later be endorsed by Paul Janssen.

The meetings consensus seem to follow a different direction, and the Paris team answered such concerns clearly and confidently:

> On trouve des malades présentant un syndrome extrapyramidal, d'autres qui n'en ont pas, sans qu'il existe de rapport entre l'activité thérapeutique et l'apparition ou non de ce syndrome. ("Discussion", 1960)

Interventions by Elissalde (Paris), Boissier (Paris), and Haene (Bruges), reinforced both Pichot's answer, and the thesis already defended by Meurice. A general agreement emerged and the extrapyramidal syndrome wasn't seen as an essential element of drug action.

Maybe surprisingly, Janssen, himself, seemed to defend that possibility, perhaps hoping to develop new substances, without neuroleptic characteristics, but capable of answering more adequately to clinical needs.

A clear differentiation between therapeutic effects and side effects emerged from the discussion, promoted above all, as we have seen, by the Paris team.

In this brief discussion, we have an example of how consensus in science could be negotiated, even if precariously. Pichot, representing the influential Paris team, set the tone for the discussion. Opposing voices (like Evrad) contested the position of power, but nonetheless, it gained general support. The final position belonged to the great industrialist - Janssen closed the discussion by subscribing to the majority position (although, as we will see, he was to defend a different theory in the near future).

The way in which the first haloperidol meeting ends is revealing:

> Je pense que c'est de cette façon-lá que, tôt ou tard, nous trouverons un nouveau groupe de medicaments, que ne seront plus des neuroleptiques, mais qui pourront donner, en psychiatrie, les résultats qu'on n'arrive pas à obtenir pour le moment. C'est pourquoi, je pense, une collaboration étroite est absolument indispensable entre le laboratoire et la clinique, le laboratoire restant impuissant a faire quoi que ce soit sans une etude clinique approfondie, curieuse et efficace. ("Discussion", 1960)

In this sentence, Janssen recognised the limitations of the neuroleptic concept, and even seemed to suggest the imminent emergence of a new drug class. Maybe there's some kind of anachronism in our stance, but these words of Janssen's almost convey that the idea of the antipsychotic drug was already germinating. That is not, however, probable, specially if we take into account the close collaboration with Hans Joachim Hasse he would develop in the next few years.

The Janssen quote also calls for a growing collaboration between researchers, and a greater proximity between laboratories, asylums and universities. These meetings were not only a way to share empirical data and explanatory theories, but also a means for creating privileged personal relationships. There, future projects were outlined, including clinical, academic and financial aspects. A growing network of interests and dependencies would thrive, and become professionalised, within a progressively regulated and complex framework making this of paramount importance to our current research.

3. An Atlantic Divide

3.1. Denber's trial

Herman Denber, the man responsible for the first clinical trial of haloperidol in the United States, was sometimes labeled an emissary between Europe and America. In the post-war period, the English language had asserted itself as the international language in scientific publications, meetings and conferences, yet, as we've encountered during our research, it was in continental Europe that the main protagonists in the history of psychopharmacology emerged. European psychiatrists, particularly the French, including Delay and Deniker, the *fathers* of chlorpromazine, had a rudimentary knowledge of the English language. Denber was fluent in both French and English. He worked in New York, but had been educated in Geneva, in French-speaking Switzerland, and so was particularly well positioned to build bridges across the Atlantic (Healy, 2002, pp. 97,109).

One of the endnotes of *Shock Therapy* (2007), Healy and Shorter's work on electroconvulsive therapy, mentions Denber's European origin, but a biographical note published in the *Psychiatric Quaterly* ("Contributors to this issue", 1958), locates his birth in New York, where he lived until he was 21 years old. In 1938 he began his medical degree at the University of Geneva and returned to Manhattan in 1943, becoming medical director of the psychiatric department in 1955.

Denber's interest in mescaline began early in his career. He was aware of its therapeutic potential, valuing mescaline's ability to favor verbalisation and facilitate symbolic expressions of internal conflict (Denber & Merlis, 1954). These results were in accordance with existing theory, such as Busch and Johnson's work with LSD and its psychotherapeutic possibilities, namely the disturbance of the repressive barriers of the conscious mind. The samples Denber used had been supplied by Smith, Kline & French, the same company that marketed chlorpromazine with increasing success, and was also pondering mescaline's promising therapeutic possibilities at the time (Shorter, 2005, p. 123).

Since 1952, scientists had highlighted potential risks associated with mescaline experimentation, like serious worsening of symptoms in psychotic patients (Hoch, Cattell, & Pennes, 1952). In 1955, Denber recognised this risk, and advanced a new function for mescaline. Unlike the earlier trials, searching for therapeutic possibilities, Denber proposed a

potential role for mescaline as a model of psychosis. His description of the clinical picture caused by mescaline (in patients already diagnosed with schizophrenia) included visual and auditory hallucinations, paranoid and somatic delusions, as well as catatonic states with negativism and waxy flexibility (Denber & Merlis, 1955). The states induced by the substance resembled what he considered to be the clinical presentation of schizophrenia, and from this similarity emerged the possibility of triggering and/or experimentally manipulating psychotic symptoms through mescaline. The pharmacological generation of psychotic states would represent their chemical embodiment. The consequences of this possibility would be multiple and far-reaching. On the one hand, starting from the manipulation of mental states altered by hallucinogenic substances, one could perhaps arrive at answers about the pathophysiology of schizophrenia, calling into question broader, more complex and subtle etiological theories, and facilitating the development of new therapeutic technologies. On the other hand, if confirmed, this culmination of mental illness in brain chemistry would be a fundamental part of the processes of the somatisation of mind and behaviour that characterise modernity (e.g. Vidal, 2009).

Despite Hoch's data, and knowing that mescaline could pose a risk to his patients, Denber continued to experiment with mescaline in psychotic patients for at least a decade (Denber, Teller, Rajotte, & Kauffman, 1962) .

Denber worked in a primarily psychoanalytically oriented setting, in this 1950's New York (Interview with Thomas Ban cited in Healy, 1998a, p. 588), but he was not skeptical of psychopharmacological interventions, quite the contrary. His letter to the editor of the Journal of the American Medical Association (J. A..M.A) on June 18th, 1955, is paradigmatic of his position as a mediator, as we have seen, between Europe and the United States, but also between psychoanalysis and psychopharmacology. In that letter, Denber merges data from 14 different institutions in Western Europe, also including results from Ward's Island, Manhattan State Hospital, in order to review the incidence of side effects during chlorpromazine treatment. There were rare cases of jaundice, hives and two cases of parkinsonian symptoms in those 4360 patients. The article ends with a passionate defense of the new neuroleptics:

> The whole question of side-reactions to chlorpromazine and, for that matter, Rauwolfia has been stressed out of all proportion to the problem and is tending to obscure the rather unusual potentialities of these drugs in management of mental patients. Continued reports of lethal reactions in "one case" will activate unconscious anxieties and fears and, in the long run,

induce a profound therapeutic inertia. Psychiatry can ill afford such state at this time. (Denber, 1955)

That same year, he became director of Ward's Island, and started to be a regular presence at international psychopharmacology meetings. In a rapid rise in the field, two years later he occupied a prominent place among the international scientific elite.

The first international meeting on chlorpromazine (International Colloquium on Chlorpromazine and Neuroleptic Drugs in Psychiatric Treatment) took place in October 1955, and was symbolically held at the Saint-Anne Hospital in Paris. It was a big 3-day event with 257 participants from 19 countries (Ban, 2007). The Paris team was present, of course, with Pichot, Delay and Deniker, but also Lehman and Azima from Canada (the latter signing the official report), the German Wolfgang de Boor, the American Freyhan and, of course, Herman Denber (Azima, 1956).

Two years later, in May 1957, the main protagonists met again in Europe for the International Symposium on Psychotropic Drugs in Milan. The German De Boor and the Swiss Radouco-Thomas proposed to found an international association to promote the study of psychotropic drugs, intending to promote communication between clinicians and neuroscientists. Herman Denber was one of the first to support this idea, but this wish came true only 4 months later at the second world congress of psychiatry in Zurich (also 1957). Rothlin, the former president of Sandoz, organised a buffet at the Zurich train station, formalising the beginning of the CINP (International college of neuropsychopharmacology), for which he was elected president. Denber, reinforcing his international prestige, was elected secretary, together with Radouco-Thomas. The environment during the early years of the CINP is described as difficult, Denber and Rothlin did not get along, allegedly for personal reasons. "Denber was a little tough and Rothlin was very insensitive" (Interview with Heinz Lehman Healy, 1998a, p. 176).

Denber had this leadership role in the CINP (a collaboration formed in Europe and with fundamentally "biological" concerns), but he was also promoting another international society at the same time. Following the model of old scientific gatherings of the XIXth century, this was paradoxically called "the group without a name". The society included annual conferences in North America, with an audience restricted to a few young researchers, and with a mostly non-biological bent, dedicating itself to psychodynamic, social and cultural

factors, as well as factors related to the therapeutic environments that might influence pharmacological treatment (Sarwer-Foner, 1966).[34]

In the concomitant development of these two prestigious international groups, we can see how, through his role as a liaison (between English and French, between Europe and North America, between psychoanalysis and psychopharmacology), the young Denber acquired a thriving institutional status early in his career.

In the United States of America, the first trials of psychotropic drugs took place in state hospitals on the East Coast. Unlike Europe, where psychopharmacology emerged closer to academic activity, in the United States, these first essays were developed within asylum psychiatry, far from the influence of the University (Interview with George Simpson, Healy, 1998b, p. 297). Denber, as the director of research at Manhattan State Hospital, was particularly well positioned to carry out such testing, and his ward became a pioneer in testing the first neuroleptic drugs. While developing this growing international visibility and continuing hallucinogenic research, Denber conducted clinical trials to test at least two neuroleptics, prior to the famous haloperidol trial in 1959. Mepazine by Warner-Chilcott Laboratories in January 1958, and thioproperazine (Majeptil) provided by the Smith, Kline & French's laboratory in 1959, the latter was carried out immediately before the haloperidol trial.

Mepazine was tested in 47 patients, of which 35 had already shown resistance to other therapeutic interventions and in only 12 mepazine was tested as a first therapeutic strategy. The results were clear in Denber's perspective: 4 patients improved greatly (8%), 12 improved (25%) and 31 (66%) showed no improvement. Denber concludes unequivocally that the drug is ineffective, publishing the results under the title "Ineffectiveness of mepazine (Pacatal)" (Denber, 1958). Shortly afterwards, in 1960, the team of Whittier and Klein, in a

---

[34] Gerald Sarwer-Foner in a 1994's interview tells an humorous story that deserves to be transcribed: "We didn't have a name, of course, so someone said, "Well it's the group that does not have a name, so we became known as 'The Group Without a Name'." Some very funny things happened. Hy (Herman) Denber tried to run a meeting in a nice warm place in Miami and he went to the hotel to make arrangements and said we wanted to reserve the hotel for a meeting and they said, "Yes sir." And then the guy asked, "Who is the president?" He said, "We don't have a president." Then they asked, "Who is the treasurer?" "Well, we don't have a treasurer." "Well, what's the name?" "Well, we haven't got a name." And at that point they threw him out. So after that we were called The Group Without a Name, and later on we were called the International Psychiatric Research Association." (Interview with Gerald Sarwer-Foner, 1994, found in https://acnp.org/videos/gerald-sarwer-foner-by-george-awad/)

sophisticated test designed with control and no influence from the industry, agreed that mepazine had no beneficial effects (Klein, 2007).

In contrast to mepazine, thioproperazine (R.P. 7843) was marketed by the influential Smith Kline & French, and had the prestige of being endorsed by Delay and his Paris team. In Manhattan, thioproperazine was tested in 23 patients, in none of which it was used as a first therapeutic strategy. The results presented were considered distinctly better than Mepazine's. Four patients (17%) improved a lot, twelve improved (52%), six did not improve (26%) and one patient got worse (4%). Denber concluded for great clinical efficacy.

> The very favourable response in a patient group with such a poor prognosis makes this compound worthy of further extensive trials. (Denber, P. Rajotte, & D. Kauffman, 1959)

These results were published just a few months before haloperidol's. Given the chronological contiguity we can reasonably suspect that some patients included in the thioproperazine trial may have been sequentially included in the haloperidol trial, or even that, perhaps at a certain point, the two trials ran concurrently, suggesting a comparative character (explicit or implicit) between the two substances.

According to Paul Janssen's interview with David Healy, Denber had spontaneously visited the Janssen Pharmaceuticals laboratories in one of his several trips to Europe, asking for samples of haloperidol, in the hope of being the first to test them in the United States.

> He came to see me after having visited Jean Bobon in Liège to see what haloperidol was doing in patients there. He came to see me asking for samples. I was very pleased because I had never seen an American psychiatrist before. Being very honoured, I gave him all the samples he wanted. (Interview with Paul Janssen cited in Healy, 1998b, p. 45)

This narrative, justifying Denber's choice as the first person responsible for an haloperidol assay in the United States, enhances casualness and highlights the role of informal knowledge networks. In his own description, Janssen seems almost surprised, suggesting that the choice of Denber was due more to chance than to personal qualities. In these sentences, Janssen implies the absence of a meticulously planned commercial strategy for haloperidol's introduction in the United States, which does not seem exceptionally credible to us. The story that Janssen tells may be best understood as a first justification for the difficulties encountered by haloperidol in North America. In this account, neither Janssen nor Searle were responsible for choosing Denber, he volunteered. The option wasn't planned within the scope of a commercial project that would, perhaps precisely because of that

decision, fail resoundingly. The informal narrative excuses the agents and limits the responsibilities attributable to them.

In a published paper describing Denber's first study on haloperidol we can find a note of recognition to Thomas Hayes, as the person in charge of providing the haloperidol samples. We can recognise Hayes' name from his presence at the first international symposium about haloperidol on September 15th, 1959, which we described in chapter 2.7.2. The three english speaking presences at this symposium (Hayes, Venning and Winter) were, as we had seen, all representatives of Searle.

The same structural manipulation of pethidine that resulted in haloperidol had previously led to the production of diphenoxylate, patented by Janssen Pharmaceuticals as an analgesic, and later to fentanyl and loperamide (Ravina, 2011, p. 63). Gordon van Armand, a Searle pharmacologist, accidentally discovered diphenoxylate's antidiarrheal activity, leading to its subsequent introduction in the United States as Lomotil, and creating a new partnership between Searle and Janssen Pharmaceuticals. The relationship of mutual interest included the right of preference over any new compound produced by the Janssen firm (Healy, 2002, p. 123). We may suspect that there is an implied criticism in Janssen's description of Jack Searle particularly around his lack of scientific curiosity or clinical enthusiasm (Interview with Paul Janssen cited in Healy, 1998b, p. 51). However, the relationship between Searle and Janssen predates Lomotil, and even as an undergraduate Janssen had already visited Searle's laboratories in the United States (López-Muñoz & Alamo, 2009).

In this context, it wasn't surprising that Janssen presented the newly developed haloperidol to Searle, nor that Hayes, Winter and Venning were invited to the first international symposium on haloperidol, or that Hayes (representing Searle) would be the one to supply haloperidol to Herman Denber.

The choice of Denber may have followed more rational criteria than a first informal narrative seems to suggest. Searle's control of the process suggests that Denber may have been chosen for bringing together a set of attributes that maximised both the chances of success and the importance of the trial. Among these qualities, his role as a mediator stood out, not only between Europe and the United States, but also, and perhaps above all, between psychoanalysis (which could maybe hinder the penetration of psychotropic drugs into North America) and the psychopharmacological approach. Other characteristics that could have

favoured the choice of Denber include: his geographical location on the east coast of the United States that asserted itself as the geographic center of psychopharmacology in the new continent (where the main laboratories were); the fact of running a state hospital, the preferential setting of the first clinical trials in the United States, and also, possibly, his growing visibility in the international institutions that were developing at the time, and that he himself helped to promote.

Denber, then, was a man invested in creating bridges, with personal and institutional ambitions, suggesting he wouldn't create ruptures, neither between Europe and the United States nor between pharmacological and non-pharmacological approaches. From a commercial strategy standpoint, Herman Denber would be the perfect choice for a drug that had found strong scientific and clinical support across the Atlantic. His intern Paul Rajotte, the second author of the study,[35] was a further guarantee that the European results weren't likely to be called into question. Bilingual, trained in Montreal, he would leave for Paris in the coming months, to train with Jean Delay (and the Paris team had highlighted the "potency" of haloperidol).

Haloperidol's trial was in many ways similar to the thioperazine trial that had immediately preceded it, both in the number of patients (30 compared to 23 in the thioproperazine sample) and in the exclusively female sample making up the trial subjects. However, the outcomes were radically different; with haloperidol only 4 patients (13%) improved significantly, 5 (17%) improved, and 21 (70%) patients maintained the same clinical status (Denber et al., 1959). These results were comparable to those obtained with mepazine, and contrasted with haloperidol's European trials, notably in Liège, but also in Paris, and other places, whose data, as we have seen, had been presented in Beerse one month earlier.

Creating a drug implies constructing a compound, but also its field of action (its indication), as well as its capacity for experimental transformation (its therapeutic properties). The process therefore implies persuading others, including the scientific community, regulatory authorities, the patients (and those that promote their interests), and the various professional groups involved in clinical practice. With the objective of acquiring credibility,

[35] Paul Rajotte would die prematurely at 35 in1966 ("In Memoriam", 1967).

and of solidifying therapeutic action, epistemological stability is critical, and the ability to replicate previous clinical trials is paramount.

The consequences of the Denber trial had such a widespread impact that it was probably disproportionate to the original sample size. For Paul Janssen, Denber's study led to the development of a long period of strong anti-haloperidol sentiment in the United States:

> […] in America, certainly at the beginning there was a very strong and long-lasting anti-haloperidol period. This was a direct consequence of the first publication in the American Journal of Psychiatry, by Herman Denber […]. (Interview with Paul Janssen, Healy, 1998b, p. 44)

The Denber study's results were probably behind Searle's loss of interest in marketing haloperidol in the United States. The market introduction of haloperidol in North America would only come to fruition several years later by McNeill Pharmaceuticals, after a long patent war with its main competitor - Smith, Kline & French (Granger & Albu, 2005).

It is relevant to highlight that amidst the five products tested in Wards Island until 1960, the 3 that obtained positive results belonged to the same pharmaceutical firm Smith, Kline & French (chlorpromazine, mescaline, thioproperazine). The two other products, coming from competing laboratories, had unsuccessful trials. That said, we do not have any other data that would allow us to suggest that Herman Denber could have an exclusive affinity to Smith, Kline & French. In our correspondence with one of his future interns we approached this subject, and although she emphasised the usual generosity of Smith, Kline & French at the time, she denied having knowledge of a privileged relationship (Personal correspondence with Mary Seeman, February 12, 2020).

Paul Janssen explains the Manhattan results mainly by the lack of direct involvement by Denber:

> He went back home but what he did then was to give the samples to one of his nurses by the name of Mrs Kauffman. And Mrs Kauffman was instructed by Denber to give the compound to 10 patients in increasing doses to see what would happen. Denber went on another trip probably. He actually never saw the patients. He came back and he asked Mrs Kauffman what was her experience with haloperidol and she said it didn't do anything at all. It was like water. It did not even induce side-effects. So he took his pen and he wrote a paper which basically says that haloperidol is a very effective drug in Europeans but for genetic reasons, completely inactive in Americans. (Interview with Paul Janssen, Healy, 1998b, p. 45)

The story, as Janssen remembers it, reduces the number of patients in the trial, if we trust Denber's published article, the sample had 30 patients and not only 10 as Janssen

recalls, but it also decreases the intensity and frequency of the described side effects. In fact, Denber says that “An extrapyramidal syndrome was the most frequently observed side-effect (12 patients), was fairly incapacitating requiring anti-parkinson drugs” (Denber et al., 1959).

Janssen’s version of events is not completely unreasonable. Ms. Kauffman is one of the authors mentioned on the haloperidol’s paper, although it is important to note that she was also referenced on the immediately previous study (Majeptil), a study that demonstrated the usefulness of the product. Nevertheless, in view of the rudimentary professionalisation of drug trials, including elementary methodology and the absence of real quantitative assessment instruments, the clinical encounter between doctor and patient could be seen as a cornerstone for clarifying the therapeutic possibilities of any compound. Referring to Denber's absence during the study is therefore a substantial criticism, and is a critique that is constructed in the form of a particularly effective narrative. Shifting the responsibilities from a man, a medical doctor, amply respected, occupying a powerful institutional role, to a woman, a nurse, unknown, and with no place in history, Janssen finds an easy justification for his product's failure.

However, things are rarely so straight forward, and the truth is, in the vast majority of haloperidol’s earlier studies in Europe, nursing staff had been central to the trial, including on issues of methodology, dosage decision and outcome description. This isn’t surprising as it reflects usual task management in the asylum. In his interview with Missa, Janssen himself describes the importance of nurses in the Dave’s trial, notably identifying the antidelusional and hallucinolytic effect:

> Mais ceux qui connaissaient le mieux le produit c’étaient les infirmiers-frères de la charité qui vivaient à l’asile de Dave et qui donnaient les gouttes d’haldol, lavaient les malades, dormaient avec eux. Ce furent eux, dans un certain sens, qui m’apprirent ce qui se passe quand on donne les gouttes, pas les psychiatres. Ils connaissent très bien les malades. Ce furent eux qui découvrirent la variété clinique et qui en firent part aux médecins: la suppression des hallucinations et des délires; le rapport humain qui devenait à nouveau plus ou moins possible; l’agitation psychomotrice qui disparaissait aussi (mais cela on pouvait déjà l’obtenir avec les sédatifs). (Interview with Paul Janssen, Missa, 2006, p. 245).

So how can we understand this difference in outcomes between the haloperidol trials in Manhattan and those in Liège or Dave? To answer this question we must first understand not only what exactly was being tested in these early trials of haloperidol, but also what efficacy criteria were used (- that is to say, what the expectations of therapeutic action were).

Denber didn't have a reductionist approach to treatment, on the contrary, he placed pharmacological intervention within an extended concept of *therapeutic milieu*. The various drugs continually tested at Wards Island were part of a broad clinical device that applied complex concepts, including for example "therapeutic community". The "Group Without a Name", organised privileged meetings for exploring these non-pharmacological technologies.

In a 1957 paper he described the three fundamental areas of assessment during clinical trials, including emotional reactions, ideational content and interpersonal relationships. In order for the clinical status to be considered improved, there had to be a decrease in the intensity of various symptoms, but the criteria were mainly focused on behaviour and cooperation within the hospital's everyday life.

> For example a patient who had been in restraint for intermittent periods during several years but was now quiet, cooperative and taking part in the ward routine would be considered improved. (Denber & Bird, 1957)

The effectiveness of a given drug was measured by the ability to facilitate cooperation with authority, rules, requirements and needs of the ward. Institutional life thus played a dual role in these trials, it appeared not only as part of the device, the therapeutic apparatus under test, but was itself a critical measure of the therapeutic response (efficacy), merging aspects of both drugs and social therapy during the trial and in its results.

> An analysis of observations made during continuous drug trials in this hospital since 1954 has shown how difficult it is to speak exclusively of a "drug effect" or an "environmental influence". (Denber, 1963)

In the same paper, Denber detailed the social interactions that were at stake during a clinical trial, and from these we can then more clearly identify a conceptual and methodological framework originating from the most recent theoretical productions around the concept of therapeutic community.

> It has been shown that both the conduct of a drug trial and the end result are equally functions of the pharmacologic effect, the broad interaction patterns between patient and staff, the attitudes of the nursing staff to the treatment, the relationship of nurses to the medical staff and the general group process operative at that time. (Denber, 1963)

The start of therapeutic community programs are frequently placed in Britian during the second world war, although their core values are likely to be found much earlier (Whiteley, 2004). Joshua Bierer's work promoting a self-regulated group at Runwell Hospital is one of the first examples cited in the literature (Shorter, 2005, p. 249), to which we will

return in the next chapter. Another example is Maxwell Jones, with whose work Denber was familiar, and referenced abundantly. Jones' methodological principles included the need for open communication, the dismantling of hierarchy and a democratic decision-making process (Whiteley, 2004).

In a 1963 article, Denber traced the processes of transformation in the unit he supervised, beginning in 1957. His depiction of Wards Island, before the introduction of therapeutic community principles, reinforced the penitentiary, punitive, almost violent atitudes, the hierarchical rigidity and absence of communication. He described a unit closer to a prison than a hospital, a place where any kind or empathetic gesture seemed impossible, a place where the expression of individuality seemed inconceivable. It was a unit described in a perfect and complete opposition to the methodological principles of Maxwell Jones. This flat portrayal, perhaps simplistic, of the initial conditions at Wards Island reinforced his own power of intervention, highlighting the transformative capacity of the program he himself introduced:

> Until April 1957, this was " a disturbed Ward" with all its principal atributes- locked doors, barred windows, agitated and assaultive patients, liberal use of camisole and sheet restraints, seclusion rooms, untidy patients, rigid rules of ward conduct, movement in and out - for the most part in groups - always accompanied by an attendant, strict attention to honor cards and privileges.(…) Showers were given once weekly and took place in assembly-line fashion, without consideration for patient privacy. Patients were forbidden to speak to staff. (Denber, 1963)

Since 1957, a program of progressive modernisation of care, including the opening of the unit's closed doors, regular meetings between staff and patients, and the banning of physical restraint, had favoured the transformation of the unit into a calm and warm environment. In 1959, during the haloperidol trial, Wards Island was, according to Denber, through this process, being transformed into a "dynamic therapeutic community". In Denber's narrative, the opening doors become central, a canonical image of psychiatry since Pinel.[36] In the words of a patient cited by Denber, "Since you opened the door, I feel free, I used to feel like I was in a prison. Now it's normal. I feel like I am at home"(Denber, 1963). It was felt as a concrete element of freedom impacting the daily life of patients residing in the

[36] For a nuanced review of "Pinelian revolution" see (Gauchet & Swain, 2012)

unit, but was also a broader symbol for valuing autonomy, transforming the Unit's mission - from a security goal to a treatment orientated facility.

The staff's intense and frequent meetings were aimed at challenging the dividing hierarchical lines in the wards' daily routine, which Denber called "quasi-feudal", in a process of progressive democratisation that would be exhaustively promoted. A more democratic organisation could then result in more humane care, stripped of the physical violence that characterised the old methods. In these papers, Denber builds an image of himself as the great promoter of change, the combative leader, determined to overcome the various difficulties that the therapeutic community project had been facing over the years.

In the midst of these transformations a new intern started working at Manhattan State Hospital. Elisabeth Kübler-Ross would definitively mark the way we think about death and mourning, both within psychiatry and in popular culture (Reed, 2004). Kübler-Ross began work on Ward's Island in June 1959, probably at the same time that haloperidol was being tested (Denber, Rajotte, & Ross, 1960) . In her biography, *The wheel of life*, Elisabeth describes her entire time in Manhattan, from her first interview with Denber to the everyday life and power dynamics in the ward, including the process of transformation into a therapeutic community (Kübler-Ross, 1998).

Kübler-Ross spent two years in Manhattan and, in 1961, was replaced by Mary Seeman. Seeman would later become a professor of psychiatry in Toronto, and was particularly interested in the role of gender in schizophrenia. It was, in fact, to her review that we resorted in chapter 2.7 (Seeman, 2019) . Mary married the young scientist Phillip Seeman who, as we will see in Chapter 5, would later play a fundamental role in the experimental "validation" of the dopaminergic hypothesis. Some say that it was during her internship at Manhattan State Hospital that Mary Seeman convinced her husband Phillip to study how neuroleptics work (Stern, 2010). Seeman describes her long experience at the Manhattan State Hospital in two relatively recent papers (2017; 2004).

From the combined descriptions of the two women, we can reconstruct an image of Herman Denber as a narcissistic, authoritarian, conflicted man, on the edge of mental illness, ready to use psychoanalytic theory and social psychiatry in order to expand his power over the clinic he directed.

Kübler-Ross refers to Denber as a "...crazy Swiss psychiatrist who drove his residents away" (Kübler-Ross, 1998, p. 110), Seeman details how after suffering an assault from one of the unit's patients, she saw the responsibility for the events re-assigned to her through Herman Denber's dynamic interpretations.[37]

Both describe a strongly hierarchical clinic, where the changes, brought about by the principles of "therapeutic community", had paradoxically increased the discretionary power of both director and head nurse, as they ran the unit like a prison (Kübler-Ross, 1998; Seeman, 2004).

Again, contrary to Denber's idyllic description, Kübler-Ross describes physical treatments used in a frankly punitive way, and Seeman describes prolonged chemical restraint through sleep cures.

Regarding the clinical trials carried out at Wards Island, which they were responsible for supervising, both Kübler-Ross and Seeman describe how patients were constrained to participate. This obligation included compliance with therapeutic agents but also with the mescaline trials. The absence of informed consent, that today is a fundamental part of any drug trial, isn't in itself surprising in light of the insufficient professionalisation of trial methodology. Nevertheless, the authors describe a more extreme phenomenon where patients were being required to participate even despite frequent protests, and whose reluctance could even be punished with "even more inhumane treatment". Seeman explains this requirement by suggesting that part of Denber's personal income may have derived from the unit's participation in clinical trials (Kübler-Ross, 1998; Seeman, 2004).

Mary Seeman also questions the liberation and autonomy that the open door of the unit could have brought. In stark contrast to Denber's depiction, she describes how the patients were not really closed inside the unit, but became in a sense closed outside the unit, forbidden from returning to their room, forced to participate in workshops focused on productive activity, eventually being threatened with physical violence or mechanical restraint if the production rate decreased (Seeman, 2004) .

---

[37]The complete anecdote, told by Dr. Seeman some years later is illustrative of power relations in a psychiatric ward: "Shortly after I started my residency, a patient punched me in the nose. My chief at the time was very much taken with the Stanton -Schwartz phenomenon, the observation that agitation in patients paralleled disagreements between members of staff and that the agitation disappeared and patients improved when the staff disagreements were resolved. My chief believed that the patient had punched me because he and I disagreed on her treatment and that the patient was doing to me what I unconsciously wanted to do to him." (Seeman, 2017)

The differences between the Manhattan State Hospital research unit described by Denber and the one we find in the Kübler-Ross and Seeman's reports are striking. They look like two radically different clinics. This contrast in haloperidol trial settings is not just contextual, it has consequences on the therapeutic apparatus under test and also represents divergent criteria for evaluating results. Patient treatment response was evaluated depending almost exclusively on staff expectations for patient's collaboration in everyday life, and in these two distinct narratives we see very disparate expectations. If we are unable to merge the two different perspectives and/or succumb to a logic of confrontation between the narratives offered, then, depending on whether we subscribe to one version or another, we have distinct therapeutic interventions being tested alongwith divergent criteria for evaluating results. This complexity makes it difficult to understand what the results of the 1959 trial in Manhattan really meant. We may suspect that haloperidol had proved ineffective in the face of the demands of the therapeutic program and the rich and dynamic social interactions that the therapeutic community promoted, or on the contrary, we may suspect that haloperidol had proved ineffective in the absence of a truly therapeutic program, or in the face of the continued presence of physical and psychological violence.

As early as the late 1950s, the effect of the general ward environment on the results of clinical trials with neuroleptics was known. Literature suggested that in well-adjusted institutions, clinical improvements are more extensive (improvements may extend even to patients who are not taking the substance) compared with improvements in more authoritarian wards (Meszaros & Gallagher, 1958).

Given all these considerations, what is left of R 1625, the compound built by Janssen just a few months earlier? Trying to keep our gaze on the compound, we see that it quickly dissolves behind complex social relationships. Substance, remaining therapeutic apparatus, and expectations of caregivers and researchers merge disconcertingly. This is one of the main difficulties in pursuing the history of psychopharmacology. How can we keep our eyes on a certain chemical compound, when it constantly appears, disappears and reappears behind this moving curtain, sometimes translucent, sometimes, frankly, opaque?

Our context here isn't just social, not only because we consider that the divide between biological and social is often superficial or tangential, but also because there is clearly the intervention of other chemical substances in this trial. There are at least three other

chemical compounds identified in this chapter; mescaline, thioproperazine and mepazine. We know that Denber continued to test mescaline until the 1960s, and we know that he tested mescaline in at least some patients during the haloperidol trial (Denber et al., 1959). If mescaline can change the psychotic condition, namely provoking or worsening it, we can suspect that its administration may alter the results of concomitant drug trials. The same is true for other psychotropic drugs. The existence of chronic patients who moved from one study to another every six months, arriving at a new substance, having been submitted to several before, may be said to jeopardise Denber's capacity to produce more generalised knowledge.

This bewilderment isn't ours, as we look through the past, on the contrary, it was felt by the protagonists of the time. Denber understood the limits to the universality of knowledge produced in clinical trials. In his psychoanalytic reflection on research in psychiatry, Denber argued that the results of an investigation are coloured by the researcher's views and interests (Denber, 1972).

This leaves us with the question of how to produce knowledge that escapes its regional and ephemeral qualities? The professionalisation of psychopharmacological trials - namely with random sampling and placebo - was intended to respond precisely to these concerns. By introducing a comparative element, the aim was to free the substance from the remaining therapeutic device, freeing the test from its context.

Interestingly, Denber elaborated an alternative theory when faced with the divergent results of the haloperidol trials in continental Europe. The ineffectiveness of haloperidol in Manhattan was a consequence of what he called "ethno-racial heterogeneity". To test this possibility, he developed a multicenter study, in collaboration with Liège's University. Joining the team that developed the first haloperidol trial he directly confronted the rift he had created. We could expect one of two results for this international collaboration: either the confirmation of the work of the Liège team, using American methodologies, or the verification of American results. However, a third solution eventually emerged, allowing the support of both apparently contradictory conclusions: both teams could be correct, and different results explained by disparate samples.

With direct support from Janssen, who was airmailing the haloperidol samples that Denber needed, he joined forces with Jackie Collard, one of the authors of the first

haloperidol study and the person responsible for its market introduction in Belgium (interview with Ferdinand Goffioul, Liège, March 01, 2019).

The subjects here were exclusively female, as was the case in Denber's first study, and in Liège's original trial. In Manhattan the trial included patients from Wards Island, whose institutional context we have already described. Collard enlisted patients from the Sanatorium de Saint Agathe, a closed asylum unit with 400 patients, located in Liège's city center. The results of this study were surprising, but not so much in terms of therapeutic response, which was significantly similar: 1 patient's condition deteriorated, both in New York and Liège (5%), 10 patients' symptoms persisted unchanged New York (50%) and 11 in Liège (55%), and only 9 patients had a clear improvement in their clinical condition in New York (45%) and 8 in Liège (40%). In the design of the study, haloperidol doses were increased throughout the trial until a therapeutic or pharmacological limit was reached (namely the onset of therapeutic response or side effects). Surprisingly, the biggest difference between New York and Liège was the dose of medication reached. In Europe, the average daily maximum haloperidol dose achieved was 8.8 mg/day, and in the United States, the average maximum daily dose reached was 146 mg/day, a difference of 16 to 1. In Manhattan, patients were being given doses 16 times greater than those administered in Europe. These quantities are impressive even to our eyes. In fact, when haloperidol was finally introduced on the American market in the late 1960s, the maximum daily amount recommended in the package leaflet was 15mg/day (Denber & Collard, 1962).

Why the need to reach the high doses we just described in Manhattan? The authors had made en effort to select uniform samples, both from a diagnostic point of view - the vast majority of patients selected in Europe and the United States had a diagnosis of schizophrenia - and from a disease course point of view - both groups seem to have had more or less the same disease duration and length of hospital stay. The essential difference for Denber and Collard between the two samples, the key difference between Liège and Manhattan that determined this divergence of doses used, would be the socio-cultural origin of the patient's ancestors and (what the authors call) the ethno-racial heterogeneity.

> De l'interaction de milieux internes génétiquement different et d'influences modificatrices de milieux externes dissemblables, résultent, selon nous, des particularités physiologiques et biochimiques dont la réactivité pharmacologique ne traduirait qu'un aspect. (Denber & Collard, 1962)

The American sample differed from the Belgian sample in terms of what authors called “racial heterogeneity” (mainly because 3 (15%) of the American patients had been classified as “race noir”), but also because of the ancestral country of origin (in the United States almost half of families came from alternative major cultural groups other than Anglo-Saxon, in Liège only 35% of parents were of foreign origin). These differences may seem minor, but they were clearly significant to Denber and Collard, who base their assertive conclusions on it.

Denber and Collard's conclusions explained the disparate results. In the process they validated the methodologies used in the original trials, and confirmed the outcomes previously published both in Europe and in the United States. The discrepancies didn’t result from authors' errors, irregular sampling techniques, nosological variations, or differences in expectations or assessment methods. The divergences resulted from a fundamental and irresolvable difference - the genetic and cultural composition of the populations of origin. This conclusion protected the original researchers and their teams from criticism, but also dismissed disagreements within biological psychiatry, and did not call into question clinical trials’ research methods. On the contrary, the divergences came from aspects outside the discipline, identity factors that escape psychopathological analysis. Genetics and culture merged undifferentiatedly to explain a difference in drug dosage of about 16 times.

When Denber and Collard justified this resistance to the drug through the heterogeneity of the sample, they seem to ignore that the “group” most represented in Manhattan was still the group of “Anglo-Saxon origin” (expression by the authors). Minimising the demographic prevalence of this group within the sample, the authors preferred to attribute the insufficient therapeutical response to a vague concept of variability of origin. Analysing results they highlighted the presence of “difference” in the American sample, including foreigners and blacks, as opposed to a Belgian sample that was seen as more homogeneous, certainly whiter.

Psychiatrist Jonathan Metzl argues that, during the 1960s, the discourse around schizophrenia underwent a critical shift, from narratives focused on female docility to descriptions of black male hostility (Metzl, 2010, p. xv). The structuring concepts of social organisation, whose paradigmatic examples are gender and race, penetrate psychiatric categories, since their initial construction and are still inevitably present. This institutional

presence does not depend on the clinicians' personal positions or sensitivities, even though the work of some of the founders of current psychiatry is often described as directly promoting racism and xenophobia (Strous, Opler, & Opler, 2016).[38]

We know how much the concept of dementia praecox owes to the idea of degeneration, a prevalent cultural theme of the 19th century, first through Morel and later through Kreapelin (although this idea is contested within the history of psychiatry, see chapter 2.6). Mental illness was then seen as a weakness of the will that would tend to strike primitive savages, children and women. Dementia praecox was originally constituted by merging biological concepts and moral prejudices about feeble mindedness (Barrett, 1998a).

Psychiatric categories are embedded in these injustices, that structured society when they were first constructed. Like trojan horses, they transport them to the present, determining concrete practices, distributing power, and institutionalising differences. But Psychiatric concepts are not static, on the contrary, as we have shown in our research, they are highly plastic, subject to negotiation, influenced by voices capable of reaffirming, but also contesting and changing them.

During the 1960s, while the dopamine hypothesis germinated and haloperidol made its way to legitimation, penetrating the North American market, the National Institute of Mental Health reported that *blacks* had a 65% higher rate of schizophrenia than *whites* (Metzl, 2010, p. xi). In that same decade, the American civil rights struggle accelerated, disquieting those that felt threatened by these changes. We can understand Denber and Collard's 1962 paper within this process. The presence in the American sample of patients classified by them as black and hispanic led to the need for doses 16 times higher than those administered in the Liège. Genetic, ethnic, racial and cultural differences are merged here in an undetermined concept with extraordinary biological activity. The so-called North American heterogeneity (identity diversity) increased social tension, conditioned resistance to treatment and forced the use of higher doses. In the following decade, haloperidol would be publicised in the main American medical journals using the imagery of the black man's rebellion, even recovering the iconic closed fist of black power (see Appendix B figure 2). “Cooperation often begins with Haldol”, it is said. A constant element since the first original

[38] Kraepelin's contribution to create the conditions for the abuses of psychiatry during the Third Reich has been debated. Among others, his role as direct supervisor of some of the most influential Nazi psychiatrists has been highlighted, as well as his views on Jews, Judaism, and homosexuality. (Strous et al., 2016)

trials, the effectiveness of haloperidol was always associated with the control of aggression, promoting docility, cooperation, maintaining order and hierarchy. This publicity is also an example of how non-specific therapeutic effects of behavioural control continue to be a relevant clinical indication, even in the 1970s.

The purpose of clinical assays is not to isolate the pharmacological effect of a substance, but rather a way of gaining social recognition as a drug (Pignarre, 1997, p. 36).The Denber trials introduced the chemical compound R 1625 into a complex and changing therapeutic device. Its negative results force a rethinking of haloperidol's social strategies.

Herman Denber was sometimes labeled an emissary between Europe and USA. A man of linguistic, geographic and theoretical bridges, he transformed himself through the haloperidol trials into a promoter of division. The results of the Manhattan trial were seen as radically different from the results obtained in continental Europe, which had been presented at the first haloperidol symposium. This divide would have considerable impact, as we shall see, not only with regard to haloperidol's path on both sides of the Atlantic, but maybe also in practical experience and theoretical construction of psychiatry.

Haloperidol became trapped in this ontological instability over the Atlantic, caught between being and not being a medicine. An European haloperidol, formed as a potent and safe drug, would be implemented progressively, changing practices, reformulating mechanisms of antipsychotic action, and contributing to the creation of pathophysiological mechanisms that would transform schizophrenia. American haloperidol, on the other hand, would remain in a kind of limbo for a few years, occupying an undefined proto-drug role, that still aroused persistent interest and criticism.

3.2. The first placebo trials

The compound haloperidol seemed to be on the way to becoming the specific treatment for schizophrenia in a substance/disease co-formation process. It sought to enter the psychiatric market in a period where changes abounded and the importance of psychosocial interventions persisted. In the first clinical trials in Europe, the substance had been tested in the context of normal clinical practice, where the presence or absence of a therapeutic effect was judged obvious. Professionalised methodologies in these trials were not contemplated, probably for reasons of practical, financial, theoretical, and ethical natures (Interview with Christian Mormont, Liège, February 27, 2019). When the substance was introduced in Manhattan, its indisputable therapeutical activity came into question and the substance's capabilities disappeared behind the scientific, biological and institutional context of the Wards Islands trials. The credibility of the drug's action was challenged and doubts arose about its commercial value.

This disagreement was not new, as among the various phenothiazines introduced in the second half of the 1950s, substances such as Pacatal had shown dubious results, and accusations of ineffectiveness had been levelled at them. Diversity in science, and medicine, exists, of course, and is necessary for the production of knowledge, but extreme perspectives on the effectiveness of neuroleptics could lead to a more existential threat to the discipline whose practice, external image, and project of modernisation were increasingly dependent on psychopharmacological approaches. Professionalized methods seemed necessary as a way to master the shortcomings of the clinical encounter and in order to acquire a superior knowledge about the efficacy of psychotropic drugs. As clinical trials became an increasingly complex and expensive endeavour, a close collaboration between the pharmaceutical industry and universities was unavoidable. Different players were to benefit from the formation of a new psychopharmacological academic-industrial complex including individual researchers, for whom professionalisation promoted internationalisation, and a reinforced authority and the pharmaceutical industry itself, that with rising costs of clinical trials, almost gained monopoly of therapeutic experimentation (Healy, 2012).

The advanced procedures of clinical trials were already known when Denber did his haloperidol study on Wards Island. In fact, according to Shorter, the first controlled clinical trial in psychiatry was exactly in Wards Island (2011).

In the beginning of the XXth century, autointoxication etiological theories of dementia praecox had led to surgical procedures in pursuit of psychotherapeutic goals. Henry Aloysius Cotton, the protagonist of *Madhouse*, a book by Andrew Scull (2005), was the medical director of Trenton State Hospital in New Jersey, and performed first tooth extractions and tonsillectomies and later complete extractions of the bladder, stomach, uterus, ovary, and testicles, describing rates of an impressively high therapeutic efficacy (Jones, 2005).

The first controlled clinical trial at Wards Island was designed as a test to Cotton's theories. In a 1922's paper, the authors explain the control's ability to make the context disappear, to make therapeutic relationships, and institutional life, invisible. Standardisation, comparing subjects submitted to therapeutic intervention, and controls, was the only way of forming more definitive conclusions:

> On the whole, then, the operated group appears to have received no more benefit than the control group.(Kopeloff & Cheney, 1922)

The 1922 essay was a mode of questioning Cotton's practices, of setting limits to his performance, of contesting his authority. Control in psychiatry was born out of controversy, disagreement, and divergence. It was born as an instrument not really for validating strong conclusions, but mostly for disputing prevailing narratives. Control was born in psychiatry as a manner of questioning power and authority, enabling the contestation of a theory and practice that were increasingly imposed with harmful consequences. Critics of the current role of controlled trials in psychiatry often return to this point, which for them is not just historical. Despite its current use as a way of validating a drug's efficacy, the fundamental pertinence of controlled trials should be to prove ineffectiveness, test null hypothesis, refute the accumulated evidence (Charland, 2013).

In the following decades, randomisation and double-blind techniques came to complement the use of control, maximising the exclusion of nonspecific effects, overcoming doctor's and patient's expectations, and dissipating the role of interpersonal and institutional factors. The therapeutic intervention was intended to stand alone under analysis, isolated and seen as the naked substance, the chemical compound and its biological action.

One of the most influential men in the rise of the placebo effect throughout the 1950s and 1960s was Henry K. Beecher. Michael Shepherd, in his interview with David Healy, explains how this man, initially mainly interested in the concrete and physical aspects of medicine, developed an impressive laboratory and team that put the placebo effect at the center of medical discussions.

> He was a powerfully built solid character, very much in the mainstream of medicine. During the war he was in charge of a base hospital when the Americans were fighting the Japanese in one of the Pacific islands. There was a terrible battle going on and the casualties were coming in and emergency surgery was going on 24 hours a day and they ran out of morphia. Well this, of course, is a disaster because they were in shock and pain and you couldn't operate. The story, as I recall it, was that accidentally one of the nurses gave an injection of still water and the patient came out of shock and lost his pain. And Beecher, who was an extremely observant clinical scientist, was struck forcibly by this observation which was repeated. I think for a time they had to use distilled water because the supplies were not coming in. (Interview with Michael Shepherd cited in Healy, 1998b, p. 240)

Shepherd's story is fascinating in the way it demonstrates the intensity of the placebo effect through an almost magical quality. In the midst of the chaos of the warfront, the simplest and most ubiquitous substance - water - soothes the soldiers' unbearable pain. The effectiveness of this distilled water is obvious, it does not require control studies, but the mechanism of its action eludes us.

The first neuroleptic - chlorpromazine - had been studied in a placebo-controlled manner by Charmian and Joel Elkes at Birmingham in 1954 (in his interview with Healy Michael Shepherd credits Charmian for the study design (1998b, p. 238)). Two years after the first reports by Delay and Deniker, the Elkes couple developed a clinical trial that comprised 27 patients, with multiple diagnoses. The patients included in the study had the fact that their behaviour was felt as a problem by the nursing staff in common.[39] Patients represented their own control in an alternation of chlorpromazine/placebo, initially in 1-week blocks, then in 3-weeks blocks, and finally for 6-weeks periods. The results were good and the study by the Elkes couple became an important piece in chlorpromazine's success story (Elkes & Elkes, 1954) .

It's important to know that Joel Elkes had a previous relationship with Smith, Kline and French, the American distributor of chlorpromazine. His post-graduate international

---

[39] The first neuroleptics had broad therapeutic indications, as we saw in chapter 2.5.

experience in the United States was partly funded by Smith Kline and French (Elkes spent 1950, and 1951 visiting different institutions in the United States)(Elkes, 1995) .[40]

Interest in placeboes continued to grow exponentially during the 1950s, and in the 3 years following the Elkes' study (from 1954 to 1957) there were 34 articles published on the placebo effect, more than all the papers on the placebo effect ever produced before 1954 (Shapiro, 1959).

In 1960, two years after the production of R 1625, it still hadn't been tested in a controlled trial, even after the results in Manhattan. Maybe because Janssen himself maintained, throughout his life, an important distrust regarding the blind nature of clinical trials. In Janssen 's view, risks of trial professionalisation included the clinical inexperience of investigators, and how their work becomes impossible to cross-evaluate, due to the characteristics of the double-blind trial:

> From that day on I have always been very sceptical when it comes to double bind trials because the same risk exists everywhere. I don't know of any learned professor or any good observer who takes the trouble of doing what protocols require in terms of observing. Certainly not in psychiatry. But what is the reliability of a psychiatric observation if it is done by somebody who does not know anything about psychiatry? I am not talking about theoretical psychiatry, I am talking about someone who knows how to observe psychiatric patients. (Interview with Paul Janssen cited in Healy, 1998b, p. 50) [41]

Janssen's resistance to clinical trials' professionalisation, and specifically to double blindness, but also (for example) his criticism to the growing exorbitant costs of introducing new drugs, can be read in light of his romanticised version of common sense. This resistance

---

40 One moment was particularly important, a meeting organised by Smith, Kline and French with the influential Seymour Kety. On that occasion a "personal link" was forged that had important consequences in Elkes later scientific career (Joel Elkes, 1995).

41Paul Janssen made these statements to David Healy, in the context of describing a visit in the early sixties to psychiatric clinic in Miami led by a Dr. Goldstein. A flawed study had been developed there denying any difference of efficacy between chlorpromazine and placebo. In the literature review that we carried out, for example, in the chapter corresponding to chlorpromazine of the comprehensive volume edited by Leopold Bellak (1958, p. 472), we did not find any record of this essay. In correspondence exchanged with Dr. Burton Goldstein, Director of the Miami Service (Chair of the Department of Psychiatry), he definitively denied that Dr. Janssen had ever visited his service. (Personal correspondence with Dr. Burton Goldstein February 25, 2020).

strengthens his image as a man of simple values, uninvested in the intellectual and ethical sophistication increasingly demanded from the pharmaceutical industry.

We can suspect that the growing importance of placebo studies threatened a particular view of psychopharmacological theory and drug development. We have seen in this thesis (chapter 2.1) how Janssen described the chemical construction of the compound R 1625 through a clear, rational design, with a determined leadership. Laboratory research was intended to build compounds, but also theory. The primacy of the double-blind placebo study called all this into question. Narratives on laboratory construction of drugs lost any meaning. Interest in the biological modes of action of the compound could be diminished. Doubts about the target tissues and the chemical interaction of the compound on those tissues lost importance. Clinical (or even social) reasons for this or that effect may be neglected. When the "new" placebo studies emerged, only one hypothesis remained, there is only one question whose answer is sought –does the drug work or not? New clinical and academic actors gain power over the drug's fate and the laboratory's rational and obstinate research becomes secondary to an empiricism whose outcome is threateningly unpredictable. From this perspective maybe Janssen's resistance to such studies is less surprising.

The name of those responsible for the first controlled trial of haloperidol may be surprising for those who know the history of psychiatry - Morgan David Enoch (working with Ashley Robin).[42]

Continuing the path of specification that haloperidol was beginning to take, in a disease-substance co-construction, Enoch and Robin developed a specific assay in patients diagnosed with schizophrenia, but, as this research will show, this diagnosis was still quite different, at the time, from the current category.

Morgan Enoch was marked by his early military experience in India, and had recently obtained the post of senior registrar, divided between London Hospital and Runwell Mental Hospital, in Essex (Keynejad, 2015).

Runwell had been built as one of the last great asylums, planned in 1928 for 850 beds in a partnership agreement between East Ham and Southend-on-Sea (CountyAsylums, n. d.). It was surrounded by extensive agricultural land, which would only be sold at the end of the

---

[42] This is perhaps especially unexpected if we take into account that Enoch would later dedicate his career to the case history, the unusual, the singular.

1950's. It had been planned as a "progressive" institution, with all the techniques considered modern and indispensable for the time, including hydrotherapy, a gym, a laboratory, X-ray, a workshop, a laundry, and - crucially - an operating room.

During the war, Runwell had become one of the first units to integrate the therapeutic community movement that we briefly pursued in the previous chapter. Joshua Bierer, a psychologist of Austrian origin, had encouraged self-organisation, cherished the therapeutic value of group interaction, and is cited in the literature as promoting one of the first examples of therapeutic community within an asylum (Shorter, 2005, p. 249).

But Runwell would also be one of the first places to perform large-scale prefrontal leucotomies (CountyAsylums, n. d.), which would become common within the institution between the 1940s and 1950s. At least 125 cases just between 1942 and 1946 (Strom-Olsen & Tow, 1949). The hospital was also one of the first institutions to introduce selective leucotomy techniques - namely the selective orbital cortex undercutting intervention which was first performed at Runwell by Geoffrey Knight in January 1950 (Strom-Olsen, 1965). The technique, although frequent, doesn't seem to have been indiscriminately adopted in Runwell, and Strom-Olsen distinctly defends its judicious use, limited to schizophrenia where severe behavioural changes were present (1949).

The sample chosen by Enoch and Robin for their trial on haloperidol was composed of twenty patients, exclusively diagnosed with schizophrenia, whose main characteristics were their tendency toward social isolation and having already had a long hospital stay before the trial's beginning. We have very little information about the interventions these patients had already undergone in the past. In particular, the authors do not clarify whether these patients had been submitted to leucotomies, but knowing that the number of interventions was high in Runwell, we can imagine that at least some of them had already undergone surgical interventions. We also do not know what types of psychosocial interventions the sample participated in, we do not know if they were in the same ward or if they were spread throughout the hospital, we do not know if they were part of the same occupational programs, and, perhaps importantly in the analysis of the results, we do not know whether the sample was male as in Dave, or female as in Glain or Manhattan, or composed of mixed genders.

Nevertheless, Enoch and Robin give us more information about diagnostic categories than previous studies, namely they precisely define subtypes of patients. The diagnostic rigor

with which patients were classified is interesting as another example of the discourse surrounding nosological specificity that emerged with haloperidol and was progressively implanted, albeit with hesitation, throughout the early 1960s. But the breakdown into diagnostic subtypes is also interesting because it exposes the way schizophrenia itself was seen in this period of transition from the 1950s to the 1960s. Of the 20 patients who made up the sample of the study in Runwell, 10 were classified as catatonic (50%), 6 as hebephrenic (30%), 2 as belonging to a simple schizophrenia subtype (10%), and only 2 as having paranoid schizophrenia (10%) (Enoch & Robin, 1960).

This composition of subtypes suggests that importance at the time was given to motor symptoms (catatonic schizophrenia) and psychosocial functioning (simple and hebephrenic schizophrenia) in the diagnosis of schizophrenia, visibly more relevant than the hallucinatory and delusional experiences that would progressively establish themselves as paradigmatic of schizophrenia in the following decades

Catatonia was first described by Karl Ludwig Kahlbaum in 1874 and was initially an independent nosological entity, derived from the concept of *melancholia attonita*, and essentially characterised by the presence of motor symptoms, namely waxy flexibility - catalepsy - and negativism (German E. Berrios, 1996, p. 383). The category became a subtype of *dementia praecox* in the influential Kraepelinian classification, after its sixth edition in 1899. This integration, although contested, persisted during the transformation of *dementia praecox* into schizophrenia and has remained so until recently (Shorter, 2005, pp. 50,51).[43]

Over the course of the twentieth century, the prevalence of catatonia as a subtype of schizophrenia has declined dramatically (in some series from 10-30% to 2-10% (van der Heijden et al., 2005)). The percentage shown in Enoch's sample (50%) would hardly be found in any hospital sample today. This process reveals the disappearance of motor symptoms from psychiatric diagnoses, and the strengthening of internal experiences in the reshaping of schizophrenia. Some authors have called this transformation: *paranoidization*

---

[43] In the latest edition of DSM 5, there is not so much a return to the autonomous unity described by Khalbaum, as some authors currently defend, but on the contrary, a vision of the catatonic syndrome as a symptomatic feature without specificity (present in several different nosological conditions), even so, the chapter on catatonia comes within the chapter on schizophrenia spectrum disorder and other psychotic disorders, showing how much the construct of catatonia owes to the historical development of the idea of schizophrenia (American Psychiatric Association, 2013).

(Stompe, Ortwein-Swoboda, Ritter, Marquart, & Schanda, 2005). This phenomenon is probably directly related to the increased notability of Kurt Schneider's first-order symptoms (previously discussed in Chapter 2.6), but also influenced by the conceptual transformation of schizophrenia's treatment. Neuroleptics, specially haloperidol, progressively established themselves as a specific drug for schizophrenia, mainly through its hallucinolytic and anti-delusional activity. Nevertheless, in 1960, at Runwell, only 10% of Enoch and Robin's sample could be characterised as suffering primarily from hallucinations and delusions.[44]

In a design reminiscent of the Elkes' trial for chlorpromazine, Enoch composed a sophisticated assay where patients would alternate between haloperidol and a placebo, in two 4-week periods and one 2-week period, in an overall trial duration of 10 weeks. As noted, the patients, divided into 4 groups, rotated between placebo and haloperidol. This complex design had the advantage of doubling the control, a direct comparative control and a longitudinal control. At any moment, patients taking haloperidol could be compared with patients taking the placebo. But the patients on haloperidol themselves, in this sequential trial design, when rotating through placebo periods were also serving as controls (Enoch & Robin, 1960) .

This type of design, with sequential drug-placebo rotations, was met with dismay in continental Europe, mainly for ethical reasons. As we have seen, the French had a more impressionistic view of clinical trials. It was difficult to justify why a drug would be withdrawn from someone who was benefiting from it. Suddenly withdrawing medication that was effective and replacing it with a placebo was seen as unethical (Interview with Christian Mormont, Liège, February 27, 2019).

The results of this first controlled trial on haloperidol were certainly disappointing: 6 patients improved (30%), 2 showed no clinical change (10%) and 12 worsened (60%). Among the six patients whose clinical condition improved were the two patients with mostly paranoid symptoms. Enoch mentioned that the diagnostic subgroups may be important in determining clinical response. The final conclusions were clear but remained disparate from the continental European data:

---

[44] Another explanation that has been offered for the decrease in the frequency of catatonia is the separation of neurology and psychiatry, with neurology dealing with motor symptoms, and psychiatry dealing with subjective symptoms.

> Haloperidol is of limited value in the symptomatic treatment of long-standing schizophrenic patients, and was most effective where the phenothiazines had already been thought to be indicated by the clinicians treating the patients study. (Enoch & Robin, 1960)

In Runwell's depiction, the profile of haloperidol's side effects was also striking. Psychomotor restlessness, pseudo-parkinsonian symptoms, and the frequency of oculogyric crisis turned haloperidol in a more "neurotoxic" drug than its predecessors, namely chlorpromazine.

Our interest in Enoch's study comes from the way it relates to the current theory and practice of psychiatry. If the method's professional aspects are akin to the randomised controlled trials that we have grown accustomed to in recent decades, hidden in its sample is a very different view of schizophrenia. This being a schizophrenia where motor symptoms, affect and the ability to function in the social and moral world were much more important, than the subjective experiences of delusion and hallucination.

One conclusion may be that in this sample, possibly in this version of schizophrenia, haloperidol was not particularly effective. Enoch and Robin's sample was selected mainly for its tendency towards isolation, a broad symptom that is difficult to define, but closely related to Bleuler's concept of autism. However, Janssen would argue that the schizophrenia where haloperidol would work was another (quite distinct) phenomenon, a phenomenon much more similar to amphetamine intoxication.

> One of my pet ideas has always been that schizophrenics for whom haloperidol works well are stereotyped in their movement and their thinking and in their behaviour. As if they have no internal inhibition in the pavlovian sense of the word. As if they cannot shift from one idea to another very easily. This is a feature of amphetamine poisoning too. (Interview with Paul Janssen cited in Healy, 1998b, p. 47)

This was a schizophrenia where hallucinations and delusional ideas were much more important than vague and complex concepts such as loosening of associations, which had characterised the syndrome until the late 1950s.

It was becoming clear that for haloperidol (and other neuroleptics) to be effective it was necessary to reconstruct schizophrenia. For the compound to become a medicine, a transformation of the nosological category was unavoidable. The process of building haloperidol required a reshaping of its clinical indication. But, interestingly, the opposite might also be true. Schizophrenia, as an idea, was increasingly under assault, its limits and contours increasingly contested. Its survival as a diagnosis depended, perhaps, on finding a

specific treatment that would allow it to adjust into a simpler, and more conventional, form. Treatment shapes the illness, and at the same time the illness finds in treatment its vindication, its survival.

Interestingly, Morgan Enoch's career followed a path opposite to that of academic psychiatry. While in the early 1960s he was one of the first to engage with clinical trials, throughout the 1960s and 1970s, while the pharmaceutical industry, hospitals and universities became more and more engulfed in the knowledge produced by large numbers generated by mass trails (Healy, Mangin, & Applbaum, 2014), Enoch built his academic career around the individual clinical encounter (2020; 1962).

Just two months after the Runwell study, another placebo-controlled trial on haloperidol was published, now in North America (Azima, Durost, and Arthurs, 1960)). Its young author, Hassan Azima, would die prematurely, at the age of 39, a few months after the publication of these results (Warnes, 2014).

Hassan was born in Iran in 1922 and studied medicine in the United States at the University of Kansas. Like Herman Denber, the author of the first American study on haloperidol, Azima was a privileged emissary between Europe and America. In fact, there are several parallels between the professional paths of the two doctors. Azima had been, like Denber, an intern in psychiatry in continental Europe. He had traveled to Paris, and was working in Delay and Deniker's team at one of the most exciting moments in the history of psychiatry - the introduction of chlorpromazine. The following publications, (Delay, Deniker, Azima, & Lemperiere, 1952) and (Delay, Laine, Azima, & Puech, 1953), corroborate Azima's presence in Paris during this period, even if questions linger about his direct involvement with this drug.

In 1955 he settled in Montreal, at the Allan Memorial Institute Of Psychiatry under the direction of Donald Ewen Cameron, where he was one of the first researchers to use chlorpromazine in the American continent (the delay by Azima and Ogle in publishing results would lead to Heinz Lehman being generally considered the pioneer in the use of chlorpromazine in America)(López-Muñoz et al., 2005).

Similarities with Denber include the role that both men played as mediators between psychopharmacology and psychoanalysis. Azima was, on the one hand, in charge of the

psychopharmacology section at the Allan Memorial Institute, and on the other hand, one of the first trainees at the Canada Institute of Psychoanalysis (Warnes, 2016).

Also like Denber, Azima had been interested in assays with psychedelics (Denber had experimented with mescaline, and Azima tested psilocybin (Azima, 1962, p. 184)).

This diverse set of technologies - psychoanalysis, neuroleptics, psychedelics, but also sensory deprivation treatments and sometimes other somatic treatments, such as electroconvulsive therapy - were assembled by Azima in the context of a precise theoretical framework - anaclitic therapy. Anaclitic therapy is built on the Freudian concept of "anaclitic object relationship", which refers to the oral gratification of the earliest stages of child development.[45]

Azima proposed using multiple methods to favor "regression" (here seen in a way that is more concrete than symbolic). This involved taking the patient to states of deep dependence, close to the first months of life, so that the patient could later re-experience the fixation positions with a new maternal figure - the therapist. This re-experience allowed a new opportunity for conflict resolution, favouring psychoanalytic progression. The belief was that all psychopathology had its origins in the way in which the first oral object relationship was established, with inadequate gratification. Through a deep regression, a corrective re-experience with the primary objects would be possible.

More precisely, the method involved prolonged periods of induced sleep - 30 to 60 days - in which the patient was awakened 3 times a day by his therapist, who fed him, performed the psychotherapeutic session and medicated him again; thus creating a state of total dependence which could later be progressively diminished (Azima, Vispo, & McKenna, 1961) .

This reification of the psychotherapeutic relationship, in which, for example, patients were often bottle-fed, or in which the therapist accompanied the patient to the bathroom to evacuate, fits, according to Mical Raz, into a wider pattern of North American interpretation of psychoanalytic concepts in a very concrete way (2010).

---

[45] First referred to in *On Narcissism - an Introductio*n, the anaclitic relationship is the one that the child establishes with the mother (or main caregiver). The mother becomes the child's first sexual object through vital care including food, attention and protection. The first sexual accomplishments were established in relation with the satisfaction of needs linked to survival (Freud, 1957).

Azima described how the regression produced by these prolonged sleep cures could be associated with the technique of *psychic driving* or *dynamic implantation* developed by Donald Ewen Cameron (Azima, 1955). This method consisted of incessant repetition of recorded messages containing psychoanalytic concepts deemed crucial by the therapist. These recordings were made with the therapist's voice (*heteropsychic driving*) or the patient's (*autopsychic driving*) and replayed in order to "implant" the problem in the regressed patient. The recordings were heard repeatedly in a continuous loop, as loudspeakers could be placed under the pillow or directly inserted into the ears (Cameron, 1956). This technique allowed individuals to distance conscious thought processes from unconscious impulses.

The association of Azima's and Cameron's methods is documented in the final sentence of Azima's 1955 article:

> Further investigation of the combination of prolonged sleep and " dynamic implantation" offers new avenues to therapeutic intervention. (Azima, 1955)

During the 1950s, after the Korean War, prisoners of war emerged as an important figure in the North American imagination. When 21 American prisoners of war refused repatriation, an existential uneasiness cropped up within American elites. The concept of brainwashing appeared as an explanation capable of capturing the public imagination (Kim, 2019).

Similarities between the language and techniques used by anaclitic theory and the brainwashing methods thought to be used in communist countries are striking. The ideas of regression, infantilisation, and complete dependence (notably with regard to the digestive-feeding/defecation cycle) are very similar to those described as being used with American prisoners of war (Buckman, 1977).

We now know that Cameron's work at the Allan Memorial Hospital was in part funded by the CIA (Healy, 2002, p. 176). It was unsurprising that the techniques of Azima and Cameron were of interest to the CIA. The ideas of regression and personality reconstruction, that anaclitic theory provided, associated with Cameron's implantation techniques, fit the needs and perspectives of the security agency. They could be especially useful in the context of behaviour and thought control experiments that CIA may have had intentions to develop in non-cooperative subjects (Raz, 2010).

Twenty-five years later, in 1985, seven of the patients treated at the Allan Memorial Institute reached an out-of-court settlement with the CIA for a total of $750,000, highlighting

the violence and intrusiveness of the procedures, as well as the lack of consent (Hockstader, 1988).

We do not have much information about Azima's direct involvement in activities sponsored by the CIA. We also do not know for certain whether during the period of experimentation with haloperidol other interventions such as psychic driving or anaclitic therapy took place. Even if this was not the case, it seems to us very likely that at least some patients in the study that we are now interested in were involved in research activities of this type at some point in their lives.

The sample chosen for the haloperidol trial, which Azima published in December 1960, included a considerable number of patients, 84 in number, who were divided into two very heterogeneous groups, with 42 patients receiving haloperidol and 42 patients receiving a placebo. The diversity of diagnoses was important, a considerable minority of patients had a diagnosis of schizophrenia, but there were diagnoses of so-called “neurotic” pathologies, notably what were then called, “anxiety hysterias”. Unlike most previous studies, the sample was mixed gender.

In neurotic disorders, 30% improved with haloperidol compared to 15% improved with placebo. In schizophrenic disorders, 47% improved with haloperidol compared with 7% improved with placebo. Drug treatment seems to be superior to placebo, but authors preferred to highlight haloperidol’s side effects. Of concern were extrapyramidal neurological symptoms, muscle rigidity, tremor and oculogyric crises:

> The final impression was that haloperidol was a moderately potent neuroleptic, much less effective than claimed by European authors, with numerous side effects. However, its greater potency in schizophrenic states indicated the necessity of further studies in this area. (Azima, Durost, & Arthurs, 1960)

One of the reasons of interest in Hassan Azima's brief article on haloperidol is the way in which the paper seems atheoretical or post-theoretical. Short, one and a half pages long, devoid of psychoanalytic language, the article contains no etiological or pathophysiological considerations. This way of hiding, removing, or even censoring, elements of the trial’s theoretical framework would become, over the next few decades, the usual way of writing in psychopharmacology, but behind this seeming simplicity we can detect some elements that reveal the trial’s unspoken theory.

Sample choice, for example, reveals a view of psychopathology as having a shared etiological origin. For Azima, all psychopathology came from early childhood experiences; within this view diagnostic categories become more a question of form than a fundamental question. Here, psychopharmacological treatment was tested identically in all forms of suffering presentation. In drug treatment, authors weren't looking for specific action against a certain disease, as we are used to seeing today, but for non-specific facilitation of the mechanisms and psychotherapeutic actions necessary to resolve past conflicts.

While Azima recognised haloperidol's results in schizophrenia, they lost importance in the global evaluation of the drug that ends up being seen as insufficiently effective. Although some specificity of action was beginning to be assigned to haloperidol, it was not yet necessarily valued. This moment represents yet another step in neuroleptics' transition towards anti-schizophrenics.

On the other hand, Azima's final conclusion allowed him to remain in an intermediate position between Europe and the United States, between the Paris team, where he had been an intern, and the results of the famous Manhattan study. Recognising haloperidol's therapeutic action but maintaining doubts about its potency, allowed the author to not commit himself definitively to any side of the controversial divergence that Denber had opened in the discourse around the efficacy of haloperidol.

The rising importance of placebo studies suggested the death of theory and the triumph of empiricism, but, as we see in the examples in this chapter, the reality is far less straightforward.

Both Enoch and Azima tested haloperidol blindly, intending to reduce the impact of their own biases and perspectives, stripping the assays from pathophysiological or etiopathogenic considerations, and crafting their articles seemingly devoid of theory. The purpose of the trials, the question demanding an answer, seems incredibly simple - is haloperidol effective or not?

Progressively, professionalized clinical trials sought to assert themselves as pure methods to collect only the necessary data, with no room for subjective interpretation. In the literature that surrounds such trials, the way in which the disease occurred, and the way treatment worked was increasingly neglected. In the articles we have seen in this chapter, a growing sophistication arose, precisely to erase all these inconvenient questions. Placebo

control was used in order to avoid diagnostic doubts and integrate the natural history of the disease. Professionalized clinical trials were not intended to eliminate the placebo effect, on the contrary, the substance, socially recognised as drug treatment, carried the placebo effect in the same way as it carries a chemical compound (Pignarre, 1997, p. 52). The trial apparently aimed to ask just one question - does this drug work?

In fact, theory is hidden within this simple language, as we have seen in the examples in this chapter. This includes elaborate perspectives on psychic functioning, on the etiology of mental illness, on the mode of action of psychotropic drugs, their strengths and weaknesses. All this remains, as we have seen, despite seeming to disappear in a game of curtains. Theoretical frameworks deeply structured the views of the authors', and fundamentally shaped the entire trial - from the clinical indications studied, to the characteristics of the sample, to the evaluation criteria, and even result interpretation, despite seeming to be of less paramount concern in the rhetoric of the published paper.

Enoch's concept of schizophrenia, for example, as well as Azima's anaclitic theory, are both hidden elements in the haloperidol placebo trials. There is no clear reference to them in the published articles, but they are nonetheless part of the context within which the clinical trials took place. When, during the next decade, empiricism seems to triumph over theory, also due to the general obligation of supervisory bodies (first in the United States after the Kefauver-Harris Amendment and then in Western Europe), theoretical knowledge continues to be very much present, persistently forming and structuring the so-called empirical scientific production.

During the following year, 1961, two other controlled studies kept the same divergences on haloperidol that had been formed throughout 1960.

The Danes had an important tradition in developing sophisticated trial designs, Mogens Schou's team had been one of the first to use double-blind, randomised trials in their lithium studies, as early as 1954 (Shorter, 2005, p. 162). The Danish team from St Hans Hospital, Copenhagen, had been present in Beerse at the first international haloperidol symposium (see chapter 2.7.2.) At the time, they had presented data from 40 patients, in an exclusively male sample, with multiple diagnoses and an average dose of 7 mg of haloperidol per day. Results had been considered good.

In July 1961 their new clinical trial was quite different. The design was an elaborate and demanding protocol, concerned with defending the characteristics of the double blind. The sample consisted of 36 patients, 16 women and 20 men. Only patients with schizophrenia diagnosis were included, and subtypes were not considered. The chosen patients had to present a good behavioural stability that would allow them to undergo periods of placebo. Previous drugs were discontinued at least 3 weeks before the start of the trial so as not to disturb results. The dose used, 8mg/day, was very similar to the previous trial. Administration was sequential with periods of about one week alternating between placebo and haloperidol.

> In patients responding to this compound we usually found good recession of specific psychotic symptoms such as hallucinations and delusions, while a general sedative effect was less pronounced. (Brandrup & Kristjansen, 1961)

The results in Denmark uphold the European trend of valuing haloperidol's efficacy, and the idea of schizophrenia, as an increasingly clear and definite indication for haloperidol, prospered. Authors referred to specific psychotic symptoms when naming hallucinations and delusional ideas, continuing a tendency towards a Schneiderian reconstruction of schizophrenia, that we have been following in the last chapters (see chapter 2.6). Schizophrenia, as a complex psychic fragmentation was slowly but surely transforming into a list of symptoms where hallucinations and delusions became fundamental to its diagnosis (in stark contrast to what had been proposed by Kraepelin and Bleuler).

Just two months later, in September 1961, it was the turn of the Americans to respond with a new controlled study, now under the responsibility of Arthur Samuels (1961). The study was carried out at Tulane University in New Orleans, where the director of the department of psychiatry was a controversial figure (such as at the Allan Memorial Institute) - Robert Heath.[46]

Samuels' study includes a sample of 20 mixed gender patients. The protocol, of which we have few elements, was defined as carefully controlled and double-blind. Still, multiple diagnoses were included, but an important weight was given to schizophrenia (half of the sample). Doses were relatively low, 2 mg/day in the first week and 4 mg/day in the second week. Patients on haloperidol were compared to the patients receiving a placebo, and

[46] See more about Robert Heath and the Taraxeine story in chapter 5.

represented their own sequential control in placebo - haloperidol alternation, a design that we have seen repeated frequently. The results were apparently good, 8 patients with complete remission of symptoms, 8 with significant improvement, 2 with slight improvement and only 2 without improvement. When compared with patients taking placebo, the results were only slightly better. Nevertheless, improvements seemed clearer when the sequential effect drug-placebo was considered in the same patient (Samuels, 1961).

At the end of 1961 the same divergence continued, and in his January 1962 review article, which explored the innovations in psychopharmacology of the preceding year, Joseph Wortis describes haloperidol as particularly effective in paranoid-hallucinatory cases. But he also quotes Azima's trial conclusions that progressively became the synthesis of haloperidol's reception in America:

> The final impression was that haloperidol was a moderately potent neuroleptic, much less effective than claimed by European authors, with numerous side effects. (Azima et al., 1960)

Concerns about side effects were problematic, namely around "extrapyramidal" effects, which became increasingly worrisome and advised greater care with doses used (Wortis, 1962). Through the next chapter, this thesis will explore more clearly the context of emergence of the description "extrapiramidal side-effects" when applied to neuroleptics, in order to continue to assess its subsequent impact in neurology and psychiatry.

3.3. Hans Steck and a brief history of extrapyramidal symptoms

The shared predicament of the winter of 2020 has shown us how the experience of a pandemic, at once intimate and universal, can sometimes cause perplexity and the strange feeling of seeing one's routine overrun by the unfamiliar. The so-called cases, which are actual infected people crossing the permeable borders of the nation-states, appear wrapped in a mantle of mysteries. The virus keeps moving inexorably but in a heterogeneous way. Receding, hiding itself, just before its expansion. The polymorphism of the clinical picture in this scenario leads to doubts and differing descriptions of the evolution and prognosis of the disease, as well as questions pertaining to its transmission. At first, during the Covid pandemic, no one understood the reasons for the vulnerability of some and the resilience of others. As a conservative practice, medicine takes time to react when faced with an unknown phenomenon. To this day, the processes of identification of a new entity and the development of new therapeutic practices are filled with obstacles and challenges.

In 1917, working in a war-torn Vienna, a young doctor was particularly interested in anatomical pathology. In his eclectic training, he had passed through Paris and Berlin, studying on both sides of a fractured Europe. He had learned with Kraepelin and Oppenheim. The subcortical structures were his primary interests, namely the brainstem, specifically pontine tumours, the main subject of his thesis (Demetriades, 2012). In the spring and winter of 1917, perhaps due to an awareness developed while working on the subcortical region, Constantin Von Economo recognised two recurring symptoms in a set of 11 patients with an otherwise heterogeneous presentation– somnolence (found in 8 patients) and ophthalmoplegia (identified in 9 patients). From this newfound clinical consistency, Von Economo created a new unitary entity – Encephalitis lethargica (Vilensky, 2010, pp. 16,17). This novel *disease* combined this persistent symptomatological core within a variable clinical condition, with postmortem histopathological inflammatory changes observed by Von Economo in 1917, albeit non-specific (diffuse alterations that affected different subcortical structures, the diencephalon and mesencephalon, but mostly the basal ganglia (Vilensky, 2010, p. 242)).

During the following decade, cases of encephalitis lethargica spread around the world and the characterisation of the acute form gave way to descriptions of the chronic consequences. As a growing number of patients with a post-encephalitis diagnosis were

checked into asylums, Economo's entity became popular among young asylum doctors. The diagnosis was often present even when the acute form was identified retrospectively, and sometimes portrayed in a broad and coarse manner. Take, for example, the Swiss case. From Von Economo's description until 1930, 364 patients with sequelae of encephalitis lethargica passed through Swiss lunatic asylums and many others were institutionalised in asylums for epileptics, the elderly or ordinary infirmaries (Steck, 1931).

Just as Von Economo was describing encephalitis lethargica, the war was forcing Hans Steck, a young Swiss doctor, to return to Zurich after an internship in Paris. Following the disappointment of not immediately becoming Bleuler's assistant in Burghölzli (Steck would eventually specialise in Bleuler's clinic just a few months later), he ended up joining the cerebral anatomy institute in Monakow for six months (Hirnanatomisches Institut) (Choquard, 2012, pp. 134,135). It was this experience, particularly the research into the anatomic lesions of *general paralysis* and its relationship to mental and neurological syndromes, which would awaken Steck's interest for the neurological aspects of psychiatric diseases (personal correspondence with his son, Andreas Steck, on April 29, 2020). Thus, an awareness of movement disorders in mental illness emerged, as well as an interest regarding a possible location of psychiatric troubles in the central nervous system. The significant number of institutionalised patients who suffered from chronic sequelae of Von Economo's disease allowed Steck to keep reflecting on and exploring this sensibility during the following decade.

Parkinsonism would be presented as the main sequela of encephalitis lethargica, or so it entered popular culture through Oliver Sachs' work (*Awakenings*). Since the beginning of the 1920s, it was recognised by Von Economo as the main post-acute consequence of the disease. Present in the vast majority of patients, parkinsonism could even develop without a clear retrospective identification of an infectious state (Dickman, 2001).[47] The descriptions

[47] Parkinson's disease was known since the beginning of the 19th century, when James Parkinson regrouped a diverse constellation of symptoms in a unitary entity. During the 19th century, it was rarely identified before the fifth decade and seen as part of the degenerative process, but in the 20th century, with the arrival of encephalitis lethargica's epidemic, Parkinson forms started affecting people of all ages and more severely (Sacks, 1999).

included tremors usually during rest that subsided with movement; stiffness, which was often severe; and a combination of motor restlessness and psycho-motor retardation (akinesia).[48]

> Patients so affected find that as soon as they 'will' or intend or attempt a movement, a 'counter-will' or 'resistance' rises up to meet them. They find themselves embattled, and even immobilized, in a form of physiological conflict - force against counter-force, will against counter-will, command against countermand. (Sacks, 1999)

Sacks' description is revealing of how, for many parkinsonian patients, the mere initiation of movement, including the internal experience of thought and affect, was shackled by two strong tendencies. In this phenomenon, which is central for Sacks' description of Parkinson's disease, we can find a similarity with Bleuler's concept of ambitendency, one of the most defining elements of his schizophrenias (Bleuler, 1937, p. 286). As we'll see in this chapter, the link that was made between schizophrenia and parkinsonism throughout the 20th century is in fact full of challenges, swaying between continuity and antagonism. Movement disorders in schizophrenia are examples of these opposing forces within the disciplines, and specifically the concept of catalepsy, as Sacks describes it with Gowers' help:

> In some patients, there is a different form of akinesia, which is not associated with a feeling of effort and struggle, but with one of continual repetition or perseveration: thus Gowers records the case of one patient whose limbs "when raised remained so for several minutes, and then slowly fell" - a form of akinesia which he correctly compares to catalepsy; this is generally far more common and far more severe in patients with post-encephalitic forms of Parkinsonism. (Sacks, 1999)

This catalepsy seems to be the same phenomenon we can find in Kraepelin's and Bleuler's work associated with *dementia preacox*. Take, for example, Bleuler's *Lehrbuch der Psychiatrie*:

> Eine merkwürdige motorische Störung ist die Flexibilitas cerea (wächserne Biegsamkeit), auch Katalepsie schlechtweg genannt: Die Kranken machen von sich aus keine Bewegungen; wenn man sie aber in eine beliebige, wenn auch noch so unbequeme Stellung bringt, so behalten sie dieselbe bei, oft viel länger als der bewußte Wille eines Gesunden es aushalten könnte. (Bleuler, 1937, p. 86)

These descriptions are strikingly similar. The doctor puts a patient in an uncomfortable position that he upholds despite the pain. This blind obedience makes us consider not only the movement disorder, but also the power relations that are established

---

[48] The jewish neurologist Friedrich Heinrich Lewy (1885–1950), who would be later forced to flee Germany's Nazi regime, proposed the term akinesia in 1923 to describe the delay in movement initiation in parkinsonism. Lewy's characterisation of akinesia is still in use (Prange et al., 2018).

between a doctor and a patient and how this differential can extend to the will and control of the body in a particularly astonishing way. Consider, for a moment, the photograph taken by Steck (see Appendix B, figure 3). In this picture, the doctor is absent, scotomizing his role in the movement, but he remains central to this interaction. Although the patient is the only one we see, we understand that he has given more than his movement, or musculoskeletal control, to the doctor, he has given away his very will to move. In these descriptions of catalepsy, which the picture illustrates quite clearly, there is, however, a hint of resistance in the seeming subordination. Persisting beyond his own discomfort, the patient's posture seems to confront the doctor who placed him in this position. Persisting beyond all reasonability, the patient hands back his pose to the doctor, in a clinical dialogue that resembles a bizarre dance.

Throughout the 20th century, parkinsonism and schizophrenia would become paradigmatic examples of their disciplines, psychiatry and neurology, whose divorce was progressively but surely affirmed. In their initial clinical descriptions, we can still be taken aback by some of their common elements, reinforcing critics of the separation between the two disciplines (Rogers, 1992) . Still the *encephalitis lethargica* epidemics deeply affected this relationship.

Although Edward Shorter gives credit to Samuel Alexander Kinnier Wilson (1874-1937) for the expression ”extrapyramidal motor reactions” first used in the article “The old motor system and the new”, published in 1924 (Shorter, 2005, p. 101), we seem to have found previous references to this expression in our research (Stertz, 1921).

Extrapyramidal motor syndrome is also the name given by Hans Steck (1926) to a combination of akinesia and parkinsonism, including the psychological pillow phenomenon,[49] inert mimicry with peribucal hyperexcitability, dysarthria that can lead to mutism and above all a global lack of motor spontaneity with psycho-motor retardation. This syndrome could appear both in patients with post-encephalitic parkinsonism and in patients with catatonic schizophrenia.[50] Resemblance between the two leads Steck to assert:

---

[49] “Psychological pillow phenomenon” refers to a classical symptom of catatonia, where the patient keeps his head elevated as if he was leaning on an imaginary pillow.

[50] The analysis of a possible continuity between extrapyramidal symptoms and catatonia has a long tradition in psychiatry (p. e. McKenna, Lund, Mortimer, & Biggins, 1991).

> L'encéphalite léthargique réalise dans ses séquelles le syndrome moteur, plus une ébauche du syndrome psychique de la catatonie.(Steck, 1926)

As we saw earlier, the anatomopathological changes of encephalitis lethargica had been located mainly in the subcortical regions. Although these lesions were seen as pathognomonic (or at least suggestive of such), the anatomopathological lesions of dementia praecox were not very specific and difficult to interpret. The presence of extrapyramidal motor syndrome in both was, therefore, a very important clue regarding the origin of the motor symptomatology of dementia praecox, and revealed the potential role of what Hans Steck called the *basis* of the brain. Or, to be more precise, the fronto-ponto-opto-strio-rubro-cerebellar system (Steck, 1926). Lesions at this level were fundamental in the etiopathogenesis of psychosis in general, and of schizophrenia in particular, highlighting not only the importance of the subcortical system, but above all its connection to the cerebral cortex. In his 1926 article, Steck brought parkinsonism and schizophrenia together, locating its lesions in tandem (functional and anatomical) in the diencephalon and the midbrain, whose importance in personality development was often minimised at the time. This neuroanatomical tracing process propelled by encephalitis lethargica served to definitively call into question the privileged location of the mind in the cerebral cortex, urging the construction of functional unitary perspectives for the whole central nervous system (Foley, 2018, p. 482) .

Hans Steck's studies about encephalitis lethargica brought not only attempts at locating psychosis and the importance of the diencephalon, but also an idea that would have a particular reach in psychiatric research for the following decades. We can even see its direct influence extend to the conception of the dopamine hypothesis. While the similarity between the parkinsonian and catatonic clinical pictures suggested, in many ways, a clinical and pathophysiological continuity, in his 1931 article Steck begins outlining a relationship that was perhaps somewhat different to this suggestion.

In his study of the post-encephalitic psychiatric course, Hans Steck (1931) divided the mental sequelae of encephalitis lethargica into two main syndromes: changes in character with the release of lower instincts (especially in the young), and bradyphrenia with global psychomotor retardation.[51] A third syndrome included patients who would develop psychotic

---

[51] In 1922 ,François Naville, had named *bradyphrénie*, a complex clinical pictured associated to parkinsonism that included diminished attention, interest and initiative (Rogers, 1986).

symptoms, such as hallucinations or paranoid episodes. The latter could resemble *dementia praecox*, but the persistence of insight and affect allowed the diagnosis to be easily differentiated. Of greater relevance to our research is a case described by Steck in which post-encephalitic parkinsonism had transformed the clinical picture of a previously diagnosed *dementia praecox*, undoing its "primary autism", annihilating delusional activity, and transforming the affect. Steck finds other similar cases in the literature, namely an elderly patient with chronic catatonia whose condition had improved after the encephalitis.

These observations crystallise and solidify Steck's appreciation of motor symptomatology in *dementia praecox* and, as we will see in this chapter, set the backdrop for his first experiments with chlorpromazine two decades later. Thus, this article begins to outline not only an antagonism between parkinsonism and *dementia praecox*, but a broader idea relating to the capacity to transform the clinical picture of *dementia praecox* through the lesions of encephalitis lethargica, acting directly on affectivity and autism. We clearly see Steck formulating an idea of ascribing an anti-delusional quality to parkinsonism. The foundations of a new paradigm were being built in these brief lost notes of a 1931 article. If parkinsonism and the subcortical lesions of encephalitis lethargica could improve the psychotic picture, then drugs acting in this area, and in this way, could also be useful in schizophrenia. We could find potential therapeutic mechanisms for schizophrenia by knowing the pathophysiological mechanisms of Parkinson's disease. One of the keys that could serve to unravel the mystery of schizophrenia was thus found. By understanding Parkinson's disease, one could find the clues for the origin and biological functioning of schizophrenia. The direct influence over the dopamine hypothesis is indisputable, as it was made explicit by Jacques Von Rossum himself, its first proponent, and whose work we will probe in chapter 5.

> In agreement with this hypothesis is the clinical observation that patients with Parkinson disease do not develop schizophrenia and that schizophrenics who become affected with the disease of van Economo improve with respect to their psychosis. (van Rossum, 1966a)

Twenty-six years before van Rossum's proposal, one of his main arguments was emerging in Hans Steck's observations. In the background, in the conceptual frame of this construction, was a hierarchical idea of the central nervous system, with a possible North American origin, but by then deeply rooted in French speaking psychiatry, directly influencing Hans Steck.

Hassan Azima, the young Iranian doctor whose career we briefly followed in chapter 3.2., did an internship in Paris in the early 1950s, becoming acquainted with Henry Ey, one of the most prestigious psychiatrists in continental Europe. In one of his reflections on the role of the concept of Organo-Dynamism in Henry Ey's work, Hassan ponders the influence of Hughlings Jackson's theories, not only on Ey but on a wide variety of authors like Monakow (Hans Steck had spent six months at the Hirnanatomisches Institut, the cerebral anatomy institute of Monakow), Bleuler, Delay, and Kretschmer. The idea of a hierarchy in the mental structure, attributed to Jackson, was becoming preponderant. The central nervous system was then seen as spatially organised by different levels of integrative configuration following evolutionary lines. The dissolution of the upper regions would lead to the release of the lower instances responsible for the diseases' main clinical symptoms (Azima, 1953). The paralysis affecting the upper centres directly created the negative symptoms. The release of the now uninhibited lower centres, freed from the healthy inhibition of the upper centres, would form the positive symptoms. The appearance of positive symptoms would then be dependent on the existence of negative ones (Berrios, 1985).[52] The presence of these principles in Ey's work assured their influence in francophone psychiatry and, therefore, in Hans Steck's practice as well.

This hierarchical conception of mental function would come together with elements of cultural evolutionism to form the schizo-primitive parallelism hypothesis that Florence Choquard carefully explores in her work on Hans Steck. As she recognises, Lévy-Bruhl's first ethnological works are among Steck's greatest influences (Choquard, 2012, p. 193)

> La mentalité primitive telle qu'elle a été exposée dans les beaux travaux du sociologue et psychologue français Lévy-Brühl a été pour nous la clef de la mentalité schizophrénique. (Steck, 1927)

---

[52] In the following decades, this separation between positive and negative symptoms would become more and more present in descriptions of schizophrenia. The expression "positive symptoms" would mostly include symptomatology that related to Schneider's first-rank symptoms, including hallucinations, delusional ideas and formal thought disorder. Negative symptoms would then include symptoms resulting from the loss of normal functions, especially in relation to the generalised poverty of the clinical picture, like changes in affect (with flattening), in will (with avolition) and in speech (Crow, 1980). Perhaps this split of schizophrenia into two syndromic complexes derived naturally from the trends we have been analysing, namely the phenomenon of paranoidization that we mentioned briefly in chapter 2.6, and its contrast with the early 20th century nosological descriptions. We may be tempted to see the direct influence of Hughlings Jackson in this splitting, but the historian German Berrios argues that this division is in fact older and probably derives from the work of John Russell Reynolds, where Jackson originally found the positive-negative division, framing it in the evolutionary theoretical framework that was hegemonic at the time (Berrios, 1985).

Lucien Lévy-Brühl (1857-1939) was a French philosopher interested in the "sociology of primitive societies" who delved into the concept of prelogical mentality. Impressed by narratives that seemed to call into question logical principles, such as that of non-contradiction,[53] Lévy-Brühl created a deep and qualitative divide between two different mentalities. These mentalities were built by opposition (especially at the beginning of his work), in a set of absolute dichotomies: western/primitive, rational/prelogical, mystical/ positivist (Saumade, 2018).

At the turn of the century, European thought was being shaped by the idea of social evolutionism as an explicit or implicit justification for colonial rule. Some of the concepts we recognise in Lévy-Brühl, such as "primitive" or "prelogical", reveal the extent to which his endeavour depended on this ideological matrix. His work, and the concept of primitive mentality in particular, received a warm welcome from the European academic elite, which had an impact not only on the young Hans Steck, but also on much of the psychiatry and psychology of the first half of the 20th century, such as that practiced by Pierre Janet or Jean Piaget. However, this was not consensual and so it remained controversial and the object of explicit criticism (van der Veer, 2003).

> Cette, forme d'activité mentale, radicalement différente de celles que notre société nous donne l'occasion d'étudier, ne cherche pas encore à comprendre où à s'expliquer son objet. Elle est orientée dans un tout autre sens: elle est inséparable des pratiques mystiques qui réalisent les participations. Ubiquité, ou multiprésence des êtres, identité de l'un et de plusieurs, du même et de l'autre, de l'individu et de l'espèce, tout ce qui ferait le scandale et le désespoir d'une pensée assujettie au principe de contradiction est implicitement admis par cette mentalité prélogique. D'autre part, elle est imperméable à ce que nous appelons l'expérience, c'est-à-dire aux enseignements que l'observation peut tirer des liaisons objectives entre les phénomènes. Elle a son expérience à elle, toute mystique, bien plus complète, plus profonde, plus décisive que l'expérience souvent ambiguë dont la pensée proprement dite sait qu'elle doit accepter et même rechercher le contrôle. Elle s'en satisfait entièrement. (Lévy-Bruhl, 1922, p. 428).

In this small excerpt from *Les fonctions mentales dans les sociétés inférieures* we can perceive several concepts that would become fundamental in Hans Steck's theoretical propositions. The idea of a radical discontinuity between our society and the form of mental activity of others, the preference for mystical explanation, the presence of subjective

---

[53] A classic example is von den Steinen's description of the identity of the individuals in the Brazilian Bororó tribe, who would define themselves as red araras (Lévy-Bruhl, 1922, p. 77).

causality, and above all the indifference to logical contradiction and the impermeability to experience.

At the beginning of the century, the European elite, and German expressionism in particular, was enthralled by the idea of the exotic. Two aesthetic processes were developing concurrently: the interest in African art that reached the elites at the time fascinating the literary elite, namely influenced by Dadaism, along with the writings of asylum patients. Art placed itself in a space that threatened the establishment, a threat to bourgeois good taste, challenging the power structures of the colonial order (Gilman, 1985, p. 228). Similarly to the intellectual trajectory of Jean Bobon (explored in chapter 2.3), Hans Steck was interested in what was then called psychopathology of expression, and was an avid collector of "magical and primitive" art. Perhaps also reflecting the peripheral origin of these productions, Steck found in them formal similarities that he deemed compelling. There was something in common between the artistic production of the lunatic Europeans and the work he attributed to the "black antipodes". From this similarity, he made an attempt to apply "ethnological" operative concepts, which Lévy-Brühl had linked to primitive mentalities, to the thoughts expressed by the patients committed to the Cery's asylum (Choquard, 2012, pp. 194-217).

> Pour le primitif, la distinction entre le moi et le monde environnant, entre le dedans et le dehors disparaît comme chez les schizophrènes... Dans les psychoses aiguës les malades participent à la destruction et à la création du monde. Comme dans l'extase mystique les limites entre eux et l'univers cessent d'exister. (Steck, 1927)

Steck identified the same radical discontinuity in his patients that Lévy-Brühl had described in primitive peoples: namely the same subjective causality, the same indifference to logical contradiction. These similarities also extended to concretism, as both *inferior societies* and patients with schizophrenia would avoid abstract concepts.[54] This deficit of abstraction took shape in a paradigmatic way of thinking through images (thinking without words / "Denken ohne worte") (Choquard, 2012, p. 195).

These immense differences in "mental functions" between westerners and primitives had a clear physical/cerebral explanation at the time. Just as Steck worked on the location of the changes to the central nervous system associated with schizophrenia, neuro-anatomical studies on the primitive brain also sought to locate this difference of mentalities. F. W. Vint's

---

[54] This idea of hyperconcrete thinking, deficit or dysfunction of abstract thinking in schizophrenia will gain relevance over the next few decades in psychiatric theory as an important factor both in terms of diagnosis and prognosis (Harrow, Adler, & Hanf, 1974).

works are illuminating in this respect. Vint compared 100 primitive post-mortem brains with the average European measures at the time, and concluded the African brain was inferior (Vint, 1934). Lunatic Europeans and *inferior societies* were thus placed in the same category, qualitatively divorced from western man, the paradigm of rationality. Their speech, their artistic production and their brains were understood to be the realisation of that difference.

In the work of Lévy-Brühl, and consequently of Steck, we can speculate on the existence of a hidden anxiety about the moral risks inherent to the colonial encounter, and similarly the moral risks of the lunacy defiance, projected in the construction of difference. By building an almost flat category, which incorporated only negative aspects, colonial exploitation and violence was justified by the denigration of *primitive* man, by the demonstration of his irremediable incapacity for true autonomy. As we saw, difference, whether of the lunatic or the *primitive* man, was seen as a threat to the establishment, and so to control. Exoticised, embodied in irrationality, in prelogical thinking, in the lower brain, in the subcortical, the difference loses this initial violence. The primitive and the lunatic mentality was both located in and understood to materialised itself within this less cortical function, a lower functioning enabled by the absence of superior containment structures. By constructing categories of difference with clear boundaries, the internal anxiety of the fear of the unknown, or the opposition to order is allayed. These absolute dichotomies between us and the other, between western and primitive, between rational and prelogical, between mystic and positivist, restore order where the violent threat of chaos, and so disorder, was implied. On the one hand, this is manifested in our idealised representation, the perfect image of the group to which we would aspire to belong. On the other, it presents an omen of what we will never be able to understand, of a mystery that has the capacity to both frighten and seduce, presenting both the imagined self and the feared self. The illusion becomes appeasing because of the absolute rigor with which these oppositions are divided, and because of the depth of the gap. Sander Giliam alerts us to the risks of these fantasies, which can infuse scientific and medical knowledge, leading, for example, to the abuses of Auschwitz and the Apartheid regime (Gilman, 1985, p. 241).

This subcortical location of psychosis, which we have examined in Steck (1926), namely due to the dysfunction of what he called the fronto-ponto-opto-strio-rubro-cerebellar system, comes from a long tradition that Swiss researcher Emilie Bovet analyses exhaustively

(2012, 2015). The diencephalic model was built not only within psychiatry but at a crossroad of disciplines that included, for example, the physiology of the hypothalamus-pituitary complex, the observations resulting from neurosurgical activity, and anatomopathological studies in patients who had suffered from diseases such as encephalitis lethargica (as we saw in the work of Hans Steck). Psychiatry seems to have intervened at a later stage, attempting to assign psychiatric pathology to the observed diencephalic changes, trying to locate and concretize psychopathology. This rise of the diencephalon quickly escaped the linguistic traditions that used to seize psychiatric descriptions, to become a transnational scientific object, accompanying the rapid internationalisation of biological technologies of therapeutic intervention, such as shock therapies or leukotomy (Bovet, 2012). In the early 1950s, Jean Delay, the psychiatrist who ran the *Clinique des Maladies Mentales* at the Sainte Anne Hospital in Paris, was already familiar with the multidisciplinary work on the diencephalon developed during the previous decades. Delay, who subscribed to the increasingly acknowledged idea of the diencephalon as an instinctive-affective regulatory structure, would progressively transform it into the central axis of pathophysiological theories of mental disorders. The research that his team carried out on the mechanisms of therapeutic action of shock treatments (especially, but not exclusively, electroconvulsive therapy,) led him to suggest that these therapies acted through a localised action at the level of diencephalic stimulation. Shock - epileptogenic or comatogenic - would be indispensable for the re-emergence of the affective tone of the cerebellar base, and this was the fundamental deficit to address in order to treat the so-called secondary schizophrenic signs (paranoid or catatonic). The shock, acting on the diencephalon, would cause the patient to come out of his autism, and the impairment in thought and behaviour would subsequently disappear (Bovet, 2012, pp. 86-91).

At the same time, Henri-Marie Laborit was working on precisely how to prevent another type of shock - surgical shock, seen at the time as an inordinate defensive reaction from the body to aggression. A surgeon in the French army, stationed initially in Tunisia and later in Paris, he researched the application of various substances with inhibitory effects at the level of the neurovegetative system. When Rhône-Poulenc's chlorpromazine was synthesised in 1950, it seemed to demonstrate a strong parasympathetic and adrenolytic capacity.[55] This

[55]Able to suppress the effect of adrenaline on blood pressure.

was the agent that Laborit was looking for to avoid surgical shock, and he quickly started using it as an anaesthetic adjuvant with considerable success. Its hypnotic (sleep-inducing) and hypothermic (with the capacity to lower the body's temperature) effects, among others, made it particularly useful in surgical activity. At the time, "open" experiments, in which a drug was distributed only for clinical research, were frequent. These trials would aim to identify doses and therapeutic indications, even without a formal or institutional framework (Pieters & Majerus, 2011). Denniker, from Jean Delay's service in Sainte-Anne, had heard about Laborit's experiments through his brother-in-law, and would soon receive the first samples of chlorpromazine sent by Dr. Beal, the research director at Rhône-Poulenc (López-Muñoz et al., 2005).

Given the acknowledgement that chlorpromazine's mode of action interfered with neurovegetative centres (namely on the sleep-wake and body temperature mechanisms), it was safe to assume that chlorpromazine would also act upon the diencephalon. From here, we can then imagine the initial interest with which the Paris team received the product. Chlorpromazine was believed to intervene in the same place as shock therapies, but with an inverse mechanism, making for a potentially auspicious use in psychiatry (Bovet, 2012, p. 236). It was therefore initially tested on the pathological clinical states thought to be most directly linked to diencephalic pathology (Delay, Deniker, & Harl, 1952). The work of the Paris team on chlorpromazine thus comes in direct continuity with their previous empirical work, and theoretical framework about shock therapies. In fact, the relevance of studying the therapeutic mechanisms of shock is mentioned in the first paragraph of Delay's presentation about chlorpromazine to the medical-psychological society (published in June 1952 in the *Annales médico-psychologiques*).

> La connaissance meilleure des modes d'action des thérapeutiques de choc, qui agissent notamment par stimulation en provoquant des "crises", au sens hippocratique du terme, et l'intégration de ces connaissances dans les données de la pathologie générale (travaux de Reilly, de Selye) conduisent a rechercher s'il existe des moyens inverses, visant à la mise en repos ou a l'interruption des processus réactionnels, qui, dans certains cas, peuvent constituer le substratum de la maladie, sinon la maladie tout entière. (Delay et al., 1952)

In this context, and as has been suggested by others (Bovet, 2015), the application of chlorpromazine to psychiatry, and its specific use in psychosis, seems not to be a serendipitous occasional discovery, but rather the result of a long empirical and theoretical

process. The established interest in the diencephalic location, and in the therapeutic mechanisms of shock therapies, led to the recognition of this substance's potential to act on that very same area. In these early conceptions (that justified the introduction of chlorpromazine and contextualised its action in the early years), we find what appears to be a peculiar paradox. While the site of therapeutic action seems relatively precise at the level of the central nervous system, its clinical indication is, on the other hand, very broad (see, for example, the advertisement for chlorpromazine in the Rhode Island Medical Journal, Appendix B, figure 4). Chlorpromazine would make it possible to appease, disconnect or exclude diencephalic activity, and would do this by acting on a wide variety of psychopathology.

The first symposium on chlorpromazine took place in Basel, Switzerland, in November 1953, reflecting the enthusiastic reception that the drug had had in the country (López-Muñoz et al., 2005), unlike other countries where the reaction to chlorpromazine seems to have been more prudent, such as Belgium and the Netherlands (Pieters & Majerus, 2011). It seems that the work done by the pharmaceutical sales representative of Rhône-Poulenc/Sepcia was responsible for boosting the initial clinical use of the drug (Pieters & Majerus, 2011). At the Cery's asylum, where Steck worked, the first administrations began in October 1952, just 4 months after the Paris team's first publication (Wyss, 1997). The introduction of chlorpromazine in psychiatry by Delay maintained the focus on the circuits at the base of the brain, and Steck dedicated his career to the study of mental symptoms with diencephalic origin.

At the time, Cery was changing as an institution (Cantini, 1997). From 1948 onwards, the institution was officially transformed into a hospital, but symbolic places of the old asylum, such as the baths, kept the memories of the past. Treatments such as lobotomy and malariotherapy persisted, together with drug therapies that combined sedatives, including barbiturates (Wyss, 1997). The mental hospital had about 730 patients divided in several services (16 divisions), depending on the severity of the clinical picture, the degree of autonomy, or the ability to work outdoors (on the farm, in the garden, or in agricultural fields outside the institution)(Cantini, 1997).

When chlorpromazine started to be administered, the doses used in Cery quickly escalated, becoming much higher than those used in neighbouring countries. They were

approximately twice as high as the ones administered by the Paris team - 100 to 200 mg per day intramuscularly for the first 10 days (75 to 100 mg in Paris), followed by 400 to 800 mg per day orally (maximum 150 mg per day in Paris).

In his 1954 article, Steck outlined a preferred diagnostic indication for chlorpromazine, an oddity when we take into account the path of chlorpromazine in its early years and its widespread use later on. He was mainly concerned with the effect of chlorpromazine in patients with schizophrenia, where the results seemed to him to be better. Of the 232 women treated with chlorpromazine in Cery, 86 were discharged (about 37%); of the 77 men who were treated, 26 were able to leave the hospital (a slightly lower percentage of about 34%).

In one of Cery's units there were women whose clinical conditions, resistant to shock treatments, electroconvulsive therapy and insulin therapy, led to long hospitalisations with persistent agitation and hetero-aggressiveness. In their rooms, the mattresses were replaced by seaweed that the nurses renewed every morning with a rake (Cantini, 1997). Steck (1954) highlights the progress in this unit, triggered by the introduction of chlorpromazine, in terms of the general environment of the infirmary, naming improvements in sociability and behaviour that allowed complementary differentiated interventions, hitherto impossible - such as work integration and group psychotherapy.

The most relevant secondary symptoms stemming from chlorpromazine's use in Swiss doses were what Steck called a true extrapyramidal syndrome. There had been previous references to extrapyramidal symptoms in the first symposium on chlorpromazine, but it was Hans Steck's description that captured the attention of his contemporaries (Wolf, Yassa, & Llorca, 1996). As we have seen, Steck was particularly attentive to any motor symptoms, whether by reasons of ideology, by training or personal sensitivity, perhaps because of his belief that *dementia praecox* was directly related to subcortical structures (as we have seen in the context of possible deficits in the upper structures).

The frequency of his new chlorpromazine-induced extrapyramidal syndrome was high, curiously similar to his therapeutic success rate, about 34% in women (78 out of 232) and 43% in men (33 out of 77). The picture so vividly described included staring and diminished mask-like facial expression ; a gait of small steps with no arm movement and

trembling of the hands and lower limbs; excessive salivation and marked facial seborrhoea. In the most severe cases, the patients also had generalised stiffness and cogwheel.

> Ce tableau akinétique produit parfois un spectacle assez impressionnant, surtout frappant lorsque nous voyons nos malades se promener em groupe, donnant l'image d'une procession un peu triste. (Steck, 1954)

The clinical picture was very similar to the post-encephalitic parkinsonism that Steck had been absorbed by for much of his career. As in the case of post-encephalitic patients, their movements became less restricted when patients were encouraged to dance to music, but unlike post-encephalitic patients, it was less common for chlorpromazine patients to complain about their constraint, and they rarely reported loss of initiative or motor drive. We're conveying here what is perhaps one of the main ethical criticisms to neuroleptic therapy, the fact that patients were often unaware of the blatant motor entrapment caused by their treatment. Unable to appreciate how their motility and initiative had been curtailed, they were also sometimes unable to clearly understand the scope of their consent (when it existed). They were diminished in their ability to oppose - or at least less likely to contest - the treatment after it started. Collaboration is a theme that resurfaces throughout the initial trials with the first neuroleptics, maximising collaboration facilitated the infirmary's internal life and reorganised its hierarchy.

As Steck explicitly points out, the main goal of the 1954 article was not just to present his results with chlorpromazine, nor to highlight its therapeutic value, which for him was indisputable. The article's purpose was rather to explore the theoretical implications of the new treatments. For Steck, the drug trial didn't have a purely empirical function, it didn't focus only on the simple, or simplified, question *does it work or not?* In fact, such an approach was in contrast with what would progressively become the norm in the following decade with the professionalisation of clinical trials (as we have seen in chapters 3.2). On the contrary, in his clinical trial, Steck saw an opportunity to potentially clarify scientific theory, to test the pathophysiological processes of the disease, and to explore experimental inquisition, using and reproducing an equivalence between the drug's mechanism and the disease's mechanism. This way of thinking about the pathophysiology of the disease from its treatment had a long tradition, as we have seen in this chapter. The studies of Delay's Paris team on shock therapies, for instance, also sought to produce knowledge on psychopathological processes. This parallelism (therapeutic mechanism/disease mechanism)

would persist in psychiatry in the following decades and was to become the main source of pathophysiological theories, namely the dopamine hypothesis for schizophrenia. In this case, the chlorpromazine trials were seen as an experimental study to assess the thesis of diencephalic location of psychosis, which Steck himself defended and who, in Jean Delay, he had found a "particularly brilliant" advocate. The therapeutic response and, above all, the extrapyramidal syndrome, whether seen as part of the treatment or the side effects, were the experimental confirmation of Delay's theory. The vivid description of extrapyramidal symptoms probably emerged with Steck, not only because of his own particular sensitivity to movement disorders, or because in Switzerland higher doses of the drug were being used, but because Steck looked for it from the start. The diencephalic hypothesis, which was the theoretical framework of chlorpromazine experimentation, required the emergence of an extrapyramidal syndrome to maintain its paradigmatic purpose.

There is a particular analogy between encephalitis lethargica and the action of chlorpromazine that stands out in Steck's article. They would both unfold in stages. An initial period marked by somnolence - which corresponded to the hypnotic effect of chlorpromazine's first days of administration, and the lethargic phase of encephalitis, followed by a second period in which the extrapyramidal syndrome would emerge. A few days after the beginning of the treatment with chlorpromazine, the sedative lost its effect and a clinical picture of movement disorder, very similar to what Steck knew from post-encephalitis parkinsonism, came to the fore. The similar outline of the two clinical pictures led to the assumption that the location of the two processes was the same. If the attack sites of encephalitis lethargica were well known - extrapyramidal and diencephalic location - then it could be inferred that chlorpromazine (and reserpine) would act in the same places and in the same way. Chlorpromazine mimicked encephalitis lethargica, the course of treatment was very similar to the natural history of the disease, but at a faster pace, resembling, to use Steck's metaphor, a film where the frame rate is accelerated.

However well Steck thought he knew encephalitis lethargica, the disease was and still is shrouded in mystery. Today it may seem absurd to shed light on the functioning of chlorpromazine by comparing it to such a mysterious entity, but *encephalitis lethargica*, however mysterious, had something that had always escaped schizophrenia - a possibility of materialisation, an anatomopathological manifestation, a place in the central nervous system.

This analogy between chlorpromazine and encephalitis lethargica brings us back to Steck's old observations of patients diagnosed with schizophrenia whose clinical picture had improved when, following encephalitis lethargica, they developed a post-encephalitic parkinsonian picture. Steck was thus reminded of his initial idea of a therapeutic side to encephalitis lethargica, which would improve schizophrenia by acting on the diencephalon.

This path of the illness - from the lethargic phase to parkinsonian akinesia - also reminds Steck of the natural history of some acute psychotic episodes, which went through an akinetic phase after a period of agitation, followed by spontaneous remission of the psychotic symptoms. Perhaps medication could be used to accelerate the onset of this inhibition phase followed by clinical improvement.

> Je pense plutôt qu'il s'agit directement de la mise hors circuit d'un mécanisme nerveux, d'un appareille mal synchronisé, par l'inhibition passagère due au médicament ou aux lésions dans l'encéphalite léthargique. (Steck, 1954)

In this example we can find symbolic elements that refer directly to an industrial, electrical or at least mechanistic semantic field (circuit, synchronisation). This perspective of the brain as a machine with an internal rhythm, with a device at risk of desynchronising, is related to the electrical model of neurotransmission that was dominant at the time. At the level of the central nervous system, neuronal transmission was then considered exclusively electric (Valenstein, 2007, p. 157). As we will see in the following chapters, when the paradigm changes throughout the sixties and the dominant model of neurotransmission becomes humorous, the metaphors about brain function will shift to the semantic field of biology, or reproduction, namely through expressions such as receptors, synaptic cleft, etc.

For now, however, it is important to note that the general acceptance of Steck's description had important consequences. The expression "extrapyramidal symptoms" entered the psychiatric lexicon irreversibly. His description influenced Delay to such an extent that the name of the new class of substances, into which chlorpromazine and reserpine fell, was derived from this constellation of side effects: namely neuroleptics. The expression was established in Europe after the Second International Congress for Psychiatry in Zurich

(1957), but it was never welcomed in the United States, where neuroleptics were instead given the name *major tranquilizer* (Healy, 2002, p. 117).[56]

Steck's analogy between neuroleptics and encephalitis lethargica would remain relevant for many years. Six years after this article, in November 1960, Smith, Klein and French - the pharmaceutical company responsible for the market introduction of chlorpromazine in the United States - sponsored a conference in Montreal whose theme was precisely the expression that Steck had upheld, "extrapyramidal syndrome". Among the remaining pharmaceutical companies that sponsored the conference, neither Janssen Pharmaceuticals nor Searle were present (the latter was then a potential distributor of haloperidol in the United States). This symposium brought together the main protagonists that we have been following in this thesis, as well as others we will soon introduce. Delay and Deniker represented the Paris team; from Liège came Jackie Collard, whose role in the first haloperidol trial had been paramount; Hassan Azima and Herman Denber, whose work on haloperidol had slowed its comercial progression in the United States, were also there. Other guests included Hans-Joachim Haase, Nathan Kline, Fritz Freyhan and Mortimer Ostow. Hans Steck was not present, but Jean-Marc Bordeleau (1961) made extensive reference to his work in the introduction to the colloquium - both to the ability of encephalitis lethargica in altering the natural history of schizophrenia as first presented in 1931, as well as to his seminal descriptions of the extrapyramidal syndrome in the 1954 article that we have discussed in this chapter.

As we have seen (chapter 3.1.), the state hospitals on the North-American east coast became privileged spaces for the introduction of new advances in psychopharmacology. Montreal was a special place, a geographical, cultural and linguistic bridge between North-America and Europe (Delay and Deniker, for example, were not fluent in the English language). The introduction of chlorpromazine in the American continent had been made in Canada: whether we consider Koeppe-Kajander's unpublished experiments in Toronto, Azima and Ogle's works at the Allan Memorial Institute in Montreal, published at a later date, or

---

[56] Later on, Paul Janssen would credit Smith, Kline and French with the introduction of the expression *major tranquilizer*. It would have been the preferred term for chlorpromazine's marketing campaign in the United States, in the hope that this expression could increase the number of possible clinical indications and maximize the chances of commercial success in that country (Interview with Paul Janssen cited in Healy, 1998b). In *The creation of psychopharmacology,* David Healy attributes the expression to F. F. Yonkman, an employee of Ciba Pharmaceutical, in the process of promoting another drug - reserpine (Healy, 2002, p. 110).

Heinz Lehman's first publication from Verdun Protestant Hospital, also in Montreal (López-Muñoz et al., 2005).

Delay and Deniker structured their Montreal presentation around Steck's two main theses: the neuroleptic/encephalitis lethargica analogy and the diencephalic location. In chapter 2.7.2., we saw how Pichot (also from the Sainte Anne hospital in Paris), had been somewhat skeptical of the thesis that extrapyramidal symptoms were important for the development of therapeutic effects during his talk at the first haloperidol conference in Beerse (1960). Delay and Deniker (1960) were less definitive. The Paris team started to be convinced of a relationship between neurological symptoms induced by neuroleptics and their therapeutic action, but they still had doubts about the nature of that relationship and preferred to highlight what they called primary effects. The psychic effects produced by neuroleptics could then be divided into a *paroxistic excitomotor syndrome* leading to a histeria-like state, a *parkinsonian syndrome* leading to mood depression, the akathisia and tasikinesia syndromes leading to impatience and psychomotor excitation, and an akinetic syndrome associated with emotional indifference (this last one brings to mind the concept of *bradiphrénie* introduced by Naville and retained by Steck). It would be this akinetic syndrome that, leading to a substantial indifference, could promote a distancing from delusional and hallucinatory contents. Therapeutic activity is a consequence of direct psychic effects, and as such is still seen here as essentially non specific. In the Paris team's presentation in Montreal we can highlight, on the one hand, how anti-delusional and hallucinolytic activity continued not to be easily linked to what they called neurological (extrapyramidal) symptoms, on the other the extent to which the neuroleptics of Delay and Deniker in 1960 continued to be far removed from the current concept of antipsychotics.

In an example of the hybrid rhetoric we have been pursuing in this research, with mixed elements of psychoanalytic and psychopharmacological approaches, Herman Denber (whom we know from the 3.1. chapter) emphasised the importance of psychodynamic factors in the quantitative and qualitative determination of extrapyramidal effects. Rigidity would be felt by the patient as a form of paralysis or death. This rigidity could then trigger other motor changes by abreaction of the unconscious conflicts (Denber, 1961).

Still in Montreal, Nathan Kline, who had been considered the *discoverer* of reserpine, [57] together with Mettler, stressed the importance of the relationship between the extrapyramidal system and schizophrenia. Like Steck in his 1926 article, Kline and Mettler (1961) found similarities between cataleptic catatonia and parkinsonism, but argued that explaining the origin, prognosis or treatment of schizophrenia based on a pathology of the extrapyramidal system would be a premature simplification.

As we have seen, international conferences were unique opportunities for the protagonists to bond, where alliances were created and rivalries played out. As we have seen and will continue to see throughout this thesis, the names of those who were present in these international meetings are recurrent. We often find a political center in the sum of their presentations, where hegemonic hypotheses converge, and to which the big names, like Kline and Denber, subscribe. As we have seen, the extrapyramidal system was, in 1960, the point of convergence of this unifying discourse, but the reasons for its importance and its direct consequences were still subject to negotiation.

While chasing Hans Steck throughout his career, we have been interested mainly in the history of the expression "extrapyramidal symptoms", which gradually gained prominence in the descriptions of haloperidol, jeopardising its commercial success. But, in the process of tracing this concept, we ended up finding three foundational ideas that would structure psychiatry in the following decades (and which are perhaps still present in current psychopharmacological thought). We didn't intend to tell the story of these ideas in this chapter, nor to pinpoint their authorship. Several authors proposed them throughout the 1950s, but Hans Steck's vivid descriptions, and their integration into arguments that conformed with the dominant ideology of the time, make him an unavoidable figure in the history of psychopharmacology.

The three lines of Hans Steck's research we have chosen to explore include, as we have seen, the subcortical origin of psychosis, the analogy between encephalitis lethargica and the action of chlorpromazine, and the therapeutic possibilities inherent to parkinsonian symptoms. These three lines form an intricate pattern, difficult to untangle. The sub-cortical

---

[57] Reserpine's path into mainstream psychiatry is unusual. Reserpine was a substance extracted from the plant *Rauwolfia* (Sarpagandha). The latter was of use in the Indian subcontinent, and present in plural medical markets since before the XXth century. Its use in insanity was documented since the 1930's. After appropriation by Swiss pharmaceutical company CIBA, its usefulness in psychosis was popularised by Nathan Kline, among others, during the 1950's (Roy, 2018).

or diencephalic location of psychosis owes a lot, as we have seen, to the ideological matrix of cultural evolutionism through the schizo-primitive hypothesis. The lesser cerebral function of schizophrenics and *primitive* societies, associated with a hierarchical concept of the central nervous system, framed the creation of the diencephalic hypothesis. The clinical and anatomopathological data of encephalitis lethargica (more) empirically materialised this fundamental idea that came from the 1930s. The second line of research - the analogy between encephalitis lethargica and neuroleptic action - came later, with the introduction of chlorpromazine, but remained within the same paradigm, proposing the same site of sub-cortical action as encephalitis lethargica, both in psychosis and in its treatment. Finally, the third line of research - the therapeutic possibilities inherent to parkinsonian symptoms - became contentious throughout the 1950s and early 1960s, but after the introduction of haloperidol, and later on with the dopamine hypothesis of schizophrenia, its acceptance would spread.

3.4. Tardive dyskinesia

In this chapter we will start by trying to understand the context in which the first descriptions of tardive dyskinesia emerged. The surprising theoretical background reveals one of the fundamental tensions in psychiatry – that between empiricism and rationalism.

> Le lagartil, même s'il produit passagèrement une certaine hypophrénie, ne produit pas de lésion durable et incontrôlable. (Steck, 1954)

This is how Hans Steck presented his new Extrapyramidal Syndrome resulting from chlorpromazine, in 1954. The great advantage of chlorpromazine in relation to leucotomy was the absence of irreversibility, and the exclusion of a true mutilation of the personality.

In the second part of the 1950s, despite growing clinical impact and academic importance of extrapyramidal symptoms, to the point that one of the most important symposia of 1960 was consecrated to them ("Extrapyramidal system and neuroleptics", International Symposium Montreal, November 1960), they continued to be seen mostly in the same way, namely - they remained reversible. Even when the first descriptions of irreversible motor phenomena appeared in 1956, they were mostly brushed aside, or overlooked.

When the Paris team presented their work on haloperidol at the conference in Beerse in 1959 (chapter 2.7.2), it included the complete disappearance of the neurological syndrome 8 to 10 days after stopping treatment (Delay, Pichot, Lemperiere, & Elissalde, 1960) . That was the general tone at that first congress on haloperidol, from the Belgian Humbeeck (1960) to the Portuguese Seabra-Dinis (1960), the complete reversibility of the parkinsonian syndrome was unanimous.

But at the Montreal Colloquium, just a few months later, a new controversy began to take shape, and though reversibility continued to be talked about in some interventions (Brodie, Sulser, & Costa, 1961; Doshay, 1961), in others the possibility of long-term neurological effects of neuroleptic therapy was beginning to take shape.

The presentation of the Paris team in Montreal was placed at the center of the rising dispute. Throughout the second half of the 1950s, Delay and Deniker had always considered the side effects of neuroleptic therapy to be transitory and reversible, even though they were aware of, and had already described, alterations in bucco-oral movements that would later come to be often seen as tardive, or persistent (Delay & Deniker, 1958; Delay, Deniker, Green, & Mordret, 1957). In their Montreal presentation, the idea of reversibility persists,

but, in a reference to the work of Faurbye and Uhrbrand, the possibility of lasting movement disorders was raised, including oral and facial hyperkinesia. Delay and colleagues even proposed regular monitoring of the reversibility of extrapyramidal effects throughout the course of neuroleptic treatment (Delay & Deniker, 1960) .

The Danes' article was a pivotal moment, representing the beginning of the international recognition of persistent neurological symptoms caused by neuroleptics. The St Hans psychiatric hospital outside Copenhagen had an important neuropsychopharmacological tradition. It was in St Hans that Mogens Shou began his career in 1944 (Healy, 2008, p. 111). It was also in St Hans that Brandrup and Kristjansen were testing haloperidol in a controlled trial (Brandrup & Kristjansen, 1961).

The first patients with lasting movement disorder as identified by Faurbye and Uhrbrand had never taken a neuroleptic drug, instead they had been subjected to electroconvulsive therapy. They presented with continuous involuntary chewing with periods of tongue emergence and intense grimacing (see Appendix B, figure 5). This clinical picture seems to have impressed the authors, who two years later, throughout the first half of 1959, continued to recognise similar symptoms in patients undergoing neuroleptic pharmacotherapy.

A review of the 500 women admitted to the department identified 33 patients with similar motor symptoms (4 had undergone electroconvulsive therapy and 29 neuroleptic therapy with chlorpromazine, reserpine, or perphenazine). An important proportion of these proved to be irreversible even after drug withdrawal. In some of these patients - 3 (10%) - the symptoms appeared only after the medication had been discontinued. The authors also described that an important percentage of patients would not realize or would not value this permanent dyskinesia, and stated it represented an important inconvenience for only a small number of patients in the study. The patients affected were generally older, often with other organic brain lesions and who had already undergone a long period of treatment (Uhrbrand & Faurbye, 1960).

Uhrbrand and Faurbye weren’t the first to describe persistent movement disorders with neuroleptics, but their paper changed the conversation around the drugs. The fact that theirs was an english language publication, the high number of cases described, the detail in their description and the visual impact of the photographs that accompanied the article

(Appendix B, figure 5), may all have contributed to the international repercussion of the Danish paper. The paper's impact was further illustrated by the Paris team's reference to it during their intervention in Montreal. Its popularity created a fracture in institutional psychiatry. Critics (Kline, 1968) would later point out that a more careful analysis of cases presented would suggest that only 13 of the 29 patients proposed by Uhrbrand and Faurbye had a completely irreversible disorder, and that 11 out of those 13 had concomitant brain lesions.

The first descriptions of persistent and irreversible neurological changes related to chlorpromazine predate the article by Faubrey et al, and had been documented in 1956, only three years after the commercialisation of chlorpromazine (Venning, 1983). Nevertheless the places and contexts of these two precocious descriptions couldn't be more different. Robert A hall and Henry Ey have so little in common that their simultaneous descriptions is surprising, and noteworthy.

Robert A. Hall worked at Agnews State Hospital in California, far from the east coast of North America, which as we have seen was, at the time, the privileged place for psychopharmacological research. Hall was an empiricist. For him, the complexity of biological systems was such that it could only begin to be addressed through the scientific rigor of physics or chemistry. In science, to assess the effect of one variable, all other variables should be held constant. Clinical experience in itself would be useful, but only as a stimulus and inspiration for systematic scientific work. For Hall, the "principle of control" was crucial for the creation of a scientific fact. His concern was to eliminate the intervention of psychological factors, which led Hall to subscribe to the principle of double blindness, in which neither the patient nor the researcher knows who, and at what moment, receives a drug or placebo. Hall did not anticipate or understand arguments against controlled designs, at a time when in medicine in general, and not just in psychiatry, sophisticated designs were rare. In a literature review by Hall himself, of 100 articles he randomly reviewed, almost half (49) had no method of control and in about 30 others, this control was deficient. In that review, Hall then underlined that only 21% of drug trials were correctly designed with placebo (Hall, 1955).

In his 1955 study of chlorpromazine, the objectives were clear from the start. Namely, to contribute scientific information on the effects of chlorpromazine (with evaluable,

controllable and reproducible data) but also to study the problems and possibilities of implementing a clinical trial with this type of design - controlled and double blind - with this type of drug. It was not Hall's priority to answer questions about the causes or mechanisms of schizophrenia, nor even about the mechanisms of drug treatment. The questions he was interested in answering were mainly methodological. How can you design and implement a double-blind study with such a drug? In Hall's 1955 article, the space devoted to methodology and results is impressive, especially when we compare it with papers by Denber (1959) or Azima (1960) on haloperidol, which we saw in the chapter 3.1, or even with the famous article by the Elkes couple (1954) on chlorpromazine. Described in detail, the methodology was itself tested, for example by testing the extent to which participants were still blinded to placebo drug distribution at the end of the trial. This complete description allowed for reproducibility. The results were also exposed in detail, and this transparency would allow independent analysis and interpretation (Hall & Dunlap, 1955).

Hall's study of chlorpromazine is yet another sign of how clinical trials were already changing, during the 1950's, especially in the United States, well before the thalidomide scandal, the Kefauver-Harris legislative change, and the new FDA practices that would eventually formalize the need for this type of design (chapter 2.2.).

In the context of this double-blind trial of the effectiveness of chlorpromazine, Hall published another article, focused on side effects and their frequency. Parkinsonian side effects, or what Hall preferred to call *neurotoxic*, had developed in about 40% of the sample. He then described, and this was possibly the first description of the condition, that in 6 patients these symptoms proved to be irreversible even 60 days after stopping the medication. In one patient the neurotoxic symptomatology started only after the medication had been stopped (Hall, Jackson, & Swain, 1956).

Hall's work thus pointed out for the first time two main features of what would later be described as *tardive dyskinesia*: irreversibility, and onset or worsening of symptoms after neuroleptic treatment has been reduced or stopped.

Henry Ey, the director of Bonneval psychiatric hospital became a major influence in French speaking psychiatry during the 1950s and 1960s (Richa, Masson, & Tawil, 2019). His *Colloques de Bonneval* were attended by the intelectual elite, from Jacques Lacan, to Georges Lanteri-Laura or Paul Ricoeur.

Ey's work with chlorpromazine couldn't have been more different from Hall 's. Ey looked beyond efficiency and methodological issues. He wanted to understand the implications that substance and its effect had on the theoretical construction of psychiatry, how substance action revealed the nature of psychopathological phenomena. In a paper with Sakellaropoulos (1956), Ey describes the story of only one case, in stark contrast with Hall's large number case study, but this simple biography, with its unique clinical history, serves to build and test a broad and comprehensive theory.

In this case study, Ey ventured into the dynamic of understanding versus explanation typical of German psychopathology. In the case presented, the authors could be tempted to understand the patient's delusion as a result of affective circumstances and unconscious demands. But chlorpromazine's clinical response with a decrease in delusional activity, demonstrated to Ey that the symptom arose in a context of a fundamental change of lived inner experiences, and was therefore a more clearly pathological process. For Ey, chlorpromazine offered the possibility of experimental manipulation of delusions that recalls Moreau de Tours' studies with hashish, Clérembaut's interests in multiple substances, and the long Anglo-Saxon tradition of working with mescaline and LSD. This study also finds a symmetry between the ability to chemically bring about delusion, and the ability of chlorpromazine to destroy it (Ey & Sakellaropoulos, 1956).

Chlorpromazine was used in Bonneval in 3 different treatments: *cure de sommeil*, *hibernation artificielle*, *cure neuroplégique*. In the first two therapeutic approaches, where the drug was used in combination, no side effects or intolerance were attributed to chlorpromazine alone. In the *cure neuroplégique* somatic events developed, these included gastrointestinal (mild), cardiovascular (hypotension), hormonal (1 case of galactorrhea and 5 cases of progressive obesity) and cutaneous symptoms. But what interests us in Ey's description is its confirmation of Hall's observations that extrapyramidal effects can, in some situations, become irreversible.

> Chez une malade, cependant (démence sénile), le syndrome extra-pyramidal persistait encore, complication regrettable, 6 mois après l'arrêt du traitement. (Ey, Faure, & Rappard, 1956)

Ey's description already included three demographic characteristics that were to be associated with a higher prevalence of tardive dyskinesia: the female gender, advanced age, and the presence of co-morbid organic brain diseases.

In the first two articles where the authors describe the phenomenon, that would later be called tardive dyskinesia, chlorpromazine serves opposite purposes. While for Hall it was a way of testing sophisticated methodologies of empirical assessment, for Ey it was a way of reflecting on the fundamental nature of psychopathological phenomena. This division reflects a fundamental tension in psychiatric research, between empiricism and rationalism.

Both Hall's and Ey's descriptions were mostly ignored. A plurality of reasons may help explain this neglect. It's conceivable that the growing enthusiasm for neuroleptic therapies did not really allow for a critical stance, and although Ey was an influential figure, he was possibly seen as being on the periphery of psychopharmacology. Finally, the affected patient's age and gender may have also contributed.

During the second half of the 1950s, other descriptions of this condition emerged. In 1957, the German Shonecker described with surprise the "strange" case of three elderly women who developed bucco-oral movements under treatment with chlorpromazine. Incessant lip and tongue movements persisted in two of the patients for at least 3 months after stopping treatment. In 1959, the French team from *Paul Brousse Hospital*, in Paris, namely Jean Sigwald and Daniel Bouttier, described another 4 cases (again, in elderly women).[58] They called these alterations facio-bucco-linguo-masticatory dyskinesia (Caroff, Ungvari, & Cunningham Owens, 2018). Despite this, it took until the Danish english-language publication (Uhrbrand & Faurbye, 1960), with which we started this chapter, for tardive dyskinesia to begin a long process of institutional recognition (Healy, 2002, p. 245).

It was only in 1964 that the expression tardive dyskinesia crystallises, and its definition was delimited into a unified entity. It clearly differs both from parkinsonian symptoms in general, and from dystonic symptoms (which other authors called neurodysleptic). The development of this new entity included the clinical picture's description, defining the affected demography and elaborating first explanatory pathophysiological proposals. In their 1964 article, the Danish team was so successful, and the concept became so precise, that the expression "tardive dyskinesia" became enduring (Faurbye, Rasch, Petersen, Brandborg, & Pakkenberg, 1964).

---

[58] Some, (Crane, 1968), atribute the first tardive dyskinesia description to the team from Paul Brousse Hospital.

The clinical picture consisted of coordinated, rhythmic, involuntary and stereotyped movements (repetitive and without apparent function). These movements could be more or less important, be restricted to a single part of the body, or be generalised, in different combinations. Patients often didn't seem to be aware of them. Symptoms often appeared associated with tremor and rigidity. As noted, in some cases it started a few days after treatment had been stopped. Demographically, the most affected population would have advanced age, female gender and organic brain disease. The syndrome sometimes disappeared a few months after stopping treatment, but could be more persistent. Medications reported to cause tardive dyskinesia included chlorpromazine, perphenazine, thioridazine, prochlorperazine, and haloperidol - the latter with two cases reported in a series of 15 patients (Faurbye et al., 1964). In reflecting on the pathophysiology of tardive dyskinesia, the authors reference the importance of Carlson's work on dopamine (see chapter 4.2.). Parkinson's could initially serve as a model for a theory of the pathophysiology of tardive dyskinesia, but the phenomenon, as recognised by the Danes is quite different from the point of view of clinical presentation, and therefore the pathophysiological explanation they propose is also quite different. Dopamine in the caudate nucleus could play a role, but the most likely hypothesis would be a localized cerebral hypoxia possibly due to decreased permeability of cell membranes (Faurbye et al., 1964). Here, we are far from the first descriptions of Hall and Ey - there is no mere finding of an inexplicable secondary symptom, but an entire entity that challenges the pathophysiological theories of the diseases that surround it.

The story of tardive dyskinesia is one that was marked by a personal rivalry that materialised in the 2nd international symposium on action mechanism and metabolism of psychoactive drugs derived from phenothiazine and structurally related compounds, had developed over the previous decade, and was related to another infectious disease - tuberculosis.

George E. Crane was born in Trieste, in Italy in 1912. He had graduated in Medicine from the Faculty of Milan in 1936, and had completed his internship in psychiatry at Pilgrim State Hospital in Brentwood, New York immediately after the war (1946-1947). He had, as was usual at the time, robust psychoanalytic training (6 years at the American Institute of Psychoanalysis 1950-1956) and had been a member of the Montefiori Hospital since 1952 in

the Bronx, New York, where he was responsible for pharmacological research and psychotherapy (NIMH, 1968, p. 96).

After the development of serious psychiatric conditions, patients treated with Iproniazid for chronic tuberculosis started being regularly evaluated by the service psychiatrist, Dr. Crane. In January 1956 Crane published an article in the American Journal of Psychiatry describing his experience, trying to assess the impact and extent of psychiatric side effects of iproniazid, and pondering if their severity was sufficient to advise against its use.

All 19 patients that Crane had regularly evaluated developed some kind of psychological change, specially emotional alterations. The majority of the sample even referred to subjective feelings of well-being, and overall Crane identified a tendency towards an increase in mental capacity and vitality. But the psychiatric effects of iproniazid were not always useful, they could be severely disabling, namely due to the emergence of psychotic episodes or manic states, which advised close psychiatric surveillance. There is no clear reference to the use of iproniazid in depressive episodes, in Crane's article, but there is a suggestion that the substance could be of value not only in tuberculosis but also in other chronic diseases (Crane, 1956b).

During the same year, his interest in Iproniazid continued, and just a few months later he published a second paper on the subject. In September 1956, Crane's view was already frankly more mature or explicit than his earlier view, regarding the use of iproniazid as a drug in psychiatry, and its mechanism of action. In the literature review, the works by Zeller and Barsky on the inhibition mechanism of the monoamine oxidase enzyme and consequent possible effects at the level of synaptic transmission are already cited. The possibility of use in depressed patients is clearly considered and the conclusion is enlightening:

> However the greatest value of this drug lies in its ability to create a sustained feeling of vitality and well being in debilitated and depressed patients. (Crane, 1956a)

This quotation synthesises the article's overall approach. Iproniazid relinquishes its identity as a somatic therapy, as a tuberculostatic drug, and its new clinical indication as a psychotropic drug is clearly established. However, George Crane's insight wouldn't go down in history and another researcher would be credited with the "discovery" of iproniazid and its therapeutic group (the MAOIs - monoamine oxidase inhibitors) – namely Nathan Kline.

Kline had a very different career path than Crane's. Born in Philadelphia in 1916, he was a controversial and divisive man. The opinion that Paul Janssen had of him is, moreover, revealing:

> I liked him. he was funny. He was also one of the first investigators of haloperidol in the states. He wrote me a letter saying: your compound is worthless(…). He was a clown. I liked his jokes and I liked the way he told his stories , like how he invented iproniazid, for instance. I never knew what was true and not true. We met rather regularly. He used to play a very important role in what was called biological psychiatry.
>
> What was his role?
>
> Well, it was very dangerous to contradict him. He was a good speaker, very outspoken and he was opinionated. To contradict Nathan kline was politically very dangerous. People were afraid of him and certainly by the end of his life he behaved like a kind of pope. At the end he had this habit of coming to congresses with a small dog on his lap and patting it all the time and attracting attention whilst smiling to the speaker. (Interview with Paul Janssen cited in Healy, 1998b, pp. 59,60)

In November 1956, concomitantly with the publication of Crane's articles, Nathan Kline (with his colleagues Jack Saunders and Harry Loomer.) started, an uncontrolled trial of Iproniazid in psychiatric patients at Rockland State Hospital (New York) (Baumeister, Hawkins, & Uzelac, 2003).

According to Kline, the patients were divided into two distinct groups, a first group of 20 patients with chronic psychiatric pathology, the vast majority with a diagnosis of schizophrenia, and a second group of patients with a diagnosis of depression coming from his private practice (Kline, 1965). In February 1957, the first results showed a robust clinical response in terms of mood, both in the inpatient group and in the "neurotic" patients followed in an outpatient setting (Healy, 1997, p. 67). .

However, iproniazid's patent belonged to Hoffman-La Roche, and its medical director in the United States, Elmer Severinghaus, a critic of the project, suspended the clinical study. Kline then secretly met with G. David Barney, president of the company, to convince him of the relevance of the trial (Sandler, 1990). Kline was already an important figure in international psychopharmacology, it was exactly in 1957 that he received the prestigious Albert Lasker Clinical medical research award, together with Deniker, Laborit, Lehmann and Noce, for his work with reserpine in the early 1950s ("Chlorpromazine for treating schizophrenia," 2020). Following this meeting, the clinical trial received the green light to proceed (Kline, 1964).

The first data was presented just two months later, in April 1957, in Syracuse, New York, at the regional meeting of the American Psychiatric Association (Kline, was the head of the research committee of the American Psychiatric Association). According to David Healy, George Crane, despite not being invited, ended up being present as a discussant (Healy, 1997, p. 68). However, before Harry Loomer formally presented the trial results, Kline had already announced them at a press conference.

Kline's importance in the "discovery" of iproniazid is illustrated by Kline's second Lasker prize. ("Iproniazid for the treatment of severe depression," 2020). This attribution was challenged both in psychiatric media (Saunders, 1965) and the courts. Harry Loomer eventually withdrew from the lawsuit, but Saunders persisted, receiving a third of the monetary value of the Lasker Prize (Baumeister et al., 2003).

In the early 1970s, when Franck Ayd, together with Barry Blackwell, was organising Discoveries in Biological Psychiatry, he hesitated to attribute iproniazid's finding between Crane (whom he knew personally) and Kline. He then spoke directly to Hoffman-La Roche who recommended Kline's name (Interview with Frank Ayd cited in Healy, 1998a).

Iproniazid's construction as a drug, of which we retain only a few frames in this chapter, followed a very different path from that of haloperidol. Iproniazid, before being a psychotropic drug, was already a substance, and more than that, it was already a medicine. The drug's aimed population - tuberculosis patients - had much in common with the patients targeted by psychotropic drugs. Both groups were victims of prolonged illness, often suffering from long hospitalisations, and sometimes even unlimitedly institutionalised. In this sense, discovering the proximities between the two populations studied, the psychopharmacological conversion of iproniazid is not so surprising (and perhaps less serendipitous than many authors consider).

As the authorship of this conversion was griped by controversy it became illustrative of what a discovery in psychopharmacology is, and how the main protagonists of these events were determined. Kline's degree of social capital was crucial in this process, namely mobilising his knowledge of social recognition processes in science and in psychiatry in particular. His expertise in relating to peers and with the press, as well as his place in international institutions, all seem to have contributed to his personal recognition. Another decisive factor was his proximity to the pharmaceutical industry, as it was finally La Roche,

initially hesitant about the clinical trial, to attribute the authorship of iproniazid as a psychopharmaceutical to Kline.

The retrospective relevance of the psychiatric conversion of iproniazid, which we sense in this struggle for a main protagonist in its *discovery*, may have several explanations. For one, this importance may derive from the clinical success of Iproniazid and the rapid growth of its use, not only in the asylum but also in private practice. The drug had a sizeable comercial outcome if we take into account that in one year 400,000 patients would be treated with iproniazid (Kline, 1964) . However, the main reason for iproniazid's retrospective relevance is likely to have to do with its effects on psychiatric theory, specifically its effect in the progressive implantation of biochemical pathophysiological theories of depression (Kline, 1964) .

George Crane had a particular interest in the study of drug side effects (NIMH, 1968). This interest had led, in the case of iproniazid, to the opening of therapeutic paths, and to a new understanding of psychopathological phenomena. But he wasn't, especially in the early 1960s, particularly critical of psychopharmacological interventions. For Crane, psychiatric drugs weren't limited to reducing symptoms, on the contrary, they were effective because they were able to correct basic disorders associated with mental illness. This perspective, that nowadays would be perhaps considered hegemonic, was, at the time, frankly in the minority. In 1960, his distance from psychoanalysis (which had, however, profoundly marked his formation) was complete. Psychotherapy should be reserved for a few well-defined personality disorders; the vast majority of neurotic or psychotic patients could be treated by a psychopharmacological intervention (Crane, 1960). The institutional recognition of drugs' role in psychiatry was exponential in the late 1950s and early 1960s, and Crane's clear anti-psychoanalysis stance (or at least a position that was favourable to the reduction of its intervention capacity) may have been one of the factors in his integration into the pharmacological research department of the National Institute of Mental Health in 1964 (NIMH, 1968).

From the 17th to the 19th of October 1967, in Paris, in the autumn that preceded the turbulent May of 1968, the protagonists of our story again met in a conference with a long and unimaginative title: Second International Symposium on Action, Mechanism and

Metabolism of Psychoactive Drugs Derived from Phenothiazines and Structurally Related Compounds.

As previously noted, these international meetings were privileged places for those who claimed to be the pioneers of psychopharmacology. As we have seen in previous chapters, in such settings, bonds of familiarity were established, but power relations were also reconfigured. Through debate and/or consensus, politically acceptable or hegemonic ideas were built, which sometimes involved explicit condescension or ridicule (Interview with Paul Janssen cited in Healy, 1998b). Personal connections, (the sometimes jocular) tone, mimicry and corporal expressions are difficult to recover in the written proceedings of the congress, but we can sometimes indirectly perceive them. Events such as what happened before and after the session, the way in which privileged relationships were created between the industry sponsoring the meetings, the elements of the clinical world (the directors of the great European and American east coast asylums), and the representatives of the academy are also difficult to rebuild. Nevertheless, all these factors participated in the construction of a new psychiatry. The Paris meeting was yet another example of the dynamics at play for the field at this particular moment.

Crane's presentation in Paris was provocative. He had joined the NIMH in the same year as the seminal Danish paper was published (1964) and realised, before many, the relevance that the phenomenon noted there would develop in the following decade. Shortly after its integration he dedicated himself to tardive dyskinesia. For Crane, the relationship between the significant increase in dyskinesia in psychiatric hospitals and the introduction of neuroleptic therapy during the 1950s was increasingly evident. Several factors pointed in this direction, including the frequency of symptoms when compared to the rarity of the phenomenon in the adult general population, the clinical consistency of the syndrome and its absence in classical psychiatry textbooks. He developed a prospective study of 400 patients, spread over five different hospitals, and observed by Crane himself at 0, 6 and 12 months. The percentage of dyskinesia was impressive at around 1/3 of the sample (20 to 40 percent). The results, as Crane presented them, suggested that 1 in 3 patients treated with neuroleptics were at risk of developing a severe and stigmatising movement disorder. Nevertheless, Crane himself recognised that not all of these conditions were irreversible, clinical instability was important in his sample and many patients improved in motor symptoms at 6 or 12 months. A

clear relation between symptoms, dose and treatment duration also could not be established. Regardless, the impact of dyskinesias in patients's lives demanded, for Crane, continued attention (Crane, 1968) .

The reception of these results was cold and Crane's presentation, despite the late hour, was followed by an emergency discussion. Nathan Kline had asked for the floor, his importance in psychopharmacology was undeniable, his two Lasker awards and the *discoveries* of reserpine and iproniazid ensured that he had the right to be heard, even if there was no scheduled time for it. His intervention was enlightening—the issue (for Kline, and perhaps for psychiatry in general at the time) was not so much the appearance of dyskinetic movements as their possible irreversibility. The question would not be, therefore, dyskinesia itself, but the possibility of it being *tardive*, or persistent. The syndrome was much less frequent than what Crane had described. But Kline offered another explanation for the orobuccal dyskinesia: dry mouth. The neuroleptics, and anti-parkinsonian drugs to which they were often associated, had the side effect of drying out the mouth. Patients would get in the habit of running their tongue across their lips to lessen that feeling of dryness. The action was perpetuated due to the patients' tendency towards stereotypic movements.

> I have seen one or two of these patients in private practice. In one case I was quite successful in deconditioning the patient. In most patients after anticholinergic agents are withdrawn , there tends to be recovery. (Nathan Kline in the Discussion following George E Crane, 1968)

Kline's intervention, initially trying to rigorously define the concept, becomes in the last paragraph a clear attempt to erase *tardive dyskinesia* as a clinically relevant possibility. We sense in this quotation a jocular tone and wonder if he concurrently caressed his little dog in his lap, as Janssen describes. But what is impressive is the authority with which he reduces a phenomenon, that had a growing scientific and above all social impact, to dry mouth. Kline transformed, with these words, a syndrome that he felt was becoming a symbol, a menacing weapon in the hands of movements critical to psychiatry, into a simple desire to wet the lips that could easily be unlearned.

This was the second act of the rivalry between Crane and Kline, but here the game had changed and power was switching hands. Kline had secured iproniazid's authorship emboldened by his social and cultural capital. But that same victory now conditioned his authority. The public moment was very different. The enthusiasm of the 1950s, in which psychopharmacology had flourished and asserted itself as a pioneering new world, was

dying. Nathan Kline was connected to the time when therapeutic groups were being discovered and clinical indications were reconstructed. The late sixties and the seventies would be different in this respect. Public opinion on neuroleptics, and on psychopharmacology more widely, had been transformed whereby from initial enthusiasm a growing skepticism had emerged. In Paris, outside the space of the congress, the tensions that would mark May 68 were already growing. The image of psychiatry in the media was changing and, especially in the United States, the judiciary would eventually intervene.

> Along with ECT, tardive dyskinesia had become a lightning rod for antipsychiatry. Putting patients afflicted with this highly visible condition on the witness stand or in front of television cameras was almost as potent a weapon as Jack Nicholson playing the patient Randle McMurphy receiving unmodified ECT. Tardive dyskinesia spread a chill over the pharmacotherapy of severe mental illness. (Shorter & Healy, 2007, p. 293)

Court cases would pile up in the United States, many of which involving costly out-of-court settlements. Initially focused on responsible physicians, these cases quickly turned towards the big pharmaceutical industries. George Crane, among others, testified for the plaintiffs and in 1974 Smith, Kline and French was forced into an expensive out-of-court settlement (Healy, 2002, pp. 248-250). As much as some, such as Kline, classified the phenomenon as minimal or negligible from a clinical point of view, the social importance of *tardive dyskinesia* grew increasingly at the risk of jeopardising psychiatry and its ongoing reforms. In vindication, Crane's work on dyskinesia would be recognised - by the judiciary, but also by historians of psychiatry (Healy, 2002, p. 247; Moncrieff, 2013, p. 77; Shorter 2005, p. 303).

3.5. From cartesian dualism to neuroleptic threshold

With the rise of behaviourism, a schism was created in American psychology, between those who were interested in studying internal experiences, and others for whom this *old consciousness* either did not exist or was considered impossible to approach as a scientific object. Eclectics, like the American psychologist Robert Woodworth, tried to walk between the extreme positions of mentalism and behaviourism (O'Neil, 1949).

The concept of *drive* emerged in English language psychology towards the end of the first world war, by the hand of Woodworth, in this fragile balance between mentalism and behaviourism. Derived directly from the semantic field of mechanics, "Drive" easily penetrated the ideological context increasingly marked by biological essentialism. For Woodworth it conveyed a machine's energy source capable of producing movement.

Behaviour was often seen as directly governed by biological principles and animal studies had aroused interest in the motivational aspects behind this, for both animals and humans. Embedded in this biological reductionism the concept of drive became a way of creating equivalences between human motives and animal incentives, that could be experimentally manipulated (Danziger, 1997, pp. 116-120).

Behaviourists, initially rejecting the doctrine of instincts, created this conceptual space that led to the expansion of the Drive concept during the 1920s (O'Neil, 1949). However, these approaches were still more interested in researching the blood and the digestive system than the brain. It was not until the 1950s, when the first neuroleptics were introduced, that the brain returned to the center of explanatory theories about motivation (Danziger, 1997, p. 120).

The influential Canadian psychologist Donald Olding Hebb explored the relationship between *Drive* and *Arousal*. He suggested that a neuronal pathway extended from the brainstem to the brain, what he calls a"non-specific projection", and had an "arousal" function, preparing the brain for the true sensory stimulus.

> And now I propose to you that, whatever you wish to call it, arousal in this sense is synonymous with a general drive state, and the conception of drive therefore assumes anatomical and physiological identity. (Hebb, 1955)

The *drive*, in addition to being a psychological concept originally, was also deeply biological. In addition to a behavioural concept, it was also neuro-anatomical. This place of

intersection contributed to its semantic instability. It contributed to the way that, as a concept, it became broad, perhaps even vague. It possibly also contributed to the difficulties in its translation. Somehow the drive symbolically took the place of the pineal gland in Cartesian dualism, but remained concealed in mechanical language. The sub-cortical space, in particular the brainstem, was beginning to assert itself as a privileged place in these intersections.

Hans-Joachim Haase was a German medical doctor, born in Berlin shortly after the end of the first world war. He studied in Bonn, and in the 1950s was working in Switzerland as an *Assistenzarztin* in Oberwil/Zug between 1953 and 1956 (later transferring to Dusseldorf)(Geburtstage, 1997). When chlorpromazine trials started he was in Switzerland.

According to Haase (1954), if we look closely at signs and symptoms that originate in the brainstem, we will be forced to challenge the Cartesian dualism, as a clear separation between the physical and the psychological becomes inconceivable. When observing patients with phenomena originating in the brainstem, we are forced to identify physical signs as well as noting mental expressions.

Parkinsonism, as we have seen in the last chapter, was a clear example of both this subcortical location and this intimate interaction between body and mind. The recognition of psychological symptoms in Parkinson's disease had a long tradition, and classic descriptions ranged from emotional depression to tactile hallucinations or memory disorders (Jackson, 1923). During the 1950s, psychological factors in Parkinson's disease were acknowledged as foundational and speculations about its psychogenic origins were frequent (Booth, 1951; Garland, 1952).

Brissaud, Charcot's student in la Salpêtrière at the turn of the century, reported a "soudure intellectuelle" that left parkinsonian patients in a state of indifference to stimuli, both external and internal. To describe this, he introduced the term apathy (Prange et al., 2018). Still in France, François Naville would call *bradyphrénie* to a set of heterogeneous symptoms of unpredictable course that were associated with post-encephalitic parkinsonism and included a decrease in attention, interest, initiative and effort (Rogers, 1986).

We can find in both concepts (*apathie* and *bradyphrénie*) an allusion to a decrease of energy potential, similar to the psychological concept of *Drive*.

Throughout his career Hans Steck had been interested in the subcortical regions (see chapter 3.3). For him, *bradyphrenie* was also a fundamental concept articulating a global attainment of psychological activity with the anatomopathological alterations of encephalitis lethargica (Steck, 1931).

If diminished mimicry and decreased movement were hallmarks of Parkinson's disease, questions lingered about the extent to which they derived from motor versus psychological origin. How could such different symptoms as motor changes or interest curtailment be related? Haase and Gross' thesis was that changes in motricity were caused by a decrease in *Drive (Antrieb)*,[59] and this link was another clear indication of the importance of the brainstem in mind-body interaction (Gross & Haase, 1954).

At least since Charcot, there have been mentions of handwriting changes associated with Parkinson's disease (1877, p. 138). Descriptions of this included tremor, but also frequently referred to a decrease in letter's size, both in paralysis agitans before the pandemic of encephalitis lethargica (Stewart, 1909), and later in post-encephalitic parkinsonism (Blackstone, 1931).

> The attention of the patient may be first attracted by an alteration in the handwriting, which becomes smaller and less legible.(Garland, 1952)

Haase would become famous for his study of handwriting in patients undergoing neuroleptic therapy, but even before the advent of chlorpromazine, Haase was already using handwriting tests to explore the changes that Parkinson's disease caused in the brainstem's drive regulation.

Haase and Gross' main thesis is challenging (1954). A physical disease with clear anatomopathological location (Parkinson's disease) would reach some of the most

---

[59] In 1961 Haase translated Antrieb by Conation. According to Danziger (1997) Conation was a nineteenth century philosophical term that never became part of common language traditionally referring to an active principle of consciousness. Its relationship with the concept of motivation, and more specifically with the concept of Drive, is explicit in Haase's definition of Conation" It includes the whole amount of psychic energy, potential as well as transformed into normal or ill -directed action" (H. J. Haase, 1961). In Haase's Conation, as well as in the concept of Drive, the references to mechanics are clear, this vision of psychic activity similar to the fuel of a machine. The psychoanalytic origins and influences on this concept of potential energy were also later explained by Haase(1965, p. 6).

The subtilities and difficulties of translating the German words Trieb and Antrieb, are various and have been extensively reviewed (Buchenau, 2002; Paccioni, 2002; Scarfone, 2004). The different historical meanings attributed in English to words like Drive, instinct, conation, volition and motivation are also full of pitfalls (Danziger, 1997, pp. 110-123). On the one hand, it is not the object of this thesis to dwell on these rabbit holes, on the other hand, the semantic references to a mechanistic imaginary in the definition of antrieb that Haase uses suggest that its translation by the term Drive is perhaps appropriate in this context, which we will do for simplicity throughout this thesis.

fundamental aspects of human action. It could do so by striking the drive, influencing this vague concept of potential energy, prior to the motor or mental act. This process became manifest through the act of writing. Given this, it is hard not to read it as an attack on Cartesian dualism. How can we accept that matter and mind are two different substances if we can touch them at the same time?

The historian German Berrios(2018) synthesises the problem in the simplest way:

> Four propositions (which can not be all true at the same time) characterize the "problem":(i) the mind is a nonphysical thing; (ii) the body is a physical thing; (iii) the mind and the body interact; and (iv) physical and nonphysical things cannot interact. (Berrios, 2018)

In Parkinson's disease, we would have an example of an injury to the physical body that would act directly but subtly both on mental acts (the mind) and on movement (the body). The fourth proposition seems to be an impossibility here, physical and non-physical elements seem to be more than interacting, they seem interconnected. This interactionist view between brain and mind is actually quite old, as trauma and brain malformation had been associated with behaviour changes for centuries. This wasn't consensual though, as psychopathological traditions persisted that clearly differentiating brain disease from real madness, and parallelism or concomitancy views, through Hughlings Jackson influence, kept their ground (Berrios, 2018). Mercier once wrote of Dr Jackson:

> All expressions that imply interaction or community of nature between body and mind, such as 'psycho-motor' or 'center for ideas', he called 'scientific blasphemy'.(Mercier, 1925 as cited in Berrios, 2018)

Haase's and Gross (1954) challenged this non-interactionist view directly. Through their handwriting analysis of Parkinson disease (and Huntington's chorea), and using the antrieb/drive concept, they seem to redefine a union (*einheit*) between mind and motricity. Their first conclusion is explicit:

> We tried to experimentally expose psychic laws, especially of the drive, in Huntington's disease and Parkinson's disease patients, which we understood, not only as psychological reactions to the disease, but essentially as an expression of one psychophysical interaction (the psychic only as one side of the body-soul unity, which is inseparable in these areas) (author's translation).
>
> Wir bemühten uns, psychische Gesetzmäßigkeiten, insbesondere des Antriebes, bei den Choreatikern und :Parkinson-kranken experimentell herauszustellen, die wir nicht nur als psychische Reaktionen auf die Krankheit auffassten, sondern im wesentlichen als Ausdruck

> eines psychophysischen Zusammenwirkens (das Psychische nur als eine Seite der in diesen Bereichen untrennbaren Leib-Seele-Einheit). (Gross & Haase, 1954)

Handwriting analysis had a long tradition in psychiatry, specially in German psychiatry. Interpretation of handwriting existed since at least the XVII's century, as seen in the work of author Camillo Baldi (1550–1635). In the XIX century, graphology journals started emerging in continental Europe, and when Kraepelin started publishing his textbooks, handwriting was already being used as a diagnostic tool. Again, some authors connect this increasing notoriety of handwriting to the newfound importance of quantifiable behaviour data as psychiatry was imposing itself as a true science (Schäfer, 2016). Kraepelin followed through extensively using handwriting as illustrative of the general clinical description (Appendix B, figure 6). So, handwriting was already well within the range of this mind-body crossroad. As a physical entity, it still had obvious expressive or hermeneutic qualities that referenced the mind and its use in clinical observation was classically recognised.

Hans Steck's paper describing his experience with chlorpromazine featured in the *Annales Medico-Psychologiques* session of November 23rd, 1954, and was printed the following month. Hans-Joachim Haase's experience with chlorpromazine was published December 20th, 1954 in *Der Nervenartz.* The two men shared much more than their first names. They worked in Switzerland a little more than two hundred kilometres apart and both had, even before chlorpromazine, an interest in subcortical regions and parkinsonism. Their first assays with chlorpromazine also appear to be similar. The majority of patients, in both trials, had a schizophrenia diagnosis - deviating from the large therapeutic scope attributed to chlorpromazine in these early years. Also, the high doses used in Switzerland differed from those used in neighbouring countries. Steck reached between 400 and 800mg per day, Haase performed rapid titrations of up to 300 or 400mg per day (contrasting with Paris where maximum doses were 150mg per day)(Haase, 1954; Steck, 1954).

Steck and Haase also shared the same observation in the construction of their main theses - the therapeutic importance of extra-pyramidal symptoms. Steck (1954) was mainly concerned, as we saw in Chapter 3.3, with the clinical proximity between chlorpromazine and encephalitis lethargica, and for him the therapeutic importance of parkinsonian symptoms derived from this analogy. Haase shared the same recognition, but stemming from a different relationship. Haase's thesis was built from the antagonism between two different concepts - Drive, or Antrieb, and fine motor skills (namely handwriting) (1954).

This antagonism, already present in his previous work on drive and handwriting in Parkinson's disease, resurfaced during his experience with chlorpromazine. Experimentation with neuroleptics (namely chlorpromazine) allowed Haase to confirm his earlier thesis that the decrease in *drive* in Parkinson's disease was not just a result of gross motor changes but was an independent sign of a hidden subcortical process. Chlorpromazine experimentally proved that *drive* alterations appeared even in the absence of gross motor changes. *Drive's* curtailment happened at the first signs of impairment of fine motor skills. In patients treated with chlorpromazine, these early parkinsonian symptoms, subtle and often identifiable only in handwriting, were associated with the decompression (steaming) of the Drive, and resulted in emotional calm and relaxation, with subsequent inhibition of the psychotic experience (Haase, 1954).

From this point of view, the first trials by Haase and Steck with chlorpromazine were also similar. For both men, empirical quantitative approaches to efficacy were secondary. On the contrary, the substance was mainly of interest as an experimental test for their previous theories (Steck was testing his ideas about the subcortical location of psychosis, and Haase was reflecting upon the connection between fine motor skills and Drive).

In these examples, to which we can add others such as the psychiatric use of chlorpromazine by the Paris team and their previous interest in the diencephalon - see (Bovet, 2015), the construction of psychiatry emerges within a curricular continuity. Both theories and new practices followed directly from the authors previous work. They interacted and reinforced each other in what appears to be, at least in these examples, a primarily authorial tradition. Looking back, the 1950s are often seen as marked by a supposed international revolution in psychopharmacology, but in these examples we find, on the contrary, strong elements of theoretical continuity developed in lines of work, in both regional and individual interests.

Initially obscured by the overriding impact of Hans Steck's work, and possibly also underestimated due to the secondary role of the German language in the psychopharmacology of the 1950s, Haase's work slowly but steadily found recognition. In the late 1950s, he received a grant from the National Institute of Mental Health, with support from the Fulbright Commission and the Medical Academy of Dusseldorf, for a one-year internship in the United States at the Delaware State Hospital (Haase, 1961).

This international experience allowed him to further test his thesis with other neuroleptics. His influence steadily gained dynamism in the growing reflection on extra-pyramidal symptomatology, and in 1960 he was one of the guests at the famous Montreal congress (which we already mentioned in chapter 3.3). Jean-Marc Bordeleau (1961), in the congress' introductory section, even referenced his name, alongside Hans Steck, as the first to recognise the extrapyramidal syndrome's importance in neuroleptic therapy.

In Haase's theory, as presented in Montreal in 1960, handwriting continued to be the central element. Handwriting crystallised and materialised the most subtle changes of movement in a concrete image that allowed the detailed analysis of patterns before, during and after treatment. Discernible signs included stiffening, narrowing, and letter size diminution (see Appendix B, figure 7). These drug provoked changes were an absolute condition for the appearance of a therapeutic effect. In the absence of handwriting alterations, none of the drugs studied worked.[60]

A quantitative relationship was starting to be delineated: the greater the affinity of a substance for the extra-pyramidal system, the smaller the dose needed to achieve writing alterations and therapeutic efficiency. The amount of substance to be administered directly conditioned two different variables - changes in handwriting and behavioural changes corresponding to treatment's effect. This would allow a direct relationship to be drawn between latter the two. A notion of neuroleptic potency began to emerge allowing the establishment of recommended doses for each drug, even if patient's individual response was variable. This quantitative relationship is important because it forms a particularly convincing argument. It is not just a single dependence between fine motor disorders and therapeutic efficacy, it is a relationship that can be seen in several different drugs, in several different patients and in several different drug doses.

Drive was still the centrepiece of Haase's theory, in his Montreal presentation. Conation/ Drive/ Antrieb referred to this potential energy prior to any phenomenological or movement realisation (1961). The therapeutic action of a neuroleptic resulted from the reduction of psychokinetic energy. The aim was to curtail only the psychologic energy that was in excess or misdirected in psychosis, avoiding apathy. Therefore, the conditions for the

---

[60] Hasse had presented data for chlorpromazine, but also prochlorperazine, trifluoperazine, fluphenazine, thioperazine (Haase, 1961).

therapeutic effect should be surveilled in the most discreet and subtle of movements - calligraphy. Extrapyramidal symptoms for Haase were not just side effects but, in their mildest intensity, were fundamental to therapeutic activity. Reducing the psychokinetic energy of patients with psychosis allowed for a normalisation of personality and a better adjustment to external reality. Paranoid-hallucinatory experiences were subsequently reduced as they were seen as dependent of affective tension and maladjustment (Haase, 1961).

As we have seen in some instances during our research, Haase's ideas were becoming a recurrent topic. They were discussed in Beerse in 1959, when haloperidol was introduced and they were extensively discussed in Montreal in 1960. In Beerse on September 15th, 1959, in the final discussion of the first international symposium on haloperidol (1960), Pichot, representing the Paris team, had completely rejected any direct relationship between parkinsonian symptoms and therapeutic effect. Elissalde in that same discussion upheld the same argument - the therapeutic results in Paris had not been dependent on the existence of an extrapyramidal syndrome.When the "Liègeois" Evrard presented Haase's ideas, namely the effects of neuroleptic therapy on handwriting and the use that could be made of this phenomenon, in calculating recommended dosages for haloperidol, the idea seemed to have been brushed aside. From what we can infer from the records published in the *Acta neurologica et psychiatrica belgica*, consensus leaned more towards a clear differentiation between therapeutic effects and side effects. Janssen, himself, seemed to defend this independence, when describing the prospects for the development of new drugs, useful but lacking extra-piramidal side-effects. In Montreal, in November 1960, Haase's ideas became central to the meeting, yet the main protagonists such as Delay and Denniker (1960) or Klyne (1961) remained sceptic.

While Haase's theories were becoming mainstream, the haloperidol clinical trials were encountering several problems (see chapter 3.1). Denber's (1959) study, in which only 30% of patients responded to haloperidol had a devastating effect on the drug's market introduction. Janssen himself would recognise it in his interview with Healy:

> (…) in America, certainly at the beginning there was a very strong and long-lasting anti-haloperidol period. this was a direct consequence of the first publication in the American journal of psychiatry, by Herman Denber (…)(Interview with Paul Janssen cited in Healy, 1998b)

But Denber's wasn't an isolated trial; the disappointing results of studies by Enoch (1960) and Azima (1960a), among others, lead Wortis (1962), in his review of new developments in psychopharmacology throughout 1961, to highlight concerns about side effects, specifically extrapyramidal effects. Those were becoming increasingly worrisome and he recommended greater care with the doses used.

Paul Janssen valued courage and persistence, transforming unexpected setbacks in opportunities (Lewi & Smith, 2007). And so secondary side-effects that began being seen as incapacitating became an opportunity and were transformed in an essential piece of the mechanism of action. This transformation, I argue, was crucial in the construction of the dopamine hypothesis for schizophrenia.

In the beginning of the sixties a close collaboration between Janssen and Haase followed suit, with samples of Janssen's freshly developed medications being sent to Haase for testing and dosage recommendation. Between 1959 and 1965 Janssen Pharmaceuticals introduced four different antipsychotics - trifluperidol -1961, pipamperone- 1961, fluanisone 1962 and droperidol 1963. As these new butyrophenones were developed they were sent to Dusseldorf where they were subjected to Haase's handwriting tests. Haase would then quantify the minimum doses necessary to provoke changes in handwriting, helping characterise the clinical profile of the various butyrophenones. (Awouters & Lewi, 2007)

Haase and Janssen's collaboration peaked in both authors publishing the book "The action of neuroleptic drugs. A psychiatric, neurologic and pharmacological investigation"[61](Haase & Janssen, 1965).

In the introduction to *The action of neuroleptic drugs*, signed both by Haase and Janssen it can be read that "As a result of the clinical observations of Haase it is shown that the neuroleptic effect in humans is indicated physically by a fine motor extrapyramidal hypokinesia, which is closely linked with the psychic activity of neuroleptic drugs." (Haase & Janssen, 1965, p. 5) . This was Haase's central thesis since 1954, now also subscribed to by Janssen. This coincidence of perspectives is not surprising given the continuity we can find between Haase's handwriting test and the animal models that Janssen had used in

---

61 In the first lines of this small book there is the following unreferenced citation "Panse is of the opinion that "basic functions" which can be accurately measured, repeated and compared must be discovered and investigated in order to define psychoses more exactly". This surprisingly contemporary concept that reminds us of the RDoC project seems to be attributed to Friedrich Panse, German psychiatrist whose career was engulfed in controversy due to his proximity to the Nazi regime, during the second world war.

haloperidol's development. Four structural concepts stand out: disposition to neuroleptic action, neuroleptic potency, neuroleptic threshold, therapeutic neuroleptic range.

*Disposition to neuroleptic action r*eferred to the patient's individual susceptibility to the drug's effect. Primarily constitutional, it could be influenced by different factors such as gender, or even concomitant somatic diseases. The variability of this disposition could reach sizeable proportions (of about 15 times).

Neuroleptic potency was the ability of each substance to develop the neuroleptic syndrome regardless of the susceptibility of each patient. Contrary to the d*isposition to neuroleptic action*, a characteristic of the patient, *neuroleptic potency* would be primarily a characteristic of the substance and depend on its affinity for the extrapyramidal system. The greater the affinity, the lower the dose required, the greater the *neuroleptic potency*. Phenothiazines requiring doses on average two or three times higher than chlorpromazine would be classified as having low *neuroleptic potency* (e.g. levomepromazine). If only 1/20 of the dose of chlorpromazine was needed, then it would be considered a very potent drug (Haase listed haloperidol as an example).

Neuroleptic threshold alluded to the minimum dose necessary for the appearance of extrapyramidal symptoms recognised in fine motor skills - specifically in writing. A lower dose would only cause drowsiness, and sometimes perhaps an antidepressant effect. Gross motor changes such as rigidity, tremor but also akathisia were for Haase, a sign of overdose, and may even be harmful having no relation to the therapeutic response.

Therapeutic neuroleptic range described drug doses necessary in order to maximize therapeutic effect and minimize side effects. Although causing symptoms in terms of fine motor skills, this level of medication would not yet cause gross motor changes. For Haase, the reason most clinicians still did not recognise the link between extrapyramidal symptoms and the therapeutic response in 1965 derived from the fact that they were only attentive to coarse motor symptoms, and did not register changes in fine motor skills.

In these 4 concepts (*disposition, potency, threshold, range*) we see the start of a different semantic geography in the approach to neuroleptics. In fact, the first metaphors we refer to, for example in chapter 3.3, came from physics, and the concept of *drive* remained in that semantic field between electricity and mechanics. Here, Haase defined an interaction between a *disposition* (referring to the individual) and a *potency* (referring to the drug). This

relationship was symbolically consummated in the concept of threshold. It seems to me that this dynamic connection is already closer to the semantic fields of reproduction, or biology, where neurotransmission would progressively but surely install itself throughout the 1960s.

It is important to understand that for Haase (1965) the therapeutic effect of neuroleptics was direct and non-specific. It could, for example, be felt by a non-ill person. The main effect was the reduction of the psycho-energetic level. This decrease would constitute treatment differently depending on the underlying pathological state. In cases of significant psychomotor agitation, behaviour could be contained regardless of etiology by decreasing psychokinetic energy. But more subtle psychopathology could also be affected. Delusions and hallucinations, seen as consequences of an exacerbated affective tension, would be impacted by this psychoenergetic decrease. Every mental act requires energy, and this energy could be curtailed by neuroleptic therapy.

> As is generally recognised the effects of neuroleptics on clinical symptoms make it clear that psychoses, especially schizophrenic psychosis, are not causatively influenced by neuroleptics, but rather, more or less compensated. (Haase & Janssen, 1965, p. 18)

The mechanism of neuroleptic action was still seen as completely unspecific, and we are still a long way from the contemporary concept of antipsychotic. It's closer to the theories proposed by Emile Meurice (see chapter 2.7.2). Therapeutic action didn't come from antagonising disease mechanisms, on the contrary, therapeutic action came from a global transformation of mental functioning. The anti-hallucinatory and anti-delusional activity was secondary to the decrease in drive. Maybe for this reason therapeutic activity was most important in cases of acute or subacute schizophrenic episodes, chronic conditions were often seen as resistant to treatment (Haase & Janssen, 1965, p. 9).

Haase maintained a multifactorial view on the etiology of schizophrenia, emphasizing the importance of genetic factors, but also personality and environmental factors. Several elements contributed to the creation of states of emotional excitability that could then lead to a schizophrenic episode, both mental and physical.

Again, as we found in our research, Haase's theoretical construction used mixed language, with multiple references to psychoanalysis. He continually emphasised the importance of psychotherapy. For Haase, the path back to normality wasn't just solving a list of symptoms, on the contrary the way to recovery included a crucial process of personality restructuring.

In his section of *the action of neuroleptic drugs* Paul Janssen details the principal characteristics of neuroleptics. Those include depression of operant behaviour, lack of initiative, curtailment of psycho-motor agitation, decrease in hallucinations and mental confusion while sedation was minimal and the patient was kept awake. These were seen as human equivalents of the animal models used in neuroleptic development. When constructing haloperidol, Janssen had used a number of animal experiments searching for chlorpromazine-like activity (detailed in chapter 2.1), comprising disappearance of operant behaviour, decrease of exploratory behaviour, amphetamine antagonism and catalepsy in higher doses. Neuroleptic potency, a characteristic of the drug that defined its affinity to the extrapiramidal system, was studied by Haase in human patients through handwriting analysis. Janssen used the same concept but applied it to animal testing. The combination of jumping box experiments in rats and dogs (described in chapter 2.1), and apomorphine antagonism contributed to quantify neuroleptic potencies, using as units chlorpromazine's equivalents. Haloperidol would be 16 to 50 times more potent than chlorpromazine. In this light, we can see clearly the similarities between Haase's handwriting test, and Janssen's animal models. Simple, measurable, reproducible, transparent, and materialised in a physical object, Haase's test enabled a quantitative comparison between drugs, doses and effects.

As detailed in the first paragraphs of this chapter, the concept of psychomotor energy potential, *drive*, had blossomed from this intersection between the ubiquity of animal models (in behaviourism), and a growing biological essentialism. It had served, from the beginning, as a bridge, creating equivalences between human motives and animal incentives (Danziger, 1997, pp. 116-120). Haase uses the concept in a similar way. The concept of *drive* enables the relation between Haase's writing test and Janssen's animal models of neurolepsis. Drive provides an explanation, and frames the empirical results attributed to the action of the substance. In so doing, it becomes a pertinent explanation for the interaction between body and mind, offering a first possible answer on how somatic therapeutical technologies, drugs, could change mental states.

Janssen's animal models had an intrinsic flaw, a primitive wound so to speak, namely the psychiatric's elite scepticism about the idea that schizophrenia could be reproduced in a laboratory. How can we imagine that those broad complex schizophrenias we talked about in

our introduction, seen as depending on a deep fragmentation of the Self, could find any relationship with animal models such as the Jumping box or the antagonism of apomorphine?

Haase's test, as a reformulation of the Jumping box, brought back the simplicity of animal models into the complexity of human consciousness, bringing the clinic closer to the laboratory. The concept of Drive provided a mechanism of therapeutic action across both settings (patients and animal model). It framed, contextualised and justified the laboratory development of haloperidol, as well as explained its clinical action. These may be some of the reasons Janssen became so interested in Haase's work.

Central to *the action of neuroleptic drugs* was this simple idea, an identity that was forming between side effects and therapeutic action, in the words of Paul Janssen, therapeutic action was "fundamentally bound up" with the extrapyramidal system (Haase & Janssen, 1965, p. 163).

From a marketing perspective this can be seen as a major breakthrough, as worrisome, distressing, incapacitating side effects become in fact essential parts of the therapeutic mechanism of antipsychotic action. Haloperidol's major "neurotoxicity" was in fact just a sign of its efficacy. This influential idea would constitute a major force behind the dopamine hypothesis for schizophrenia. In fact, van Rossum, in his 1966 article which articulated the dopamine hypothesis for schizophrenia for the first time, would return to it.

> As implication of the present hypothesis of dopamine receptor blockade by neuroleptics is that their parkinsonoid side-effects cannot be disconnected from the neuroleptic action. (van Rossum, 1966a)

The action of neuroleptic drugs was printed in the Netherlands, just one year before the Dutch van Rossum formulated the dopamine hypothesis for schizophrenia. There is this close geographical proximity between major events in this process – Dusseldorf (Haase), Liège (Bobon), Beerse (Janssen), Utrecht (van Rossum). As previously noted, the places that emerge in this story are very close to the linguistic frontier of the two major cultural continental powers, Germanic and French. The next section examines contributions from other geographical areas, namely the United States and Sweden. As the concept of neuroleptics mature, and its impact in clinical practice became salient, basic chemical research started investigating possible neurochemical mechanisms of action.

4. The brain
4.1. From the spectrophotofluorometer to the serotonin hypothesis

In this chapter the background to our study changes. We abandon the asylum, the main scenery of part 3, and we return to the laboratory. This transformation involves distinct conditions in variable control and subsequently a new epistemological texture in the collected data. In the laboratory, knowledge is expected to be more stable, more reproducible, more mechanistic and more explanatory. Another difference in relation to preceding chapters, is the absence of the psychiatric patient. Despite our research concerning explanatory models of a psychiatric disease, in the current chapter the patient vanishes. In his absence, two other characters become central: techniques and drugs. Substances had emerged in the laboratory and returned to the laboratory after being found useful in the asylum, bringing with them a memory of illness and a promise of therapeutic intervention. The drug (in this chapter reserpine, and in the next, chlorpromazine and haloperidol) replaced the vanishing patient. It is in the mechanistic exploration of the drug's action that the mechanistic formulations of the disease were constructed. This path is characteristic of biochemical hypotheses in psychiatry, and of the dopaminergic hypothesis in particular, and helps explain one of the main features of contemporary psychiatric theory- pharmacocentrism.

First an empirical question was raised: does the drug work? A response was built through an heterogenous process of clinical trials developed in the asylum. Then a second question emerged, theoretical in nature: how does the drug work? That answer was created in the laboratory. Drugs and illness were seen as acting through the same mechanism in opposite directions. The drug initially forged to treat the disease, gained the power to redefine and to reshape the illness in its own image.

In 1965, concomitantly with van Rossum's proposal of the dopaminergic hypothesis, the director of the National Institute of Health, James Shannon, spoke before the US Congress. While van Rossum built a theory that went from the empirical effectiveness of drugs to the speculation of the pathophysiological mechanisms of the disease (see Chapter 5), Shanon, on the contrary, defended, before the American Congress, an empirical approach to industrial pharmacological research which didn't, necessarily, require a complete understanding of underlying mechanisms (Slater, 2004).

This tension, between pharmacological empiricism and theoretical construction of explanatory mechanisms, is recurrent in psychiatry. The two forces expanded the discipline's body of knowledge in different but complementary directions and often coexisted in the development of therapeutic technologies in general. As the example of haloperidol shows, the construction process of therapeutic technologies wasn't purely empirical or purely theoretical, but an intricate endeavour in which both approaches coexisted and were difficult to disentangle. This is also a problem for history as a discipline, challenging us to avoid simplified and one-side narratives as we try to grasp the complex hybridisation of a past event.

The iconic image of Shannon speaking before Congress highlights another element: The US Congress itself, which was important not only as a symbol of political power, but in the concrete definition of regulatory policies and funding opportunities. The US Congress was influential over the professionalisation of clinical trials, and in establishing new drugs introduction processes (as seen in Chapter 2.2). However its role in financing, expanding and industrialising biomedical basic research was also crucial. In this respect, both the National Institute of Health and James Shannon himself played a key role.

In this chapter, we will continue to explore the differences between both sides of the Atlantic and their consequences in the elaboration of psychiatric theory. We have already identified, for example, contrasts in drug reception, specifically around haloperidol's clinical applications. However, those differences probably existed in broader contexts and dynamics that are worth recognising. In fact, although most psychopharmaceutical drugs were developed in post-war continental Europe with private funding, basic biomedical research on the mechanisms of drug functioning were developed mainly in the United States with public funding, dependent on the political interests of the American Congress.

In order to understand this financial framework, one needs to return to James Shannon's career, beginning 24 years earlier, when the Second World War created an exponencial growth of public investment in scientific research, and malaria became a worrisome military factor.

Both malaria's importance in the historical development of colonialism, but also the impact of colonialism on malaria and its geographical distribution have been highlighted in the past. Similarly, the impact of war on the infection's expansion, the intensity of its effects

on public health, as well as the impact of malaria on the balance of forces of armed conflicts have also been highlighted. Malaria, which seems to be easily influenced by socio-economic determinants and political organisation, has shown its own ability to influence these same historical processes (Packard, 2021).

During Second World War, malaria posed a risk to Allied forces, with the subsequent progressive increase in world demand for quinine, mostly produced on Java Island.[62] Threats to Java, and challenges to the control of its raw materials, were growing, and, in 1941, an American program to replace quinine became unavoidable. Only one year later, Java's Japanese occupation took place, and malaria research became crucial (Slater, 2004).

James Shannon was, in 1941, a young nephrologist directing a research unit, located at the Goldwater Memorial Hospital and associated with New York's University (Costa, Karczmar, & Vesell, 1989b; Interview with Julius Axelrod in Healy, 1998a, pp. 30,31). He was charged with creating a clinical laboratory to test various antimalarials that were under development at the time. In an essentially empirical approach, such as the one he would advocate in his speech before Congress near the end of his career, Shannon was chosen to gather a pluralistic team focused on a precise and urgent research goal. During this mission, he is described as having been a keen scientific leader (Costa et al., 1989b).

Julius Axelrod, in his interview with David Healy (1998a), recounts a story, with legendary undertones, in which Shannon called all the pharmacology professors in the country, and said "send me your best people". The remarkable number of young talented scientists he assembled together profoundly marked the history of science. Among them were Sidney Udenfriend and Bernard Brodie, and eventually, Axelrod himself. Their later success was perhaps driven by their individual qualities, but probably also by having started their careers exactly in this precise team, in this time and place.

The anti-malaria program of World War II would become a model for biomedical research, notably through the National Institute of Health. The figure of Shanon is an example of this continuity. In 1948 Shannon became director of the National Heart Institute, between 1952 and 55 he became associate director of the National Institute of Health, and finally director, between 1955 and1968 (Slater, 2004). Still according to Axelrod (Interview

---

62 Quinine's production global concentration in Java during the 19th century follows the illegal and systematic theft of seeds in Bolivia in the context of Dutch colonial expansion (Eyal, 2018).

with Julius Axelrod in Healy, 1998a) Shannon had a privileged relationship with two important American politicians Fogarty (Rhode island) and Hill (Alabama), being able to convince them of the importance of understanding biological processes. This ability to convince Congress allowed generous public funding for the NIH, freeing scientists to do basic research - with no pretensions of direct empirical application.

In reality, Axelrod's simplistic narrative summarises a difficult political lobbying process that involved, among others, Mary Lasker and her friend Florence Mahoney,[63] in a complex organisation, that included: the U.S. Congress (in the person of Representative John Fogarty who headed the "appropriations subcommittee for the NIH"), the Senate (in the person of Senator Lister Hill), and various outside experts, the annual negotiation of the NIH's budget became a careful ritual, a periodic staging that has been compared to a kabuki dance (Rettig, 2002). It is interesting to see that while women, such as Mary Lasker, were mostly excluded from roles of political decision, and absent from the leading positions in scientific research, they found in this funding architecture an effective instrument of action that, although discreet, had an important social impact.

The war transformed basic biomedical research in the United States through a process of centralisation, industrialisation, bureaucratisation, and professionalisation. The expansion of public funding then persisted in the post-war period, and during the cold war, perpetuated by personal connections between scientists, private lobbyists, and the political power. The effectiveness of this elaborate funding system is reflected in the growth of The National Institutes of Health's (NIH) budget from $700,000 in 1945 to $1.5 billion by 1970 (Healy, 2002, p. 150). This generous and stable funding over decades was a key factor in the subsequent transformation of scientific investigation, particularly in neurosciences, attracting and retaining human resources in the field of health (Bernard Brodie, for example, came from organic chemistry) and redirecting scientists from empirical research to the exploration of fundamental mechanisms. This multidisciplinary network not only directly supported experimentation, but also provided a competitive and critical environment where projects could thrive. Finally, the same generous and stable funding, allowed the development of techniques and instruments that expanded both the number and scope of possible questions.

---

[63] Mary Lasker was the founder of the influential Lasker prize. As seen in chapter 3.4, Nathan Kline gained it twice (1957 and 1964), Bernard Brodie would also receive the prize in 1968.

For the anti-malaria program at the Goldwater research Unit, Shanon had recruited the young Bernard Brodie, who was born in Liverpool but trained in Canada at McGill, as well as Sidney Udenfriend, an American of Central European origin who was a biochemistry graduate at New York University (Interview with Julius Axelrod in Healy, 1998a; Sciences, 2003, p. 277).

Interest in fluorescence as a quantitative method was born in the context of malaria research, where there was a need to quantify the serum levels of anti-malarials. The Goldwater unit was supported by the military, allowing them privileged access to multiple instruments, including the Beckman DU spectrophotometer. Udenfriend, however, preferred the Coleman Fluorometer, as with it he had developed techniques that allowed blood and urine measurements of drugs under investigation (including quinine and chloroquine, for example) (Udenfriend, 1995). Understanding a drug's serum quantification, and correct pharmacokinetics, is critical when choosing the correct dose, within the therapeutic window, to render it effective in fighting the disease but keeping side effects to a minimum. Brodie and Udenfriend's work in Goldwater is still seen as a crucial contribution in determining anti-malarial posology during the war.

After World War II, Rolla Dyer, the director of the National Institute of Health at the time, and an admirer of Shannon's work at Goldwater, was inspired by the war's scientific achievements. Aspiring a rapid development for his institution, he recruited Shannon to direct the National Heart Institute in Bethesda (Slater, 2004). Shanon convinced Brodie to follow him, and recruited several of his colleagues (e.g. Axelrod, but also Udenfriend and Bowman)

Descriptions of Brodie's personality are vivid. Julius Axelrod recounts that he might have been a boxer (he may actually have even won the Canadian Army Championship (Costa, Karczmar, & Vesell, 1989a)) or that at one point in his life he might have made a living playing poker (he may have paid McGills enrolment fees playing poker, (Costa et al., 1989a)). Axelrod describes him as charismatic but with "a lot of problems" (interview with Julius Axelrod in Healy, 1998a). Arvid Carlsson corroborates this picture full of contrasts. He wasn't a "traditional scholar", and some considered him "nuts".[64] Coming from a background in organic chemistry, his ignorance in physiology made him undervalue the complexity of the

[64] "But that is also the reason why some people think he was nuts, because if you look at him from a certain point of view, he was"(interview with Arvid Carlsson in Healy, 1998a, p. 55).

brain. From Carlsson's words emerges a man interested in finding simplicity in the greatest complexity (interview with Arvid Carlsson in Healy, 1998a). Merton Sandler was even more explicit in his comments, highlighting a history of substance abuse - amphetamines and barbiturates, which made him an unstable,"Crazy Man" (Interview with Merton Sandler in Healy, 1998a).

In any case, it was under his leadership at the National Heart Institute that Udenfriend returned to fluorescence in the early 1950s (Udenfriend, 1995). For some, this return already accompanied a growing interest in serotonin, at least since Gaddum's experiments (Sciences, 2003, p. 277).

John Gaddum, who had actively participated in Henry Dale's research on peripheral neurotransmission,[65] later become interested in serotonin and LSD. From the relationship between these two substances, the germ for the first neurochemical hypothesis for psychosis was born, profoundly marking Brodie's thought.

The existence of an entity responsible for vasoconstrictor properties in defibrogenated blood had been recognised since the late 19th century. In the 1930s and 1940s this substance was studied by Irvine Page's team, and named serotonin, as the name conveyed the importance of the substance's biological action in its identity (Green, 2008).

However the Italians, Vittorio Erspamer and his team, were working on the identification of another substance, with a completely different biological distribution, present in mammals' gastric mucosa. They called it enteramine, as the name conveyed the importance of its distribution in its identity (Vialli & Erspamer, 1937).

The two compounds, serotonin and enteramine, lived side by side, identified by their biological location and physiological function. The process of creating an identity between the two implied the construction of a new substance. Maurice Rapport (1949), from Page's laboratory, extensively studied the chemical structure of serotonin and proposed the term 5-hydroxytryptamine (C10 H12 ON2) or 5HT as a new identity.

This new nomenclature was a sign of the times, of a new neurochemistry that didn't depend only on tissue testing, but sought, through complex techniques, to define substances with more stable identities, less dependent on the experimental context. Transforming the identifying process of a substance in the capacity for laboratorial synthesis, instead of its

---

[65] Dale received the Nobel prize in 1936 (with Otto Loewi) (E.S. Valenstein, 2007)

isolation in biological effects, fundamentally changed the history of serotonin and enteramine. Both were now 5HT. Transforming an identity that was defined by its experimental effect, by its behaviour in the laboratory, by its activity, and localisation, into a chemical identity, constituted as substantial, inherent, permanent. A perfect new equality was born from two substances, until then so different.

After meeting Gaddum in the United States, Maurice Rapport was providing Gaddum with the 5HT samples he needed for his research(Green, 2008). Yet another example of the close personal relationships that sometimes connect key players in science, and of the power those relationships may have in shaping future knowledge. Two papers by Gaddum on the new 5-HT, both from 1954, reaffirm its nomenclature and promote it as a central substance in the formulation of neurochemical hypotheses.

In "The distribution of substance P and 5-Hydroxytryptamine in the central nervous system of the dog", Gaddum and the Edinburg's team (1954) tried to extract the substances from the brain. To identify them, the team mainly used tests on biological tissues, still confirming identities from their effect or function. Complementary techniques such as Paper Chromatography were used to try to increase specificity (differentiating different chemical structures by their solubility in paper, chromatography allowed researchers to confirm the purity of a sample in a way that tests on biological tissues would hardly allow). In the paper's introduction, questions arose about the substances' role in the brain, namely as chemical transmitters. As we have observed several times throughout our research, and Elliot Valenstein clearly demonstrated (2007), chemical neurotransmission in the central nervous system was received with skepticism during the 1950s and even on into the early 1960s. Perhaps this is exactly why this speculation, vaguely presented in the introduction, does not materialize in the paper's conclusions. The presence of 5HT in the brain suggested that it may have a highly specialised function, but Gaddum and his colleagues do not clarify its role in neurotransmission.

In "Drugs witch antagonize 5 Hydroxytryptamine" (Gaddum & Hameed, 1954) the Edinburgh team studied the ability of some drugs to decrease or prevent the action of 5HT in biological tissues. The tissues chosen were rat uterus, guinea pig intestine and rabbit ears. The description of the methods reminds us of the complex simplicity of the laboratory techniques used. Complex because they involved several different technically demanding

steps, but simple because they seem easily reproducible without sophisticated instrumentation. The use of biological tissues was used to identify and quantify the presence of substances. It was inexpensive, seemed easily reproducible, and relatively sensitive but involved time-consuming processes, was unspecific and almost certainly required procedures in which animals would suffer during tissue extraction.[66]

The use of biological tests allowed substance identification through its physiological effects, going from function, physiological activity and biological property to an identity that was supposed to be chemical but could hardly be epistemologically stable, as we saw in the dynamic identity - serotonin/enteramine/5-HT. It is therefore not surprising that these techniques were described as more sensitive than specific, easily identifying the presence of a substance, the origin of the property under study, but with difficulty in determining with high certainty if this property could be attributed to this or that substance. The substance retained a certain ontological instability even if its properties were well defined. Tests on biological tissues were therefore time-consuming and unspecific, as Gaddum himself recognised in a presentation at the National Institute of Health symposium in 1958. New chemical methods being developed, such as fluorescence, would probably, at least, save time (Gaddum, 1959).[67]

Gaddum's experiments concluded that LSD was a potent 5-HT antagonist - but not in all tissues. It suppressed the action of serotonin both in the uterus of the rat and in the ear of the rabbit, but did not act in the intestine. The existence of different receptors is only speculated (Gaddum & Hameed, 1954).

Gaddum's interest in LSD led him to experiment personally. Repeatedly, at least 4 times, between April 3 and June 1, 1953, he took between 30 µg and 86 µg. He described the intoxication highlighting sensory-perceptual changes (mainly visual) and thought content modifications (including self-image). Gaddum assumed that these psychotomimetic effects of LSD could be due to its action on 5HT (Green, 2008).

5HT existed at the central nervous system and was antagonised by LSD, both of these properties were demonstrated in tests on biological tissues. Additionally, there seemed to be

---

66 There is no reference in this paper, nor perhaps one would expect there to be, to animal welfare. After extracted, biological tissues were seen as experimental materials, decontextualised from their original animal body.

67 As Bruno Latour (1994) would suggest this kind of transformation has consequences in labour organisation in the laboratory, when technical skills are redistributed between crafted humans and new methods, there can be important changes with conflict, and renegotiation.

an important similarity in chemical structure between the two substances. From these observations Gaddum concluded that 5HT had an extremely specialised and important role in brain function, specifically in maintaining mental sanity. Gaddum's experiments and speculations were reproduced and found recognition on the other side of the Atlantic. Take for example the words of Woolley and Shaw of the Rockefeller Institute:

> The thesis of this paper is that these pharmacological findings indicate that serotonin has an important role to play in mental processes and that the suppression of its action results in a mental disorder. In other words, it is the lack of serotonin which is the cause of the disorder. If now a deficiency of serotonin in the central nervous system were to result from metabolic rather than from pharmacologically induced disturbances, these same mental aberrations would be expected to become manifest. Perhaps such a deficiency is responsible for the natural occurrence of the diseases. (Woolley & Shaw, 1954)

This is a first sketch of a neurochemical hypothesis, very similar in argumentative structure to the dopamine hypothesis of schizophrenia. If a psychotomimetic is antagonistic of a certain substance, then the existence of this substance must be fundamental to healthy functioning and its deficit may be the origin of disease. A relationship is established between a substance with an action on behaviour (LSD) and a natural endogenous substance in the central nervous system. Behaviour and substance materialize in the biological tissue of the brain, justifying a pathological state. The argument is very similar to the one that we will see used by van Rossum in 1966, for the dopaminergic hypothesis (and that we can briefly summarise in this way - if a psychotomimetic (amphetamine) stimulates a certain endogenous substance (dopamine), then the excess activity of this substance could correspond to the pathological state).

Even if Gaddum's speculations, in our retrospective gaze, seem to us "ahead of his time", and have a contemporary appearance in the argument to which he vaguely alludes, and in the concepts of "transmission", "receptor" and "antagonism" that he frequently used, we should not read his work anachronistically, and forget that the role he reserved for serotonin, as important as it was, would probably not correspond to the contemporary concept of neurotransmitter.

In any case, Brodie's laboratory at the NIH was interested in serotonin and Gaddum's work, but his physiological techniques were seen as time consuming, limiting their use. Identifying substances through characteristics depending more directly on their unique chemical structure, skipping the complex biological tissue handling, would allow for rapid

tests capable of differentiating between substances similar in their action. Studying serotonin would be easier. The team that came from the Goldwater project (namely, Brodie's team) had experience quantifying substances in biological systems (anti-malarials' serum levels), but with the instruments available there were still important limitations to the substances studied (they had to have an absorption band near 365A band of the mercury arc and to emit light in the visible spectrum) (Udenfriend, 1995).

Bowman, a physician, more interested in instrumentation than in clinics, developed a close collaboration with Udenfriend, constructing several prototypes that Udenfriend could then test in the laboratory (Udenfriend, 1995). In 1955, the team would present a preliminary result of a prototype instrument they would call a spectrophotofluorometer. It allowed them to extend the fluorescence analysis to both the visible and ultraviolet regions, facilitating identification and quantification of organic compounds. Among the substances studied, 5-HT and LSD occupied a prominent place (Bowman, Caulfield, & Undenfriend, 1955).

The history of the spectrophotofluorometer, told by Udenfriend much later (1995), has several interesting incidents that reveal the importance of National Institute of Health's public funding, the network of informal knowledge that the NIH provided, and the connections established between the NIH and private industry.

Bowman and Udenfriend needed expensive components for the spectrophotofluorometer's construction, including two ultraviolet monochromators, which at the time costed 5.000 dollars each (the equivalent, according to Udenfreind, of 100 thousand dollars in 1994). After some hesitation, and mainly because he knew them personally, James Shannon approved the purchase of one of these devices. The relationships established in the Goldwater project carried over to the NIH. The other ultraviolet monochromator, also had a singular history. According to Udenfriend, it was a used device of German origin, brought to the United States after the war, and obtained through Bowman's personal contacts. In Udenfriend's words:

> Bowman contacted several associates and found one who was willing to "lend" us an old Steinheil quartz prism spectrograph that had been ''liberated'' from Germany during the war. (Udenfriend, 1995)

It is not entirely clear why "lend" and ''liberated'' are in quotes, but we can assume that the instrument had been looted by the allies at the end of second World War.

The example shows how post-war scientific institutions helped create a network of scientists that supported each other, favouring privileged access to instruments, and facilitating means of recognition. Udenfriend details the difficulties encountered in publishing their first fluorescence paper, after being officially rejected by the *Journal of Biological Chemistry*. It was through the personal intervention of Jesse Greenstein, who worked at the National Cancer Institute and whom Udenfriend knew personally, that the paper was finally published in *Archives of Biochemistry*.

Udenfriend's recollections also illustrate the relationships that the NIH was developing with private industry. From the beginning, Udenfriend's project was to build a prototype with NIH funding, demonstrating its usefulness in the laboratory and then attract instrument manufacturers. Interest came from Aminco (American Instrument Company), a small private company in Maryland. Udenfriend and Bowman were offered a financial compensation- but the NIH didn't allow them to receive it. The Aminco-Bowman spectrophotofluorometer was reportedly a major commercial success with 25 units sold in the very first weeks, despite its high price ($8000, or what would have been over $80,000 in 1994).

> Many of those who first purchased the Aminco-Bowman or Farrand fluorescence spectrometers (about 1958) applied them to the quantitative assay of serotonin and the catecholamines and to various pharmacologic agents that modulated these hormones and neurotransmitters. One reason for this was that the new field of psychopharmacology was then growing extremely rapidly and the National Institute of Mental Health was so generous with its grants that it made it possible for grantees to purchase an instrument(…). (Udenfriend, 1995)

Bowman had integrated a set of complex components and theories into an industrialised and commercialised instrument that quickly spread through university laboratories and research centres. All these instruments had a strong impact on the research conducted subsequent to their purchase. Quantitative assays of substances present in the central nervous system and investigations on how those quantities could be influenced by drugs (reminiscent of Gaddum's experiments with serotonin and LSD) would become very frequent in the following years. Laboratory methods were now easier, faster, more sensitive and more specific.

Brodie's lab at the NIH was the first to benefit from this new instrument, and much of his team was then working around serotonin. Not only Udenfriend, but also Donald F.

Bogdanski, Alfred Pletscher, Parkhurst Shore, and Brodie himself. Two papers published in *Science* magazine in 1955 (May 25th, and October 4th) continue the theoretical tradition of the serotoninergic hypothesis, as had been outlined by Gaddum, and serve to solidify Brodie's emerging argument.

In *Serotonin release as a possible mechanism of reserpine action*, (Pletscher, Shore, & Brodie, 1955) reserpine was administered intraperitoneally to rabbits. At different times after administration the animals were killed, and serotonin was extracted and quantified. The team concluded that the concentration of serotonin in the intestine decreased progressively over 16 hours after reserpine administration. To analyse the serotonin concentration Pletscher used a colorimetric method,[68] developed by himself, which was insufficiently sensitive for the brain, but useful in the rabbit's intestine where serotonin was higher (Alfred Pletscher (in T.A. Ban & Sulser, 2011, p. 421)). Bowman's newly constructed spectrophotofluorometer was also used to confirm the identity of the extracted substance. Reserpine was seen as releasing serotonin from the intracellular space, and this release was postulated as the main mechanism of reserpine's therapeutic action in mental disease (Pletscher et al., 1955).

The other 1955 paper, *Evidence that serotonin has a role in brain function* (Brodie, Pletscher, & Shore), has been described as one of the most "celebrated pieces of work in early biochemical psychopharmacology" (Healy, 2002, p. 205). When Thomas A. Ban interviewed Alfred Pletscher in 2002 he referred to this paper as the discovery "that opened up the field of Neuropsychopharmacology" or that "profoundly affected the development of neuroscience"(in Ban & Sulser, 2011). In the same vein, Arvid Carlsson would also say in his interview with Healy "This really bridged the gap between biochemistry and psychiatry - and neurology as it later on turned out. So I think it was a very important discovery"(interview with Arvid Carlsson in Healy, 1998a, p. 52). For such a transformative paper it was surprisingly sparse in methodological description, especially when compared to what was usual at the time. We don't even know which animal was studied, but we do know that the spectrophotofluorometer was used. Results were also presented synthetically. After a reserpine injection, the decrease in the brain's serotonin concentration was remarkable and rapid, within 30 minutes the concentration had declined by 75%, levels would remain low

[68] Although Alfred Pletscher belonged to the Swiss pharmaceutical company La Roche (owner of iproniasid), he was doing an internship in Brodie's laboratory, considered a reference in biochemistry. This is just another example of the fluid relationship between the pharmaceutical industry and state research.

and only return to normal 48 hours after administration (Brodie et al., 1955). Much of the short article was devoted to speculating about the consequences of this result, in an unexpected theoretical tone. Empirical data were interpreted as reinforcing the emerging hypothesis of chemical neurotransmission in the CNS, and Brodie unequivocally referred to serotonin as a possible neurohumoral agent.

Results suggested that reserpine caused a decrease in serotonin in biological tissues and specifically in the brain. Perhaps looking back, the simplest interpretation would be to relate the therapeutic action of reserpine to this obvious depletion of serotonin, but Brodie chooses to see it in a different way. Since Gaddum, the psychotomimetic effects of LSD were seen as possibly due to serotonin antagonism, a consequence of LSD's capacity to decrease serotonin's biological activity. Serotonin depletion in the context of a psychosis treatment would bring this serotonin hypothesis into question. However, Brodie preferred to continue to support Gaddum's main arguments, trying to maintain the integrity of the serotoninergic hypothesis for psychosis. This was the intellectual tradition in which his research was included, if serotonin decrease was part of the disease, as the LSD's studies might suggest, reserpine could only justify its therapeutic mechanism if it was increasing serotonin's activity.

In spite of laboratory data, and facing opposing results, Brodie's team elaborates a complex explanation in order to reinforce Gaddum's theory:

> Our present concept, on the basis of the available facts, is as follows: serotonin in brain is normally present mainly in a bound form, thus being protected from the highly active enzyme, monoamine oxidase (9). After reserpine administration, brain cells lose, in part, their capacity to retain serotonin. As a result, serotonin is liberated and metabolised by the action of monoamine oxidase.Although reserpine rapidly disappears from the brain, the effect on the capacity of cells to retain serotonin persists. Since serotonin is still being formed during this period, much of it is presumably present in a free or physiologically active form. This free form of serotonin is considered as the mediator of the prolonged reserpine action. Since free serotonin is rapidly metabolised, the total serotonin remains at a low level. (Brodie et al., 1955)

Here, Brodie proposes an increase in the biological activity of serotonin through its release from the cell. This concept of "free serotonin" made it possible to make the quantifiable decrease of serotonin compatible with the supposed increase of its effects. We can criticise Brodie for re-interpreting the experimental data to make them conform to the prevailing hegemonic theories (or to the theories that he subscribed to), but if this is so, we

must also recognise that in this same article he takes a much more revolutionary divergence, breaking with a larger prevailing paradigm that framed his research activity - the electrical neurotransmission in the CNS. Serotonin goes from having an unspecified although intriguing role, in Gaddum's work, to a clear mediator function, revealing that an underlying conceptual framework of chemical transmission was already present.

This is a particularly interesting example of how scientific activity is sometimes in a precarious balance between conservatism and innovation. Some empirical studies in psychiatry, often the ones considered to be the most innovative and transformative, were also extremely conservative, strictly following the established intellectual habits. During my research, I found that pivotal moments that seem to radically question the more hegemonic paradigms, in Kuhn's sense, frequently weren't due to interpretation of new empirical data. On the contrary, the biggest changes in the discipline seem to have been the consequence of research programs with rigid theoretical frameworks. Examples abound, from Brodie's work to the Paris team's chlorpromazine's introduction. These approaches weren't revolutionary but deeply conservative. Reframing came from scientists focused in maintaining research programs even when faced with contradicting empirical data. This paradox reflects the social nature of science, as an activity that men do together. Within an idea that was already known, already elaborated, already finding some confirmation - the serotonergic hypothesis for schizophrenia - Brodie inserted the germ of an absolute paradigmatic transformation- from electrical neurotransmission to humoral neurotransmission.

> These studies pioneered a novel methodological strategy using drugs as tools; they were used to expose neurochemical changes of physiological relevance and then to study the relationship between neurochemical and physiological change. (Costa, Karczmar, & Vesell, 1989)

The use of reserpine as a bridge between a behavioural alteration and a neurochemical change, relaunched a powerful research program (which, in a way, Gaddum had already started with LSD). Researching mechanisms of neurochemical action of the newly introduced psychotropic drugs became widespread, as medications became instruments investigating the brain's normal and pathological function. This line of research had two immediate consequences, on the one hand a refocusing of etiological theories of mental illness on neurochemistry, and on the other hand a reinforcement of the theoretical justification of

pharmacological therapeutic technologies - to the detriment of electroconvulsive therapy, neurosurgery and psychoanalysis.

The international reception of these articles was enthusiastic, and Brodie's laboratory at the National Institute of Health became the center of attraction for most young people wanting to make a career in neurosciences, welcoming researchers from Britain, Asia, and even continental Europe (Healy, 2002). A young swede, Arvid Carlsson, would be among these many trainees, but his journey to the NIH is described in the next chapter (chapter 4.2).

Reading Valenstein's *The war of soups and sparks*(2007) we may retain the idea that we have often alluded to – namely, that the concept of chemical neurotransmission in the central nervous system encountered a persistent skepticism throughout the 1950s and 1960s. If so, Brodie and his team at the NIH represented an important transformative faction. In 1957, two years after the famous 1955 paper, Brodie and Shore outlined their conceptual framework of brain neurotransmission in a longer theoretical article. This is an interesting article, not only because it clarifies the extent to which peripheral chemical neurotransmission was already Brodie's model for brain neurotransmission, but also because of the specific recognition of serotonin and norepinephrine as neurotransmitters - although the term itself is not used, as Brodie preferred central neurohumoral agents, chemical mediators, or synaptic transmitter agent (Brodie & Shore, 1957).

> Similarly, in the brainstem, nerve impulses along presynaptic fibers might release serotonin in minute amounts at synaptic junctions. This release of free serotonin might act as a chemical mediator of responsive brain centers that in turn send impulses along postsynaptic fibers. Ordinarily, free serotonin could be considered to be present at the synapse for only a short time following presynaptic impulse. (Brodie & Shore, 1957, p. 633)

At this point in time, this isn't yet an overly sophisticated view of central neurotransmission, as it doesn't explicitly contemplate the concept of receptor nor the idea of reuptake for example. However a general framework of neurotransmission seems to take shape here.

In this same paper, there is a theoretical reflection about another antipsychotic - chlorpromazine. Although most of Brodie's work had been about reserpine, chlorpromazine's mechanism of action was even more elusive. The article suggested that chlorpromazine could function as a catecholamine neurotransmission blocker.

> Chlorpromazine could be assumed to inhibit the sympathetic system by blockade of the chemical mediator that activates the sympathetic centers. What could this chemical mediator

> be? Norepinephrine is a suitable candidate, although the evidence for it is entirely circumstantial. (Brodie & Shore, 1957, p. 639)

There is no mention of dopamine yet, the most likely candidate seems to be norepinephrine. The justification for norepinephrine's role came from another drug - amphetamine, a substance that had been an important asset in the making of haloperidol (see chapter 2.1). The possibility suggested is that the central effects of amphetamine could be mediated by norepinephrine and blocked by chlorpromazine. The proximity of this to the seminal article by Carlsson and Lindqvist (1963), which we will address in the next chapter, is striking, as we shall see.

4.2. The rise of dopamine

This chapter is, in many ways, similar to the previous one. The laboratory is still the backdrop to the discussion. Serotonin, the main actor in chapter 4.1., is replaced by catecholamines (and by dopamine in particular), but parallels extend to the role those substances played in the research careers of two different scientists, Brodie - who was introduced in the previous chapter and Carlsson, who will be introduced in this one.

At his Nobel lecture, Arvid Carlsson (2001) recalled the time when he was a young medical doctor researching calcium metabolism. He was working with a Swedish drug company, and using this research as his PHD thesis (Carlsson, 2000). This proximity between university and the pharmaceutical industry wasn't unusual (Andre Pinchard is another example, working simultaneously for Janssen Pharmaceuticals and Liège University, see chapter 2.4). When competing for an associate professorship in pharmacology, Carlsson was alerted that calcium metabolism wasn't the most compelling topic of the time by the expert committee. One of the central pieces of this research follows this brief, but recurring, moments when the social aspects of science, institutional and interpersonal relationships, emerge and redefine careers, reorienting research projects, and fundamentally changing future empirical data. Following the input of the research committee, Carlsson would change his career plans. Leaving behind working closely with the pharmaceutical industry as in the Calcium metabolism studies, he was now looking for a new opportunity, a new emerging field. This being so, it is important to note that any researcher looking for a place to do pivotal research would consider Brodie's laboratory at the National Institute of Health.

Aiming to join the National Institute of Health, Carlsson contacted Prof. Sune Bergstrom,[69] and Bergstrom then directly approached a friend of his who worked at the NIH - Bernard Witkop ("Arvid Carlsson," 1999). Witkop delivered Carlsson's letter of reference to his colleagues at the NIH, first to Udenfriend and later to Brodie. This is another example of the informal knowledge networks developing in neurosciences during the 1950's. Extensive and international, they often had explicit references to friendship bonds, and had mostly been built in new disciplinary meetings and associations. These networks include academia in the

[69] Bergstrom would later (1982) receive a Nobel prize for his work with prostaglandins (McCook, 2004)

strictest sense, but also industry, scientific journals and state laboratories. They were constructing theory, building consensus, forming and imposing paradigms but they were also very practical places of competition, and support. Networks impose fashionable themes, help in the redefinition and reorientation of research programs. They allowed confrontation with different points of view, and often lead to fractures, but they also facilitated the dissemination of empirical results and new emerging theories, promoting newly constructed objects. Networks weren't only rational in nature as connections between scientists often included affective ties, promoting those who entered these privileged circuits, and mostly excluding women and other disempowered identity groups.

> When I came there, in late August 1955, the first thing they did was to invite me to the cafeteria for lunch. Brodie and Udenfriend were there and I figured out that that was the time when Brodie finally made up his mind whether he would accept me or whether he would give me to Udenfriend. He accepted me (Interview with Arvid Carlsson in Healy, 1998a, p. 51).

What led Brodie to choose Carlsson as his trainee? Taking into account the place of the meeting, a cafeteria, we can suspect that it probably wasn't due only to his previous work, or his knowledge of relevant literature. What would have happened if at that moment Brodie hadn't spontaneously agreed to be responsible for Carlsson and had turned him over to Udenfriend? Perhaps Carlsson's career would have been hopelessly different, and his later works would have had quite another object of study. And without Carlsson's work on catecholamines, what would the dopaminergic hypothesis be, our object of study? Carlsson's brief description of the moment when Brodie chose to accept him in his research project is yet another example of how science is also built outside laboratories, outside offices, in university corridors, in cafeterias. And the importance of these spaces is not just as a backdrop, as a landscape that we imagine behind the events that remain unchanged. On the contrary, they modify the way we see these encounters. These informal spaces reveal the importance of affective factors, personal understandings and unreflected affinities in knowledge construction. They favour a view of science as an elite private club.

In Carlsson's description of his arrival at the National Institute of Health, there is a feeling that anything would be possible, the outline of a dazzle, the edge of something new, the verge of a revolutionary period for neuropsychopharmacology. The lab was still crammed with boxes of equipment that had been purchased but not yet assembled, and Brodie received plenty of visitors. Arousing this interest, according to Carlsson, was a growing recognition of

the importance of pharmacokinetics (on which Brodie had worked since Goldwater), the new spectrophotofluorometer (when Carlsson arrived at the NIH, it was just a prototype spread out in a darkened room), and the articles on reserpine and its action on serotonin (Interview with Arvid Carlsson in Healy, 1998a).

Carlsson's work at the NIH continues Brodie's line of research by investigating serotonin's intracellular storage mechanisms, as well as its release triggered by reserpine. Carlsson returns to the blood, which had been the crucial element in the substance's first identification (1957). However his approach was no longer interested in the physiological action in peripheral tissues, as problems of identity and quantification had then been resolved with fluorescence techniques. Even so, and despite the time-consuming tests in tissues having been abandoned, his laboratorial work was still delicate and laborious. In his interview with Healy, the methodological difficulties encountered become evident:

> I worked, I think, for more than one month on this - I isolated the platelets, put in the reserpine and measured serotonin in the supernatant and in the platelets - and found no effect. That was frustrating because as you already indicated I was entirely new in the field, so they thought probably I was just a joke. But then what happened was that I ran out of the sample of reserpine and they gave me a new one and, as soon as I got that, it worked beautifully. I think there was something wrong with the first batch of reserpine. (Interview with Arvid Carlsson in Healy, 1998a, p. 53)

Laboratory work was slow, tedious, and often marked by failure. In this description of Carlsson and his research we can also find a tension between theoretical and empirical knowledge. Working with platelets, *a priori* theoretical knowledge seems to be fundamental. Early experimental data did not seem to fit what was then thought to be known about reserpine. As the strength of the hypotheses suffered with preliminary results, Carlsson seems to have persisted in the methodology until circumstances allowed hypothesis confirmation.

The unreliability of results could threaten the integrity of the study's conclusions. This insecurity was appeased by Carlsson's explanation of poor reserpine quality. Our research shows that some epistemic instability is recurrent in pharmacological clinical studies- as we saw in haloperidol's example - without fundamentally jeopardising the therapeutic principles and methodologies of clinical trials. Clinical variables are multiple and difficult to predict. In the laboratory, however, the reality is perhaps different from that of the clinic, and since the scientist is more able to control the elements under study, one could expect greater stability in results, with subsequent reproducibility.

Working with platelets, during his stay at the NIH, Carlsson was focusing on the biological mechanisms that may underline Brodie's theoretical propositions (Brodie related reserpine's clinical action with an intracelular release of serotonin - see previous chapter). In the 1957 paper, there were two laboratory results repeatedly addressed - the release of several molecules of serotonin for each molecule of reserpine used, and the absolute dependency of the phenomenon to room temperature (preferably occurring at 37º). Carlsson started to imagine a complex chemical mechanism that could explain serotonin intracellular storage and its release by reserpine – two sides of the same puzzle (Carlsson, Shore, et al., 1957).

According to Carlsson's description he was also doing work about ATP in platelets and reading his Swedish colleague Nils-Åke Hillarp's work around the importance of ATP molecules in adrenomedullary granules, the main secretors of catecholamines. If ATP could be involved in the storage or secretion of both serotonin and catecholamines, then their mechanisms could be similar and both influenced by reserpine.

> Since this was the case, I felt it was a reasonable hypothesis that the storage mechanism for serotonin and catecholamines could be basically the same and therefore if you gave reserpine something might happen to. So I told Brodie, shouldn't we do that and he said 'no, that would be a waste of time because it's serotonin that's important'. He insisted on serotonin for an unreasonably long time - why did he do that? (Interview with Arvid Carlsson in Healy, 1998a)

The 1957 paper on platelets, and the importance of Hillarp in Carlsson's later works, suggest they may have played an important role in his intuition about the importance of catecholamines. However we should keep some healthy skepticism from a posteriori narratives of discovery, more so when narrated in the first person.

Carlsson was a foreigner with no experience in psychopharmacology. What exactly led him to see something that Brodie's sophisticated team was unaware of and had downplayed? According to Carlsson, Brodie was too invested in Gaddum's theories, and too focused on serotonin, to admit the possibility of alternative mechanisms for reserpine's action. And it would be exactly Carlsson, the young pupil, to "shatter" Brodie's theory leaving him "very disappointed" (Interview with Julius Axelrod in Healy, 1998a, p. 44).

On his return to Sweden, through a series of works with Nils Hillarp, but also Rosengren and Bertler, Carlsson, and the Lund team proposed that reserpine caused a depletion of noradrenaline in several biological tissues. This sequence of works ends in an article published in Nature (Carlsson, Lindqvist, & Magnusson, 1957), that tried to definitely

resolve the puzzle- the clinical effects of reserpine resulted from its action on serotonin (as Brodie said), or from the depletion of catecholamines (which the Swedes were increasingly illustrating).

To understand which would be the main factor in reserpine action, 16 hours after the injection of reserpine to a group of mice, when they were already presenting neuroleptic motor symptoms, mice were given 5 - hydroxytriptophan (precursor of serotonin) and 3,4 dihydroxyphenylalanine (the important substance called Levodopa- precursor of catecholamines - adrenaline, noradrenaline and dopamine)). While 5-hydroxytryptophan did not have any consequence in the mice, levodopa would have an effect described as surprising. This short article served to bury Brodie's theory. The clinical effects of reserpine, namely neuroleptic motor symptoms, were reversed by the precursor of catecholamines and therefore would probably derive from the action of reserpine on catecholamines and not on serotonin as Brodie believed (Carlsson, Lindqvist, et al., 1957).

When returning from Bethesda to Lund, Carlsson immediately transformed Brodie's language around the hypothesis. From “serotonin release”, the term used by Brodie to talk about serotonin liberation from intracelular storage, Carlsson preferred the expression “serotonin depletion”. This language change denoted, in fact, the abandonment of Gaddum’s original theory. While the term release suggested an increase in biological activity despite the quantitative loss of the substance, as Brodie preferred to think, the term depletion no longer assumed only the loss of serotonin, but also the decrease in its biological activity.

Carlsson's team had already been promoting catecholamines’ importance (and among them dopamine), but it is in the 1957 paper that catecholamines emerge as more important than serotonin. Levodopa’s ability to reverse reserpine-induced neuroleptization was highly suggestive of the emerging importance of catecholamines. Moreover, being able to reverse parkinsonism caused by reserpine, a bright future was outlined for levodopa as a drug with possible application in Parkinson's disease (Hornykiewicz, 2010). As we can see here, it was psychiatric drugs, namely reserpine, seen as an experimental model of parkinsonism, that opened and illuminated new therapeutic paths for Parkinson's disease.

The following year, the Lund team, in this case Bertler and Rosengren, took the next step in this research. Bertler and Rosengren were graduate students preparing their theses under Carlsson's guidance ("Arvid Carlsson," 1999). Examining brains of several different

mammals with fluorometric techniques (Carlsson had purchased a spectrophotofluorometer when returning from Bethesda), they identified a heterogeneous spread of dopamine, with a preferential location in the striatum. This peculiar distribution - different from other catecholamines - suggested dopamine had a functional role, and wasn't only a catecholamine precursor (Bertler & Rosengren, 1959).

Dopamine asserted itself as a substance, as an agent of autonomous value and likely clinical relevance, precisely through this unique anatomical distribution. The differentiated pattern suggested dopamine had an action of its own. Its accumulation in the striatum thus appeared very early in the history of dopamine, and is inseparable from its emergence as a substance. The role of the striatum in extrapyramidal motor symptoms, and parkinsonism, had already been referred to multiple times (Goetz, 2011). If reserpine caused a parkinsonian syndrome, then possibly the drug could be acting in this striatum's dopamine. This was more plausible even when we consider that L-DOPA administration alleviated parkinsonic symptoms (Carlsson, Lindqvist, et al., 1957).

Ronald Kuntzman had shared the laboratory with Carlsson at the National Institute of Health in 1955, and on the occasion of Carlsson's death, he recounted a surprising memory. Kuntzman mentioned that, when he was at Bethesda, Carlsson already entertained the idea that dopamine would have a function of its own and wasn't just a precursor of norepinephrine (Kuntzman, 2018).

This is surprising, especially considering that the very presence of dopamine in the mammalian brain would only be demonstrated two years later (Montagu, 1957).[70] All memories are present constructions, gazing back, and perhaps we can interpret this recollection in light of this movement. Given the importance of dopamine in Carlsson's later career, namely the Nobel Prize, it is perhaps not surprising that Kuntzman's memory attributes this extemporaneous insight to him, prior to empirical data.

Even so, we cannot exclude the possibility that Carlsson, still at the NIH, in the summer of 1955, already understood the importance of catecholamines, and suspected a specific function for dopamine. If that was the case, it would be theoretical knowledge, or intuition, prior to most laboratory investigations. Dopamine was constructed as an actor, as an

---

[70] Carlsson argues that Montagu's compound "X" generally viewed as the first identification of dopamine in the brain (e.g. Hornykiewicz, 2006) is more likely to be a mixture of several different compounds, and the Swedish team should also be recognised for identifying brain's dopamine ("Arvid Carlsson," 1999)

element capable of modifying brain function, in this short time period and this precise geographical location: Sweden between 1957 and 1959. Kuntzman proposes that it already existed, as a concept, as an intuition in Carlsson's mind, and the laboratory process was a way of revealing, of realising this idea. Improbable as it is, we can see in it another example of neurosciences' knowledge advancing hesitantly between theoretical intuitions, research traditions, paradigms and laboratory processes.

Bertler and Rosengren (1959) tied up the loose ends of this research. The "new" substances were increasingly finding a function of mediation, even though the term neurotransmitter or even neurohumoral agent rarely appears in the published paper. That function was being built through two sources of information: the way they might be affected by psychopharmaceuticals and their neuroanatomical location. This article made a bridge between these two instruments, combining anatomical and pharmacodynamic data. The article specified and located the action of reserpine, reaffirming dopamine as the main element of its mechanism of action - these arguments would be fundamental years later in the elaboration of the dopamine hypothesis for schizophrenia. Van Rossum was familiar with the Swedish team's work, and cites the article by Bertler and Rosengren in his seminal paper proposing the dopamine hypothesis (van Rossum, 1966a).

Through Bertler and Rosenberg's paper, reserpine's parkinsonic effects became more clearly associated with dopamine's depletion in the striatum. However, there was no suggestion that this mechanism was part of an antipsychotic therapeutic action, let alone that schizophrenia could be in relation with dopamine's biological action. The dopamine hypothesis would emerge only years later, but the pieces of the puzzle were beginning to be assembled.

The work of the Swedish scientists, who circulated around Carlsson and Hillarp, between Lund and Stockholm was laying the ground for van Rossum's work. It is difficult to attribute the exact authorship of each scientific proposition among this group. At Hillarp's insistence hierarchy was ignored, and the relative importance of each individual contribution was neglected. The articles were most often signed by several hands and had the authors distributed in alphabetical order. Carlsson, himself granted with a Nobel Prize, recognised the importance for his career of having his name starting with a 'C'. Being at the beginning of

the alphabet, he was often the first element in the authors' order (Interview with Arvid Carlsson in Healy, 1998a, p. 59).

Hornykiewicz and Ehringer, from the Pharmacologischen Institute, at the University of Vienna, were strongly influenced by Bertler and Rosengren's paper. Later Hornykiewicz (2008) would describe it as "one of the most important events triggering our study". Its main conclusion that specific concentration of dopamine in striatum was a sign of possible dopamine involvement in Parkinson disease inspired the Austrians to study dopamine distribution in post-mortem human brains. They used 17 brains, including 6 brains from patients with documented Parkinsonism - 4 with post-encephalitic Parkinson and 2 with idiopathic Parkinson. The article describing this investigation, "Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramine)" (Ehringer & Hornykiewicz, 1960), would also be an important reference in van Rossum's work (1966a). Requiring a chemical definition, unlike noradrenaline, the chosen title is revealing of dopamine's novelty, and the mystery that surrounded it. The results of this study were dramatic. Brains of patients with post-encephalitic parkinsonism presented a large decrease in dopamine concentration, especially in the caudate nucleus and putamen. This decrease persisted in patients with idiopathic parkinsonism, although to a lesser extent. Authors found it reasonable to connect clinical presentations of parkinsonism to variable degrees of dopamine decrease. The attribution of a complex disease, which already had not only a well-described natural history, but a concrete neuroanatomical materialisation, to a chemical substance that until recently was unknown to exist in the brain was highly controversial.

The Austrian's post-mortem work brought the human being back to the research process. Patients were mostly neglected by the Swedes in favor of mammals that allowed greater freedom of experimentation and variable control.

In a short timespan, Dopamine emerges on brain biochemistry, with a specific distribution in the striatum, and quickly becomes an important factor in parkinsonism. Although concomitantly (see chapter 3.3.) parkinsonism and schizophrenia already had a long history of antagonism, a dopamine's potential role in psychosis wasn't yet contemplated in these articles (Bertler & Rosengren, 1959; Ehringer & Hornykiewicz, 1960).

Even though, in the early 1960s, reserpine's therapeutic action mechanism was seen as connected to serotonin liberation, or, perhaps increasingly, associated with catecholamines

depletion, other neuroleptics' mechanism of action remained elusive (including chlorpromazine's and haloperidol's) (Baumeister, 2013).

Data available at the time suggested that chlorpromazine did not directly influence brain monoamine levels, but work by the Lund team (Carlsson & Lindqvist, 1963) insisted on a possible link to monoamines. A neuroleptics' direct effect on catecholamines' concentration had already been excluded, so the team designed a complex laboratory procedure to investigate different elements of the neurotransmission process. Brain chemical neurotransmission was becoming more and more the exclusive model of brain function and drug action for the Swedish team, and their insistence on monoamines should be read in this context. Carlsson, in a 2011 personal communication to Professor Baumeister (2013), confirmed that the reasoning behind their 1963's assay relied "entirely" on a model of chemical neurotransmission. It is important to understand that this perspective wasn't widespread within the scientific community at the time. Carlson(1990) described, for example, the extraordinary resistance chemical neurotransmission in the brain encountered at a CIBA symposium on adrenergic mechanisms in London in 1960.

The 1963 experiment included 9 mice previously treated with nialamide (a MAO inhibitor). One hour later several drugs were administered - including haloperidol and chlorpromazine. Catecholamine's concentration, including norepinephrine and dopamine, was calculated, and didn't appear to be influenced by neuroleptics (here called Major tranquillisers). Two other substances were monitored, Normetanephrine and 3-methoxytyramine, both known as catecholamine metabolites, and found to be markedly increased.

Carlsson and Lindqvist explained these results by framing a sophisticated view of neurotransmission and revealing new possible mechanisms of pharmacological action. A neuroleptic induced blockade of monoamine receptors would be the key element. The subsequent increase in metabolites would be due to a compensatory mechanism. Presynaptic neurones would increase catecholamine release when faced with a receptor blockade, with subsequent increase in catecholamine metabolites (Carlsson & Lindqvist, 1963).

The possible existence of substances capable of blocking receptors had been recognised almost since the foundation of the receptor concept itself. J. N. Langley, after proposing the idea of a "receptive substance" in 1905, argued that atropine could connect to

these “receptive substances” in the heart, blocking muscarinic effects. Throughout the first half of the twentieth century, and despite the work of Langley’s students at the Cambridge school of physiology, including Hill, Clark and Gaddum himself, among others, receptors continued to be an interest, more theoretical than practical, of basic pharmacological research (Prüll, Maehle, & Halliwell, 2009, pp. 107-124). In the sixties, the first steps towards the materialisation of its importance began.

As brain chemical neurotransmission was developing, receptors, and receptor theory became fundamental. Carlsson’s work illustrates this point (but so does van Rossum’s). This transition from electrical neurotransmission to chemical neurotransmission, implied a language transformation, with a translation of concepts from the semantic field of mechanics/ physics to the semantic field of biology/reproduction. From Hans Steck’s work (1954) expressions like “appareille mal synchronisé”, the new brain pathology, lay, in the 1960’s, in the seminal connection between transmitter and receptor.

Carlsson and the Lund team, like Brodie and his team in the previous chapter, showed an important tenacity, a persistence in a certain line of investigation beyond what would seem reasonable to others. In Brodie’s view serotonin was the main factor explaining neuroleptic action, even though empirical data pointed in other directions.[71] Similarly for Carlsson, catecholamines, and dopamine in particular, occupied a central role. Although the substances didn’t appear to be quantitatively affected by neuroleptics, the team persisted in their initial intuition – of the importance of catecholamines - by studying their metabolites. Between one team and the other, between Lund and Bethesda, the concept of brain neurotransmission became increasingly, perhaps even exclusively, chemical and gained enormous sophistication.

The work of Carlsson and Lindqvist didn’t propose any pathophysiological mechanism for schizophrenia, and there was no reference to illness or patients. The authors were interested in neurotransmission changes caused by drugs, and what those revealed about the mechanism of neurotransmission itself.

This idea of catecholamine receptor blockage by neuroleptics would be increasingly internalised by neurosciences, in a slow process. While Brodie's work on serotonin peaked around two years after its publication, with a slow decline thereafter, Carlsson's work on chlorpromazine and catecholamines would not peak in citations until 1976 to 1978, 13 to 15

[71] See Chapter 4.1

years later, (Curzon, 1990). This slow but unwavering penetration of “receptor blockade” into the explanatory mechanisms of neuroleptic action goes beyond the temporal scope of this thesis. It suggests that this sophisticated vision of brain chemical neurotransmission faced an initial strong resistance. Sweden, was understood to belong to the periphery of neurosciences, which were still perceived of as centred in Oxford and Bethesda. This is a further sign of the centrifugal vision of scientific production, in which knowledge was created in english speaking countries for consumption in the periphery, as discussed at the outset of this research. It was in those academic and institucional centres that paradigms were founded and big questions were formulated (despite the reality of the internationality and intersectionality of scientific research).

As noted, funding for research projects is critical, it can guide the project’s conceptual orientation, defining the instruments that may be acquired and the researchers selected. In the previous chapter, we described how the NIH's scientific success derived from a stable and growing public funding, generated by a sophisticated political process. In this chapter, where the research was carried out in Sweden, between the 1950s and 1960s, we can find, perhaps with some surprise, the same North American federal budget, now among the sources of funding for the Carlsson and Hillarp teams:“This research was supported by the United States Air Force under Grant No. AF-EOAR 63-14” is frequently found in the end of many published papers.

During the 1960s, the US Air Force financed part of the international scientific research and Sweden was one of the main beneficiaries. In 1966, for example, it was the seventh most benefited country in the world (Services, 1969, p. 1559). One of the main purposes of this fund was to maintain a general knowledge of most basic science developed abroad, specially if it could have practical applications for the US Air Force (as explained by General McNickle deputy chief of staff, research and development, during a US Senate hearing April 1969 (Services, 1969, p. 1557)).

This funding possibly reflected Sweden's importance in the Cold War’s fragile political balance. It also, definitely, demonstrates the United States power in the reshaping of the international post-war scientific community. The military was strongly invested in this civilian industrial-academic complex, perhaps expecting to find useful practical applications

but probably mostly interested in the geopolitical consequences of these new globalised scientific networks.

This kinship between psychiatric clinic, basic academic research, and the pharmaceutical industry was built serving the interests of its main actors. It was also built, as we can now see more clearly, in a certain international formulation shaped by post-war geopolitical interests.

5. Constructing the dopamine hypothesis

Theoretical formulations about schizophrenia's etiology and disease mechanisms have a long history that preceded the development of neuroleptics. Although, as we will see in this chapter, chlorpromazine and reserpine played a fundamental role shaping biochemical theory for years; biological explanations had already explicitly started trending in the years before neuroleptics appeared. Leopold Bellak, in his 1958 review, reported a new "biological renaissance" as an understandable reaction to the expansion of psychoanalysis during the second world war. Many of these theories played with the idea that something in the blood of patients could produce some kind of toxic effect or psychotic symptoms (Bellak, 1958, p. 46).

During the 1940's and 50's this idea of a toxicity in schizophrenic blood kept gaining empirical support. One example is Roland Fischer's *Stress and the Toxicity of Schizophrenic Serum* (1953). Fischer tested the effect of acute schizophrenic serum on larvae of *Xenopus levis* (African clawed frog). Comparing the effect between schizophrenic and normal blood, Fisher found significant differences in toxicity. Interestingly enough, these diferences disappeared under certain meteorological conditions. This toxicity was detected in various settings from plants (Macht, 1949) to tissue culture (Fedoroff, 1956). Schizophrenic blood became capable of killing the seed, killing the larvae, gaining destructive symbolic power. This metabolical auto-intoxication theory, or the idea of a schizophrenogenic substance in blood was very popular (Fabing, 1958). The endotoxin, the chemical substance poisonous to the brain could be the answer to the problem of schizophrenia. There were many candidates from adrenochrome to tryptophan metabolites.

In a 1958 article, Robert Heath and his team from Tulane University in New Orleans, described psychotic symptoms in healthy volunteers after the administration of a strange substance. Taraxein had been isolated in the blood of schizophrenic patients by an obscure (and unreplicated) procedure, two years before. Human volunteers who were injected with taraxein were mostly inmates from state penitentiary, 3 volunteers were schizophrenic patients in remission. Heath emphasises that the first and most consistent symptoms appearing were primary or fundamental (including autism, depersonalisation, and a blank look in patients' eyes). But afterwords secondary symptoms as delusions, or catatonic stupor would develop. In recovering schizophrenics even small doses would produce very intense

reactions (Heath, Martens, Leach, Cohen, & Feigley, 1958). Heath had solved the riddle of schizophrenia, the key lay in the blood, an enigmatic protein extracted by a mysterious procedure. Since October 1955 (so before taraxein) Heath was experimenting with cow's brain septal extract as a treatment for schizophrenia. In 1958 Heath used septal extracts to counteract taraxein in two monkeys (Heath, Leach, Byers, Martens, & Feigley, 1958). These two convictions (taraxein and the role of the septal area) would combine nine years later in a complex theory, that framed schizophrenia as an auto-imune disease, and taraxein as auto-antibodies against the septal region (Heath & Krupp, 1967). No one could replicate Heath's team's work, neither isolating taraxein, nor demonstrating specific anti brain antibodies in schizophrenia (Baumeister, 2011).

Heath and his team's work was incredibly problematic, not only because of the difficulty found in replicating its findings but also due to its methods, objectives and subject selection. The role of African American prisoners has been singled out as being particularly problematic. Twenty years later, Harry Bailey, one of Heath's colleagues described their work in the following terms: " So, in New Orleans where it was cheaper to use niggers than cats, because they were everywhere and cheap experimental animals, there wasn't much working there, the people we have been picking for the operation has (sic) really been at the bottom of the can" (Washington, 2006, p. 357).[72]

The taraxein story is an example of how scientists and their teams can construct/find data to support their convictions, even when all experiments are double-blind and controlled. It is a story of how expert power can affirm itself in a scientific program disregarding ethical boundaries. But the taraxein story is also an example of a scientific community resisting expert authority, critically scrutinising and replicating.

But taraxein wasn't the only endogenous substance suspected of provoking psychotic states, another important theory became known as the transmethylation hypothesis. The historian David Healy considered transmethylation hypothesis the dominant biological explanation for schizophrenia during the 1950's and 1960's. (Healy, 2002, p. 182)

---

[72] Heath's program of deep electric stimulation has also been particularly criticised. From the 1950s to the 1970s, 60 patients were implanted with deep brain electrodes. In one of them electrical stimulation was used to try to change sexual orientation. Critics highlight the lack of scientific data supporting these interventions, and the cruelty in the methods used (Baumeister, 2000)

In “Schizophrenia: a new approach” Humphrey Osmond and John Smythies (1952) described their frustration with the state of affairs concerning the scientific knowledge of the disease, particularly the obscure causation, limited treatment options, and difficulties planning effective research programs that could offer answers in the future. Similarities between mescaline intoxication and schizophrenia were then highlighted, finding parallels in commonalities between the chemical constitution of mescaline and adrenaline (this had already been noted by other authors). The biochemical explanation proposed suggested that during the last stage of cellular synthesis of adrenaline (transmethylation of noradrenaline) a disordered transmethylation could form a compound similar to 3.4-dimethoxyphenylethylamine, known to have catatonic properties – a proposal completed with insights from organic chemist John Harley-Mason

The years following Osmond and Smythies’ article transmethylation hypothesis gave rise to multiple research programs trying to identify and quantify the mysterious substance in blood and urine. With time, the hypothesis changed, integrating negative findings, and proposing new avenues of discovery. In this sense scientific hypotheses sometimes look like living entities, evolving as a way to survive. Nevertheless, during this process they can be quite productive in terms of knowledge construction. For instance, the transmethylation hypothesis, having converged attention towards adrenaline metabolism, may have contributed directly to Julius Axelrod’s work with monoamine re-uptake, for which he later won a Nobel Prize (Healy, 2002, pp. 182-191).

These hypothetical psychogenic substances (that include taraxein and transmethylation) were born from this idea of a kind of endogenous poisoning that came directly from Kraepelin (Noll, 2004)**,** but they were, of course, also strongly influenced by the idea of modelling psychosis, of working with psychedelics and their promised possibility of provoking or manipulating the complex psychotic picture through a compound. If these theories were vastly productive in theoretical knowledge building, their effects on clinical life, on the day to day organisation of psychiatric wards, was, on the contrary, minimal. After the market introduction of neuroleptics, and through their expanding social impact, a new dialogue had to be created between the two distant places of the asylum and the laboratory. Transformations, opportunities and challenges that the neuroleptics had opened up in their empirical use in the asylum needed urgently a theoretical framework to be constructed in

Universities and national laboratories. Brodie and Carlsson's careers were encompassed by this quest. Their aspiration to explain how reserpine, chlorpromazine and haloperidol worked in the asylum took them to a relatively new and growingly complex model of central neurotransmission. From doubly electric to firmly chemical, from mostly serotonin influenced, to the growing recognition of a specific dopamine role. This knowledge building keeps following the same path, from potential mechanisms of drug action, to more ample understandings of global human functioning and this path was closely intertwined with the interests of the pharmaceutical industry. This entailed creating a model of the human mind and of human disease that would be ready and able to welcome new biological technologies (neuroleptics in our case, but also notably anti-depressives). As we have seen, a new complex industrial research merging industry, laboratory, university and hospital, with hybrid financing origines, transferable human protagonists, exchangeable instrumentation and sometimes similar interests, was increasingly imposing itself and reframing practices, reconstructing nosology, remodelling explanations in order to transform psychiatry into a more "natural" science.

Theory was born from this intersection between a drug's therapeutic mechanism and the pathophysiology of the disease. As such, biochemical theory construction in psychiatry is sometimes accused of being hopelessly pharmacocentric (Kendler & Schaffner, 2011), and, as such, reflecting the hybrid interests of its protagonists. Janssen himself estimated that by the end of the sixties, the academic world had produced more than a thousand articles about haloperidol (Valenstein, 1998, p. 36).

One of those theoretical approaches is an interesting example as it came directly from the pharmaceutical industry.

In 1963 G. R. Venning was trying to connect the dots between tranquillising activity and extrapyramidal symptomatology. He was searching for a possible connection between the physiology of the brain and the pharmacology of neuroleptics, trying to localise their action. He proposed that the neuroleptic action on behaviour involved the basal ganglia of the extra-piramidal system, and in that way he tried to materialise Janssen and Haase's agreement about the relation between extrapyramidal side-effects and psychotherapeutic action in neuroanatomy (see chapter 3.5). Finishing the article we can find the following acknowledgement:

I would like to thank Dr. Paul Janssen for his advice amid for drawing my attention to the original observations which form the basis of this hypothesis (Venning, 1963).

Venning was, at the time, medical director at Searle & co. - Janssen had a long relationship with Searle, he had previously visited as an undergraduate (López-Muñoz & Alamo, 2009), and Searle marketed other Janssen medications in the United States (Healy, 2002). Both Venning and Winter had been present in the first haloperidol symposium in Beerse (see chapter 2.7.2). They were the first company to be approached by Janssen proposing market introduction in the United States. Again we can see this link between basic science and comercial interests, as the construction of pathophysiological explanations becomes an important part of the comercial endeavour. Venning's article again reinforces the idea of side-effects as essential to the therapeutical action, moreover localising them in the brain. This materialises this connection, giving us a physical, concrete place, an image we can visualise. This concreteness, this visual quality that neuroanatomy can provide is a particularly effective way of crafting and selling the neurobiological narrative. Nonetheless due to negative results in the first clinical trials, namely the Denber study (1959) (see chapter 3.1), Searle subsequently refused to market haloperidol in the US (Healy, 2002), this being accomplished much later by McNeil Pharmaceuticals. Although psychiatric historical literature is surprisingly imprecise about the moment McNeil pharmaceutical did introduce haloperidol from 1965 (Healy, 2002, p. 124), 1967 (Shorter, 2005, p. 292), or 1969 (Granger & Albu, 2005; López-Muñoz & Alamo, 2009). We would be inclined to place it at 1967, as McNeil laboratories official literature on new drugs was first published September 1967 in Clinical Pharmacology & Therapeutics ("Haloperidol (Haldol)," 1967).[73] Interestingly enough, Venning's paper is the main reference in the mode of action chapter. Anyway, a time-lapse accompanied the continental rift we described in chapter 3.1 and 3.2, when Americans started using haloperidol, Europeans were already using it for 7 to 11 years. It is our opinion this time-lapse reflected itself in the neurochemical pathophysiological explanations of schizophrenia.

It was in Europe, in the Netherlands, in 1965 that the Dutch pharmacologist Jacques van Rossum delineated, for the first time, what is arguably the most influential pathophysiological theory in psychiatry, the dopamine hypothesis for schizophrenia.

---

[73] This can be further corroborated by a reference in a review paper from the University of Miami (Goldstein, Clyde, & Caldwell, 1967).

The last protagonist of our thesis had multiple common characteristics with the first. They were almost the same age, van Rossum (11th April 1930) was born only four years later than Paul Janssen, and merely 75 km from Turnhout, in Berghem, Holland. They spoke more or less the same language (Belgian Flemish being a dialect of standard Dutch). Maybe more surprisingly they entertained the same nostalgic view of the agricultural world. Janssen's grandfather owned a large farm, and he romanticised the farmer's way of thinking. In an interview shortly before he died Janssen said: "I think the decrease in the number of farmers has led to less common sense in the world" (Janssen, 2002). Van Rossum between his many interests, from university research, to anti-doping, to running a private pharmacy, at some point had his own farm with cattle, and sometimes he would come from the farm, still dirty from working in the fields, and teach students classes (Interview with Douwe de Boer, Maastricht, 28th February 2019). This similarity likely reflects the importance of agriculture in Dutch history, but, I think gives us a more complete understanding to how much these two men had in common beyond their interest in pharmacology. We can also look at agriculture in a more symbolic sense, as this men shared a taste for simpler, empirical explanations. Their tastes contrast with the cosmopolitan psychiatric elite of the time, namely the French speaking school. As we have described with Hans Steck 's interest in exotic art and anthropology (chapter 3.3), Jean Delay's interest in literature, Bobon's interest in language and psychopathology (chapter 2.3). Farming could possibly be seen as a way of opposing these intelectual trends, favouring simple, sequential, rational, approaches to science.

Van Rossum's thesis was presented on the 14th March 1958 (one month after haloperidol's synthesis) under the supervising influence of Everhardus Jacobus Ariens. Ariens, who had established the pharmacological institute in Nijmwegen, had greatly contributed to drug-receptor theory through the concept of "intrinsic activity" (Prüll et al., 2009, pp. 120, 123). This concept referred to the drug's ability to effectively promote a response after combining with the receptor. Substances would vary quantitatively in this capacity, importantly contributing to the drug's biological potency (van Rossum, 1958) .

From the beginning van Rossum was interested in pharmacodynamics, specifically drug-receptor interaction, working with Prof. Ariens who had greatly contributed to the field seemed an obvious choice, and a close collaboration followed, although later in life he became rather estranged from his former supervisor. In our interview with his last PHD

student, van Rossum was described with strong words, emphasising his scientific brilliance as well as his personal shortcomings, his social awkwardness, his honesty and his pride. This probably contributed to difficult relations with his peers, and may be a factor in his neglected position in the history of psychiatry (Interview with Douwe de Boer, Maastricht, 28th February 2019). The historian David Healy describes him as an obscure figure (Healy, 2002, p. 207), while another historian of psychiatry, Edward Shorter (2005), doesn't even refer to van Rossum in his extensive historical dictionary.

Pharmacodynamics was the study of structure-action relationships (structure here refers to the chemical, molecular configuration of drugs) and van Rossum was interested in how the drug associated with another hypothetical structure in the human body responsible for triggering the bodily response (the so called receptors). He wondered about how changes in the drugs chemical structure could influence the combination with the receptor, and subsequently prompt response. As we have seen previously in this thesis, although receptor theory was such a complex and thriving scientific field, receptors per se were only hypothetical beings.[74] There had to be a real structure responsible for translating the drug into a physiological response. Even if they were not directly observable, the assumption of their concreteness was a crucial part of receptor theory research. Here, experimental work and theoretical construction were inextricably tied (van Rossum, 1958, pp. 12-58).

Through his whole career, van Rossum was particularly drawn to psychomotor stimulant drugs, specifically amphetamine. Its chemical simplicity allowed for easy laboratory procedures. It was also easy to quantify in human fluids, guaranteeing unlimited experimental possibilities. In the 70 and 80's when stimulant abuse in sports became increasingly recognised as a social problem, van Rossum would become a national reference, and would later even lead an anti-doping laboratory (Interview with Douwe de Boer, Maastricht, 28th February 2019).

In the first chapter of this thesis we briefly overviewed the history of amphetamines, as the medication had been singled out in a posteriori narratives, by Janssen himself, as fundamental in haloperidol construction. Even if this foundational role can be called into

---

[74] Oxford professor W. D. M. Paton (1960) would describe receptors in the following way: "Here is one of the humiliating paradoxes of pharmacology: we believe in "receptor groups": and yet they are still purely hypothetical entities, unseen by eye or microscope, evidenced only by circumstance. We can as yet only study the way they behave, and try to construct plausible models accordingly."

question when we read competing narratives about haloperidol synthesis, the anti-amphetamine tests were present from the beginning, not only in haloperidol's construction, but even in Courvoisier's work with chlorpromazine. In the fifties, one of the key characteristics for newly synthesised substances wishing to be neuroleptics was their capacity to antagonize amphetamines.

In the end of 1957 Brodie's team presented their work raising the possibility that amphetamine acting through catecholamines (specifically norepinephrine) could activate "sympathetehtic centres". It followed, in a way by design, that chlorpromazine (known to antagonize amphetamine) could maybe block this chemical mediators (Brodie & Shore, 1957). van Rossum had visited Brodie in the National Institute of Health in 1960, in the context of a Fulbright travel grant (Pieters & Majerus, 2011) and knew about his work with amphetamines.

Similarly, as with Paul Janssen shortly before he graduated, or Arvid Carlson shortly after finishing his PhD, young European scientists were visiting the United States for relatively short periods. These were probably more networking travels than educational. Their relatively brief duration, and in the case of both van Rossum and Paul Janssen, their multiple US destinations, suggested training was probably a minor factor in such trips.

Two articles, variously published in 1962 and 1964, give us an account of van Rossum's own early works with amphetamines. In collaboration with the Nijmegen University technical center, van Rossum had developed an apparatus able to register cumulative locomotor activity in mice. The instrument included light beams on an animal cage and photoelectric cells whose output were connected to a cumulative recorder. This apparatus objective and standard observation of the spontaneous movement of mice through time enabled him to build time-response and drug response-curves to psycho-motor stimulants. Those would become important assets in his later work on the mechanism of action of central stimulants (van Rossum, van Amerom, et al., 1962) . The complex apparatus served a simple goal but its mechanisation, and its imperviousness to the observers subjective dispositions enabled the design of clean cut curves, that the inventors wished were epistemologically stable and reproducible.

In his 1962 article, published with van der Schoot and Hurkmans, van Rossum explored the differences between amphetamine and cocaine pharmacodynamics.

Amphetamines and catecholamines (specifically noradrenaline and dopamine), were seen as very similar structurally.[75] This similarity suggested that amphetamines could maybe mimic catecholamines action in the brain combining directly with catecholamine's receptors. Cocaine on the contrary seemed to be very different structurally from both amphetamines and catecholamines. Its mechanism for acting in the brain should then be different. One reasonable mechanism of action could be an indirect stimulant effect - acting on the receptors through the release of catecholamines instead of acting directly. van Rossum's team used its cumulative movement recorder to experiment with reserpine, strongly suggesting this was the case. Reserpine effect of catecholamine depletion was by then well understood (see chapter 4.1.). When reserpinized mice were given amphetamine, the substance replaced depleted catecholamines and the psychomotor stimulant response was still observed. But when reserpinized mice were given cocaine, stimulant response didn't emerge. this was seen as "proof" of the indirect action of cocaine (van Rossum, van der Schoot, & Hurkmans, 1962). In 1962, reserpine was still having a major role in the understanding of neurotransmission. The idea that it depleted neurotransmitters opened up exploratory experimentation of neurotransmission models, namely finding substances that directly interacted with our mysterious receptors.

In the 1964 article with Hurkmans, using a cage similar to the one he had standardised in his 1962 article, a much more complex classification of psychomotor stimulant mechanism of action emerges. Four different mechanisms were proposed,[76] but more importantly dopamine, instead of noradrenaline, started being recognised as the main catecholamine involved.

Indirect evidence for this privileged dopamine role in the psychostimulant effect over neurotransmission existed already, coming from essentially two different origins.

The first of these was neurochemical – that is to say, the heterogenous distribution of dopamine in the brain. Carlsson's students, Bertler and Rosengren, had identified much higher concentrations of dopamine in the extrapiramidal system, namely the corpus striatum

---

[75] He would later rather emphasise a structural resemblance between amphetamine and dopamine in contrast with noradrenaline (van Rossum, 1966).

[76] The four different mechanisms of action proposed included: Acting directly on receptors (like amphetamine and derivatives), acting through the release of stored catecholamines (benzylamphetamines and analogous), acting after decarboxylation (alpha-metylmetatyrosine). Cocaine could act by preventing uptake of released catecholamines or by releasing catecholamines by mobile stores (van Rossum & Hurkmans, 1964) .

(see chapter 4.2). Dopamine's preferential location was highly suggestive of its autonomous role in brain function (in detriment of a limited role as a percursor, as was previously understood) (Bertler & Rosengren, 1959). This finding was almost concomitantly reproduced in human brains by the Japanese team from Osaka University. Dopamine was essentially concentrated in the subcortical nuclei, part of the extrapiramidal system (Sano et al., 1959).[77]

The second indirect evidence was clinical (or neurological) - as seen in the therapeutic effect of levodopa in patients with Akinesia. As we had seen in the last chapter, since 1957 it had been shown by the Swedish that levodopa (3,4 dihydroxyphenylalanina) was able to reverse neuroleptization in reserpinized animals., and not 5 -hydroxytriptophan (serotonin percursor) (Carlsson, Lindqvist, et al., 1957). This had taken the catecholamines to center stage of brain neurochemistry but also opened up pharmachotherapeutical possibilities. Oleh Hornykiewicz was a researcher from Viena University, who had been working with dopamine since his postgraduate international experience at Oxford. In 1961, he convinced the reluctant neurologist Walter Birkmayer,[78] from the Viena geriatric hospital in Lainz, to jointly develop a trial of levodopa in patients with parkinsonism. The "patient material", as the authors refer to the subjects of the experiment, included 20 inmates suffering from post-encephalitic parkinsonism, arteriosclerotic Parkinson or Parkinson disease. Doses up to 150mg were injected intravenously with impressive clinical effects, notably the complete abolition of akinesia (Birkmayer & Horrnykiewicz, 1961). Birkmayer and Hornykiewicz published in November 1961, but since the April of that year Andre Barbeau had been experimenting with oral doses of levodopa. An article detailing the results of the trial was rejected by *Neurology*, a choice for which its director would later apologize (Goulet, n. d.). The history of neurosciences sometimes neglects the contributions of the French Canadians (e.g., Lees, Tolosa, & Olanow, 2015). This neglect maybe stems from the inicial scepticism in relation to

77 Bertler and Rosengren is dated to August 27th 1958 and was published the January 15th 1959, Sano et al. was received for publication only January 26th, 1959. Isamu Sano had completed his undergraduate medical studies in Osaka, and part of his post-graduate studies in continental Europe (Germany). He would be the first to report specific dopamine reduction in a Parkinson's disease patient's brain, and to treat patients with D,L-Dopa. These experiments, reported in an article from 1960 published in Japanese, would be generally overlooked (Foley, 2000).

78 Before his work in Parkinson's disease Walter Birkmayer had a disturbing political past. He belonged to the SS and was a dedicated Nazi party.member, promoting the spread of Nazi forced sterilisation programs and admonishing parkinsonian patients not to reproduce. (Czech & Zeidman, 2014)

pharmacological interventions in Parkinson disease in general, but maybe also from the French Canadians peripheral position**.**

These almost simultaneous parallel works - the Swedish and the Japanese on one side, the Austrian and the French Canadians on the other, highlights the growing international research activity, where scientific information was shared more effectively, and arguably faster. Scientific meetings, many of them sponsored by the pharmaceutical industry, and medical journals, that had also a close relationship with the comercial interests, were certainly important factors in this post war networking.

> From neurochemical and neurological findings it becomes obvious that psychomotor stimulant drugs may increase locomotor activity by interaction with receptors for dopamine in nuclei of the extrapyramidal system. (van Rossum & Hurkmans, 1964)

This phrase synthesises one of the principal conclusions of van Rossum and Hurkmans article. Beyond doubt, not only dopamine, but dopamine receptors and specifically those residing in the extrapyramidal system became the central explanation for psychostimulant action. These mysterious entities - the receptors- were being understood in a very concrete and even localised manner. Neurotransmission seems to be understood in a firmly chemical, almost contemporary fashion. Acting on dopamine or directly trough receptor interaction, from 1962 to the 1964 article, we can see not only the growing complexity and sophistication of the model, but also the specificity of dopamine receptors and their placement characterisation in the extrapiramidal system. These were still very contested conclusions, and we can find in the expression “becomes obvious”, more than a recognitions of simplicity, a sign of the personality traits Douwe de Boer, van Rossum’s last PhD student, talked about in our interview. Van Rossum bestowed an assortment of arrogance and brilliance. Although dopamine was gaining importance in the global stage, it was still not internationally recognised that interaction with dopamine receptors was the sole, or principal, mechanism of action of psychostimulant drugs.

The above sentence is also very similar to the first sentence of the article where van Rossum exposes the dopamine hypothesis:

> Evidence has accumulated recently that psychomotor stimulant drugs such as dexamphetamine act by virtue of activation of dopamine receptors in the central nervous system. (van Rossum, 1966a)

"The significance of dopamine-receptor blockade for the action of neuroleptic drugs" was published on April the 1st in 1966 in the *Archives internationales de pharmacodynamie et de therapie*, but the main idea had already been presented in the joint meeting of the Belgian and Dutch physiological and pharmacological societies, in Amsterdam, November 6, 1965. The Belgian physiological and pharmacological society had anual meetings since its founding in 1947, many were joint meetings with foreign societies. Its connection to Janssen pharmaceuticals was maybe inevitable, considering the enormous success of Janssen's enterprise and the small scale of the country. One of the society's meetings was even held in Beerse, and the reports would be systematically published in the *Archives internationales de pharmacodynamie et de therapie*. The *Archives* was one of the longest-lived pharmacological journals from 1894 to 1996. founded by French physiologist, Marcel Eugène Émile Gley and a Belgian pharmacologist Jean-François Heymans. In the beginning this was mostly published in French, but by the mid sixties the english language already dominated an important part of the works published (Starke, 1998).

In nine pages van Rossum explains the empirical data that supports his hypothesis. The latter can be divided in two separate but subordinate arguments. The pharmacological hypothesis - wherein neuroleptics work by blocking dopamine receptors, and the etiological hypothesis - which states schizophrenia could then be dependent on the overstimulation of these dopamine receptors.

During this thesis, we have been following most of the data presented by van Rossum, that we can now divide in two simple conceptual directions: one that goes from Bertler and Rosengren (1959) (concerning dopamine in extrapiramidal system), to Hornykiewicz and Birkmayer (1961) (Levodopa treating Parkinson in the extrapiramidal system) to van Rossum and Hurkmans (1964) (amphetamine acts through dopamine receptors in the extrapiramidal system) and finally the development of neuroleptics as amphetamine blockers (notably haloperidol). Another conceptual direction stems from haloperidol's construction by Paul Janssen as a cataleptic, the formation of the "anti-schizophrenic" drug during haloperidol's introduction in clinical practice, and Janssen and Haase's proposed equivalence between catalepsy (extrapiramidal side effects) and "anti-schizophrenic activity" (1965).

This is an artificial division, but through it we can understand how the first line of thought produces the mechanism of action of neuroleptics hypothesis, and the second line of

thought justifies implicating schizophrenia's etiology. In van Rossum's text we can identify both lines of reasoning exposed as a linear argument, without contention and without controversy, which, in turn, perhaps even reflects a vision of science as a body of knowledge that advances inexorably and logically directed toward the future. A linear progressive science would be a simplistic approach, as science is rich with alternative views, and conflicting results. This optical illusion of simplicity and linearity is maybe further reinforced by our own narrative structure. Our starting point, here, is van Rossum 1966 text detailing the experiments and theories that contributed to the dopamine hypothesis. The works cited, concepts used, protagonists referenced have been retold in a mostly chronologically manner starting in chapter 2.1 with the construction of haloperidol. As this progressive narrative emerges, during our thesis, we should remind ourselves that this is still an historic work. As such, our retrospective look is inexorably destined to identify patterns and conceptual directions, that could answer our inicial questions in the midst of alternative explanations, and disparate experimental results.

Despite van Rossum's exposed certainties, researchers entertained, for example, different explanations for psychostimulant's mechanism of action. The role of other catecholamines including noradrenaline were being highlighted (Stein, 1966) and even beyond the growing neurotransmitter field, "totally different biochemical processes" were still being explored at the time (Sanan & Vogt, 1962). One notable example was related to cellular energy metabolism in the brain, and studies that seemed to show that amphetamine and related compounds increased brain ATP levels (through synthesis) reinforced this hypothesis (Lewis & Van Petten, 1962).

van Rossum's major influences comprised the Swedish (Arvid Carlsson and his students), the French-Canadian (Barbeau and Sourkes), and the Austrian (Hornykievicz and Birkmayer), but also, and maybe foremost, Paul Janssen, forerunners to his own research and eventual hypothesis (that is our primary concern in this study).

The Swedes, including Carlsson, had been extensively working with catecholamines, and dopamine in particular (see chapter 4.2). It is not surprising that their work is frequently referenced by van Rossum. The classical paper authored by Carlsson's students, Bertler and Rosengren (1959) is cited, underscoring the relevant role of dopamine's heterogeneous brain distribution. This very specific disposition was later further substantiated by the nigrostriatal

pathway reflecting the groundbreaking histochemical work being done in Sweden and reifying dopamine's importance in a neuroanatomical structure (Andén et al., 1964).

One notable absence is Carlsson and Lindqvist's "Effect of Chlorpromazine or Haloperidol on Formation of 3-Methoxytyramine and Normetanephrine in Mouse Brain" (1963). As we have seen in chapter 4.2, the authors proposed that neuroleptics work by blockade of monoaminergic receptors.[79] This is sometimes referred to as the key "discovery" for the understanding of chlorpromazine and haloperidol's mode of action (Gründer & Cumming, 2016; Healy, 2002, p. 207; Howes & Kapur, 2009). Carlsson himself describes it as the basis for the dopamine hypothesis of schizophrenia ("Arvid Carlsson," 1999). Its absence from van Rossum's article therefore merits questioning. Some authors, notably Curzon (1990), highlighted the delayed recognition of Carlsson and Lindqvist's paper. Its inicial invisibility has been explained by the lack of interest in monoamine receptors in the early 1960's or by the papers generic conclusion (Baumeister & Francis, 2002). In this context maybe van Rossum simply hadn't read it. Another, possibly more plausible, explanation for this absence is that it offset the main argument of van Rossum's paper: the primacy of dopamine in schizophrenia and its treatment. Carlsson's paper still emphasises all brain monoamines including noradrenaline and serotonin. Although it shared the same sophisticated view of neurotransmission it didn't really serve to advance van Rossum's main conclusions and therefore may have been omitted.

One important allusion present in van Rossum's paper is the idea of an antagonism between Parkinson's disease and schizophrenia. The capacity for encephalitis lethargica to reverse the clinical features of dementia praecox was a well known mysterious clinical feature that had been described in classical literature, namely by Hans Steck (1931), and gained relevance in 1950's when neuroleptic's parkinsonian symptoms were identified (see chapter 3.3). This classical allusion endows the dopamine hypothesis with historical grounding. It's fundamental for any new idea in science to try to clarify unexplained renowned data. If the symptoms of Parkinson's disease depend on a decrease of dopamine activity in the extrapiramidal system (as was progressively understood), and schizophrenia was an excess of dopaminergic activity in the same system (as the dopamine hypothesis

---

[79] This hypothesis was grounded on data showing accumulation of catecholamine metabolites in the mouse's brain after neuroleptic administration (chlorpromazine and haloperidol) (Carlsson & Lindqvist, 1963).

suggests), then the diseases' clinical and behavioural effects should be complete opposites. The capacity of the dopamine hypothesis to interpret a historic clinical question is a first demonstration of its unique explaining power.

Paul Janssen's influence in van Rossum's work is remarkable. 3 of the 35 cited references were authored by Janssen (almost 10%). This would be maybe frowned upon today. An academic article exposing for the first time a new etiological hypothesis for a concerning disease cited the leader of an important pharmaceutical enterprise multiple times. As the industrial-academic complex in psychiatric research developed in the next decades, these crucial relationships persist, but become more discreet. The 3 Janssen references included in the text were: "Is it Possible to Predict the Clinical Effects of Neuroleptic Drugs (Major Tranquillizers) from Animal Data?"(Janssen, Niemegeers, & Schellekens, 1965), Personal communication (Janssen, 1965), and *The action of neuroleptics* (Haase & Janssen, 1965).

"Is it Possible to Predict the Clinical Effects of Neuroleptic Drugs (Major Tranquillizers) from Animal Data?" is essentially another detailed description of the animal testing Janssen's laboratory had used in the last decade, now applied to 40 different neuroleptic drugs - including butyrophenones, phenothiazines, reserpine and related drugs. The results were individually and systematically presented in a complex graphical structure. The article is grounded in an empirical atheoretical appearance, but the changing psychiatric paradigma are also well represented. In fact, in its first paragraph we can identify the major trends in psychiatry that we have been following during this thesis. The two major transitions were the transformation of neuroleptics in antipsychotics, and in an almost concomitant and parallel fashion – the paranoidization of schizophrenia.

In the paper, agitation and disruptive behaviour is still highlighted as the main usefulness of neuroleptics, even if relief of psychotic symptoms are clearly mentioned. More "neurotic" symptoms as anxiety or depressed mood are also referred to but with a clearly minor emphasis in contrast with earlier literature. In these descriptions we can maybe identify an intermediate stage between an initially very large spectre of disorders in which neuroleptics were considered, to a much more specific "antipsychotic" action, whose concept was emerging exactly during the 60's. Contributing to this new idea was the introduction of haloperidol, early on with Pacquay's studies (see chapter 2.6). Nevertheless, for the concept

of antipsychotics to be finally reified, and able to impose itself in a still suspicious psychiatric community, it needed a specific mechanism of action in the brain that could support this complex idea. The dopamine hypothesis would be a key player in this process.

However, in Janssen's article another fundamental transition seemed, on the contrary, to be almost complete. As the authors create the equivalence between psychotic symptoms and hallucinations and delusions, schizophrenia's transition from a global disorder of the self to a more specific paranoid symptoms disease, seems to have been achieved. The route from Bleuler's complex concept to a simplified disease, inspired by Schneider's work, seems to have arrived at its destination (for more see chapter 2.6).

The second Paul Janssen reference in van Rossum's article is to a personal communication in 1966, this might mean that private correspondence was exchanged between Janssen and van Rossum, and implies there may have been a personal relationship between the two, even before the dopamine hypothesis was proposed.

Finally, the third reference is Janssen and Haase collaborative work: *The action of neuroleptic drugs* (1965). In chapter 3.5, we have already extensively detailed Hans-Joachim Haase's thesis, famously supported by Paul Janssen in the work they published together. Their central idea was the equivalence between psychic activity of neuroleptics, and motor extrapiramidal signs. The mechanism of action of neuroleptic drugs inexorably produced the two phenomena side-by side, in a dose dependent manner. This correlation re-emerged in the van Rossum article, and was seen as confirmation of the dopamine hypothesis.

> An implication of the present hypothesis of dopamine receptor blockade by the neuroleptics is that their parkinsonoid cannot be disconnected from the neuroleptic action. Actually the catalepsia test in animals is a suitable test procedure for the evaluation of neuroleptic agents. (van Rossum, 1966a)

In this phrase, we can again feel some of van Rossum scientific hubris. He presents Haase's thesis as an inescapable consequence of his own proposed idea. Furthermore, he retrospectively vindicates and racionalizes Paul Janssen's development of haloperidol (and other butyrophenones). Still, even if presented as an implication, as in this quote, it seems to me increasingly clear that behind the idea that schizophrenia could be an overstimulation of dopamine receptors, and that neuroleptics could work by blocking this overstimulation, lies Paul Janssen's work. This suggestion prompts certain questions, namely: What provokes a certain thought? Where does an idea come from? How are the logical consequences of a

thesis to reinforce its main argument? Here, probably, the main argument was based on its logical consequences. The pivotal role of Janssen's construction of haloperidol can be further substantiated in a letter from van Rossum to the historian Alain Baumeister, dated 13th April 2001:

> In the laboratory of P. Janssen (Belgium) a blockade of amphetamines stimulation's was used to evaluate neuroleptic drugs. From this the idea developed that the therapeutic effect of neuroleptics in treatment of schizophrenia is due to blockade of DA receptors in the brain. (van Rossum's correspondence cited in Alan A. Baumeister & Francis, 2002)

The simplicity of this explanation reveals the intelectual debt van Rossum's dopamine hypothesis owes to Paul Janssen. The role neuroleptic amphetamine antagonism (and haloperidol development) had played in van Rossum theory has been amply recognised in the literature (Baumeister & Francis, 2002; López-Muñoz & Alamo, 2009), where it is described as the central percursor for the dopamine hypothesis, and consequently for the rise of biological psychiatry.

In the same year that the dopamine hypothesis was published, Janssen and van Rossum met personally when van Rossum was presenting his main conclusions at the fifth international congress of the International College of Neuropsychopharmacology (CINP).

A fabulous photo of the congress dinner is shown in Appendix B, figure 8, although the image quality is lacking. A panoramic view of the dinner room at the Sheraton-Park Hotel impresses first by its size, as it records forty round tables, each seating 8 to 10 guests. Looking at the image, we see a gala crowd in evening attire - men are formally dressed, in jackets and ties, women are in evening gowns. At the time the photograph was taken, almost all seem to have stoped talking, drinking or eating, and are looking at us for a fleeting moment. Most of these people are dead now. In the front table Heinz Lehman (from the program committee), and Jean Delay (the president of the meeting's executive committee) are easily recognised. In the latter's presidential address one phrase captured the mood of this event: "Clinical psychopharmacology forces a psychiatrist to think physiologically" (Delay, 1966 as cited in J. Elkes, 1988). The new and sprawling theory being constructed was to change the clinician's way of thinking. The emerging concepts of neurotransmission were to have concrete consequences in the practice of psychiatry.

Joel Elkes' memories of this meeting highlights more personal features, including side visits to labs and clinical facilities, the late night suppers, and musical moments:

> As befits our field, there was lively interaction between the theoretical and the applied, between academia and clinical practice, between practitioners and industry, and between east and west.(Elkes, 1988, p. 18)

These meetings were a way of personally meeting, sharing not only theory and data (most of which we can still access in published papers) but also jokes, stories, personal ambitions and animosities. Those compose a context that is now mostly lost but that this photo captures amazingly well. This context is also part of the scientific construction. In it, privileged personal relationships flourish, as others are set aside. In the hundreds of people present we can't really identify any person of colour. As Elkes puts it, these were opportunities for academia, clinical practice and industry to come together, and construct a promising future, that included new compounds, simpler nosology, and sophisticated clinical trials. That evening, Janssen and van Rossum shared a dinner table (Pieters & Majerus, 2011), and we can maybe identify their figures in the back, center right, close to the stairs.

Till the 1970's van Rossum's dopamine hypothesis is globally seen as having been mostly neglected in the academic mainstream. The historian David Healy distinctively described this indifference with the expression "But the world took no notice" (2002, p. 209). We should be skeptical of this more categorical dismissal. As we have seen throughout this thesis there were important differences between continental Europe and the United States that were structural to both the research and practice of psychiatry. These differences included, for example, clinical trial logistics that in Europe were connected to universities, while in the United States were allocated to state psychiatric hospitals. Other examples of this Atlantic wedge include the dynamics of production of new compounds, and the proximity between pharmaceutical industry and the academy. Haloperidol's late entry in the United States, due to a difficult clinical reception (see chapter 3.1.) and patent disputes, reflected, and further risked growing, this divide. In this context, continental ideas might have been initially neglected in anglophone countries but still prospered in European universities, and find ground in the sprawling continental psychopharmaceutical industry.

Science also needs a certain concreteness in order to allow abstract concepts and hypotheses to be visualised. For all his logical theorising, van Rossum's grounding in historic and recent research was lacking empirical data. Or maybe, we can say it lacked realness, it lacked a material quality. Receptors, as we have seen, were hypothetical beings. No one had seen them, no one had isolated them, no one knew their exact composition. They were a

concept used to explain the way drugs work in the body. Talking about the blocking of neurone receptors, as a way of changing behaviour was still, in a sense, very abstract.

Perhaps more general social conditions and broader psychiatric trends weren't completely ready to embrace the new simple biological explanation. Nosology was in the process of going from the plural schizophrenias to a singular one, as paranoid features became its mainstay. Haloperidol's clinical positioning was a sign of neuroleptic's growing push for an anti-shizophrenic, or at least, an anti-psychotic specificity. Both these conditions were integral to dopamine hypothesis success. van Rossum's argument going from the neuroleptic mechanism of action to the disease pathophysiology (or etiology), inexorably needed both neuroleptic specificity and disease homogeneity to become intelligible. Both concepts were still in development during the 1960's.

Nevertheless we know van Rossum's dopamine hypothesis was at least read by some of the most important protagonists in the neurosciences of the time (e. g. André Barbeau (1969), Marthe Vogt (1969), and the Swedish team (Andén, Corrodi, Fuxe, & Hökfelt, 1967)). Paul Janssen also seems to have been attentive to van Rossum's work, and only one year after their meeting in Washington he references the aforementioned work of van Rossum, in his retrospective review of butyrophenone development (Janssen, 1967, pp. 217,247).

In 1969, our main protagonists met at Liège, the city where haloperidol was first used, for the Semaine interdisciplinaire des neuroleptiques,[80] to agree on the main argument of the dopamine hypothesis. The idea for a long closed meeting (it took a whole week),[81] with all the most important international researchers appears to have been born from the complicity between Paul Janssen and Jean Bobon.

Further consolidating this hybrid origin, is the profile of the person chosen for the organising committee: Andre Pinchard. The event's *secrétaire* was the same young intern to whom Janssen had attributed the first haloperidol administration, and who was, by 1969, a liaison consultant psychiatrist working at both the *clinique universitaire* and at Janssen Pharmaceuticals. Other participants included many of the characters we have been following during these thesis. From Liège came, of course, Jackie Collard and Albert Dresse. Also

---

[80] Interdisciplinary week on neuroleptics

[81] For contrast the fifth international congress of the CINP in Washington, was only 4 days.

invited was the illustrious Belgian psychiatrist Jean Titeca - redactor of *Acta Neurologica et Psychiatrica Belgica* where the papers presented in the first international symposium for haloperidol had been published. The Paris Team included Pierre Deniker and Pierre Pichot. The Americans were also in attendance with Fritz Freyhan (New York), Leo Hollister (Palo Alto), and surprisingly Herman Denber (New York) the man whose disastrous haloperidol trial had jeopardised its American success. The Swedish team that worked with Arvid Carlsson (Nils-Erik Anden and Kjell Fuxe) were present. Other renowned researchers included Thomas A. Ban (Montreal), Philip Bradley (Birmingham), Itoh Hitoshi (Tokyo) and Palle Kristjansen, already present at the first Symposium international sur le haloperidol" (Denmark). More peripheral European clinicians as the Portuguese Barahona Fernandes were also present. In total, a hundred and twenty-one men and three women were invited: the women being, Denise Albe-Fessard (Paris), Françoise Mellerio (Paris) and Alice Leeds (from the N.I.M.H., Maryland).

This was a two-fold event with the more serious academic part settled at Liège, and the more amusing and personal part staged at Janssen's laboratory in Beerse. Researchers' wives were invited and during the day went to see the cosmetics lab while the men visited the pharmacological facilities. This gender divide was mostly unquestioned and naturalised. This presence is also a signifier of the importance of leisure activities in the creation of the personal relations that were so integral to the meeting's key objectives. Women weren't signing papers, or presiding congress tables, but were seen as an important part of the scientific process in the network creation including lobbying and funding (see chapter 4.1). The reception itself was a luxurious party under a big improvised tent, with the personnel masked as Bruegel's characters. One of the persons present described to us the almost Dionysian atmosphere,[82] that can be captured in some of the photographs of the event (see Appendix B Figure 9-12). Despite the comparatively strict dress code, we can't find in these photographs the same formality of the Washington photo. We see participants talking, drinking or singing, and no one stoped to look at the lens. Wine was served in big rustic cups, that the Brueghel 'characters' were diligently refilling. Hitoshi Itoh, a very respectable Japanese researcher from Keio Gijuku University, is seen standing over his chair chanting in his mother tounge. One respectable French professor stood over barrels of wine, and poured

[82] Interview with Christian Mormont, Liège, 27th February 2019

his wine mug over his head. One other psychiatrist, returning home, passed through Liège and found himself in Aix-La -Chapelle completely drunk. This was “phenomenal” - in the words of Christian Mormont, at the time a young psychologist, every big name in psychiatry and neurosciences was singing, and making public declarations.

In one of the photos we can see the VIP table, and find Mme Janssen between Jean Bobon et Pierre Pichot (Appendix B, Figure 11). This can be seen as a symbolic moment marking haloperidol’s success. Its recent introduction in the United States, and growing clinical impact and revenue, was certainly something to commemorate. The arrangement of these figures are striking, particularly as they map onto the history we have outlined. Jean Bobon (symbolising Liège’s pioneering role in haloperidol’s introduction), and Pierre Pichot (representing the prestigious Paris team where neuroleptics had first find its place in psychiatry);in the middle, the sober Mrs Janssen, can be seen representing the powerful industry seducing the academics attention.

The presence of Jacques van Rossum as the leader of the pharmacology round table in this closed event is further indication that van Rossum’s voice was heard, at least in Europe. Participants in the round table were mostly representatives of the more influent pharmaceutical companies with interests in psychiatry, some of them important competitors of Janssen. The list included Max Taeschler (Sandoz), Iver Moller Nielsen (Lundbeck), Louis Julou (Rhone-Poulenc), David Tedeschi (Geigy Pharmaceuticals), and Gunther Stille (Wander Labs). There were also academics Jacques- Robert Boissier (Paris) and Axel Randrup (Denmark) , and clinicians Ib Munkvad (Denmark). If the table’s leader was van Rossum, the table’s main discussant was Paul Janssen.

In the meeting’s proceedings, later published edited by Daniel P. Bobon, Paul Janssen and Jean Bobon, the main conclusion of the Pharmacology round table was clear:

> The most likely mechanism of action of neuroleptic drugs is their competitive antagonism to DA for specific receptors in the brain. (van Rossum et al., 1970, p. 31)

This seems to me a clear evidence of the dopamine hypothesis gaining growing support among the pharmaceutical industry, even if it was having difficulty penetrating mainstream psychiatry.

The close proximity we see between institutional research, clinicians, academics and industry influences strongly demonstrates the new framework upon which psychiatry would develop in the next decade, from simplified nosology to expensive and sophisticated clinical

trials. Common etiological and pathophysiological considerations furnished the common ground, and the shared language that would develop. This meeting, with its two locations, Liège and Beerse, and the dichotomous poles of the public university and private laboratory unites these three different worlds - the clinical personified in Bobon, the comercial conducted by Janssen, and the academic represented by van Rossum. The dopamine hypothesis is the materialisation of these personal relations.

For haloperidol to enter the new and competitive American market implicated local market strategies. Studies from the beginning of the 1970's show that the psychopharmaceutical industry was investing strongly in advertising in medical journals and marketing from medical representatives. At the same time as psychiatry was submitting to strong pressures of professionalisation, from the anti psychiatry movement, the need for explanations based on biological mechanisms of action was becoming stronger. Psychotropics quickly picked up biological novelties to describe drug effects (Hemminki, 1973). Even if the dopamine hypothesis was rising in Europe, it was short of a "laboratory confirmation", Philip Seeman was particularly well placed to find one.

Seeman was married to Mary Seeman, the young psychiatric intern, that replaced Elisabeth Kubler-Ross at the Manhattan state Hospital. His interest in psychiatry came from this marriage (Seeman, 2022) . Since the 1960's he started searching for a biological cause for schizophrenia, and soon he realised that the key to understanding the illness would come from the mechanism of action of neuroleptics (Madras, 2013). This follows the work of van Rossum closely. Seaman knew his research well, and abundantly references it in his papers. Janssen had also followed Seaman's work since the mid-sixties, namely about membrane permeability as a hypothesis for the mechanism of action of neuroleptics (Janssen, 1965). The two, Paul Janssen and Phillip Seeman seem to have developed a personal relationship, a friendship even (Seeman, 2022).

In 1971, just two years after the Interdisciplinary Week on Neuroleptics, haloperidol and Paul Janssen would become key protagonists in Seeman's endeavour. Seeman asked Janssen Pharmaceuticals for radioactive haloperidol for his laboratorial procedures. Janssen sent a sample, but the radioactive level was insufficient. So Seeman asked again and Janssen talked directly with M Winand from IRE Belgique (National Institut Voor Radio-Elementen, Fleurus, Belgium) asking him for the haloperidol needed (Madras, 2013; Seeman, 2010). In

this simple, albeit long, exchange, we can nonetheless see the confluence of academic, comercial and political interests.

Using the new radio-labeled haloperidol Seeman identified what he called with some lack of imagination " the antipsychotic receptor" and would later be known as D2. Moreover, Seeman placed all tested antipsychotics in a potency scale that directly correlates with their capacity to block the D2 receptor (Seeman, Chau-Wong, Tedesco, & Wong, 1975) .

In practice, in Seeman's work, haloperidol was used as the neuroleptic, the representative of class to whom others were compared, and we can imagine that Janssen would be very invested in this perspective.

In Fig 5 of Seeman's seminal paper is a chart comparing IC50 values for the various neuroleptics in blocking the binding of radio-labeled haloperidol with the average clinical doses for controlling schizophrenia. This relation delineated a diagonal and very convincing line. The chart is reminiscent of Haase and Janssen's previous proposals on neuroleptic thresholds, and Haase's tables on neuroleptic potency. It is certainly a visual corollary of Seeman's laboratorial work, but also the physical reification of van Rossum's dopamine hypothesis. The image has demonstrated an important power of persuasion and is sometimes named as one of the factors behind the general acceptance of the dopamine hypothesis.

Paul Janssen would be one of the first people to see this chart. In July 1974,[83] the meeting of the International college of Neuropsychopharmacology (CINP) in Paris was a singular moment in the history of psychiatry. Hanns Hippius was president, Paul Janssen[84] was treasurer, part of the executive committee. The social program included a welcome reception on a warm summer evening in the "Palais Royal" gardens, and a party in " Bois de Boulogne". According to Seaman's (2010) recollections, in this same meeting he warned Solomon Snyder that he could procure himself radio labelled haloperidol for confirmation of his work from the Belgium institute, but most importantly, in the evening reception, he approached Paul Janssen and showed him the aforementioned figure comparing the blocking D2 capacity to neuroleptic potency.

---

[83] Seeman's recollections reference July 1975, but different sources would suggest July 1974 (Ban & Hippius, 2012) .

[84] Janssen would later be president of the CINP from 1980 to 1982 (van Gestel & Schuermans, 1986).

He laughed and said that averaging the clinical doses for each antipsychotic was like averaging all the religions of the world. (Seeman, 2010)

Conclusion

This research set out to contribute to the understanding of the construction process of a very influential idea. The dopamine hypothesis traveled from a local origin in the center of the European continental power to become an international force written in the principal narratives contemporary psychiatry uses to define itself. During our work we understood the diversity of actors in this creation, from geopolitical forces, to changes in the ideological background, from substances, or techniques to human protagonists.

Asking how the dopamine hypothesis was constructed is also asking how does science work? How is scientific knowledge produced? But science isn't a monolithic and uniform activity, on the contrary, it changes over time and space, it changes between disciplines and within the same discipline, it changes between different scientific cultures and within the same culture.

In the last fifty years a picture of science as a value-laden process has emerged. While we perceive hypothesis construction and theory choice as following particular ways of belief formation, we are also progressively accepting some curtailment on objectivity. As values become internal qualities to science, it becomes necessary to examine scientific construction process more as a social endeavour, and less as a progressive assembly of discoveries.

As we looked at psychiatry, and into some extent, neurosciences, during the eight years that preceded the formulation of the dopamine hypothesis, we can see very different paths of knowledge creation. Scientists were working in different settings (from the laboratory to the asylum), with different funding (public, private or both), having different personal ambitions and following different conceptual approaches (e.g. empirical or theoretical). The most blatant discord in this process concerned opposing views of mental illness, and the role medications could or should play in the treatment of the mentally ill. Nevertheless, a new powerful industrial-academic complex growingly appeased this divide. A reframing of the powers at play took a generation of young ambitious scientists, pharmaceutical industry leaders, medical doctors, and psychiatrists, finding common ground and recreating values, theory, practice, career management and patient care.

Contributing to this common reframing of psychiatry was its thriving internationalism. As we have seen, most actors in the history of dopamine and neuroleptics in

general had an international experience as undergraduates or shortly after graduating. Our four main protagonists Paul Janssen, Jacques van Rossum, Hans Joachim Haase and Arvid Carlsson spent some time in the United States of America. Some of these experiences were personally funded, others by the Fulbright program, others still by the pharmaceutical industry.

Joel Elkes, whose 1954 clinical trial of chlorpromazine has been credited as one of the most convincing evidences of the drug's usefulness, had previously (in 1950) travelled to the United States with a Smith Kline and French sponsorship (the company that would later market chlorpromazine in America). Although, as we have seen, according to researcher Michael Shepherd, Joel Elkes' wife Charmian Elkes was actually the main force responsible for the planning of the trial (Interview with Michael Shepherd cited in Healy, 2008, p. 238) .

These international experiences, mostly via the Atlantic, seem to have been a kind of rite of passage, normally before or immediately after graduating, they appear as an important step towards integrating the academy. The young scientists didn't really seem to aspire to a career in a foreign country, their period abroad was generally short and the return to the homeland was originally scheduled. More than acquiring academic knowledge or technical capacity, the more or less short stays suggested the importance of creating a personal network, of understanding the mood of the time, of grasping the worldview from the center of power in the discipline. Their recurring funding through the Fulbright program is an example of the political role the United States played in reframing the international scientific community after the second world war. The industry funding shows to what point the pharmaceutical companies were invested in this new international configuration. Their interests shouldn't be reduced to a simple *quid pro quo*, concerning any specific medication, their funding is so influential exactly because there were normally no clear strings attached. Their impact can be seen in the shaping of the personal network, the determining of various agendas, guiding the central discussion.

This international network was reinforced by international associations, their meetings, congresses and symposia. On their account, our actors continued to meet and share knowledge, perspectives, values, techniques and funding strategies. They nurtured close relationships, friendships even, through correspondence, house visits and drinks. It is during these years that the most important international associations emerge. The CINP

(International College of Neuropsychopharmacology) was founded in 1957 and the ACNP (American college of Neuropsychopharmacology) started in 1961. From the beginning the pharmaceutical industry was an active partner. The CINP first president was a former director of Sandoz (the major Swiss pharmaceutical company) Ernst Rothlin, and Paul Janssen, founder and director of Janssen Pharmaceuticals, would also be president from 1980 to 1982. The pharmaceutical industry routinely paid clinicians and scientists' travel expenses.

International magazines, growingly dominated by the English language, also had a role in the internationalisation of new concepts and technologies. Their editors were part of the same network that was being established. They were at the same dinner-parties, touching shoulders with the academy and the industry. The example of Jean Titeca's (editor of *Acta Neurologica et Psychiatrica Belgica)* invitations to Beerse (both in 1959 and 1969) showed the importance he had for both the academics organising the meetings, and Janssen Pharmaceuticals funding them. The magazines' choice of published content certainly reflected the view of the discipline their editors had acquired in those privileged moments. During this research we could sometimes feel the industry's influence in the magazine's editorial choice, for example when the *Acta Neurologica et Psychiatrica Belgica* chose to publish the entire proceedings for the first Symposium international sur le haloperidol, even though haloperidol had only recently been developed and its future importance could hardly be predicted. *Les feuillets psychiatriques de Liège* are another example of this proximity, sponsored by Janssen Pharmaceuticals, they had a very eclectic set of contributions, from psychoanalysis to psychopharmacology. The industry is said to have had limited direct impact into editorial choices, but the persistent funding streams suggests an interest in forging the internationalisation of the Liège team. *Neurology'*s refusal to publish Andre Barbeau's trials with L-dopa is illuminating in another sense. Considered out of pace with the majority view of Parkinson's disease, the article was rejected. International magazines facilitated easy internationalisation of technologies, and, as such, they held enormous power in shaping what was, and what wasn't, central to the discipline at any given time.

This international network included formal and informal aspects. Examples of both abound during our research. A more formal collaboration can be seen for example in the person of Alfred Pletscher, even though he belonged to the Suisse pharmaceutical giant La Roche, he was working in an American national laboratory (the NIH). More informal

elements in the building of international neuropsychopharmacology were mostly collected from written memories. As an example we can remember Arvid Carlsson's description of how he integrated the National Institute of Health (he asked a local professor, that knew somebody that worked in the NIH and could then recommend him directly to Brodie).

The sprawling industrial-academic complex, formed from this international hybrid process, constituted the new playing field where young scientists had to project their personal and academic ambitions. There they could find mentors and competitors, and sometimes one became another (see, for example, the histories of Brodie and Carlsson, Divry and Bobon, Ariens and van Rossum). There they could find the central theme of the moment, and how it changed during time, but they could also find, in the landscape behind these immediate discoveries and moments, the slow process of major paradigm transformation, to which they were competing to contribute. Their success would rest upon the way their research programs would interact with these mainstream's transitions, but was also dependent on less specific and more personal characteristics. The reasons for choosing Jean Bobon or Herman Denber to conduct the haloperidol trials may still be elusive, but almost certainly personal characteristics played a part. In a more clear example, Carlsson and Brodie's first interaction in the cafeteria seems to have had important consequences for both their personal careers, and the construction of knowledge in neuropsychiatry. Likewise, some of van Rossum's personality traits are sometimes implicated in the disregard to his international position as an historic figure.

Within these less specific factors in the metamorphosis of psychiatry and the rise of neuropsychopharmacology we can speculate, maybe with some petulance, that the profile of our scientists may have changed. We have seen for example, how Steck's interest in exotic art and anthropology framed his theoretical work, and how important language psychopathology was for Jean Bobon, or literature for Jean Delay. These more philosophical and artistically inclined men, gave place to a much more practical generation. van Rossum and Janssen's admiration of agriculture's simplicity is in stark contrast to the earlier philosophical and artistic interests of the key players in this history. This new generation admired common sense. It preferred straightforward clarity to the ambiguous and complex reasonings of psychoanalysis or classical psychopathology. This taste for the elementary would arguably profoundly shape psychiatry, as we have seen. The new mechanistic brain, importing

reasoning strategies and metaphors from biology became understood more easily. All of these factors helped to lay the groundwork for the ever expanding but growingly simple DSM endeavour.

Although the years described in this research are characterised by profound, maybe even paradigmatic, changes, in individual scientists' work, on the contrary, we identified strong elements of continuity. Haase and Steck's work with chlorpromazine was centred not in an empirical trial of efficacy, but in the pursuit of further advancing their previous questions and interests. In Steck's case the subcortical location of psychosis, and in Haase's case the relation between drive and fine motor skills. These hypothesis preceded chlorpromazine's introduction, but it was exactly chlorpromazine's newfound importance that gave relevance to their previous work, which was unrecognised at the time. Other such examples include Brodie's interest in serotonin as the key for schizophrenia, and how it seems to have continued well beyond the laboratory data but inadvertently contributed to the affirmation of neurochemical transmission, or Carlsson and the Swedish team's persistence in the importance of catecholamines to chlorpromazine's mechanism of action, despite initially lacking experimental confirmation, leading them to purpose a receptor blocking mechanism. van Rossum's interest in psychostimulants (and amphetamines) in particular is also a constant in his career, well before the dopamine hypothesis and long afterwards. These scientists curricula or interests seem to place them in unique positions as their research programs become suddenly at the center of the scientific community's attention. They don't seem to be repeatedly changing their interests following the mainstream's fashionable idea (although we have seen examples of that), rather, their personal scientific traditions seemed to cross paths with the presumed center of the ideological complex, which, once formed, gave them voice and recognition.

Some empirical studies in psychiatry, many times considered to be the most innovative and transformational, were also extremely conservative, following established intellectual habits. During my research, I found pivotal moments that seem to radically question the more hegemonic paradigms (in Kuhn's sense), frequently weren't due to analysis of new empirical data, but, on the contrary, the biggest changes seem to be consequence of specific research programs, with more or less rigid theoretical frameworks. These approaches weren't revolutionary but deeply conservative. In our examples, it wasn't

progressive science, the scientific activity more interested in transforming paradigms, that was found to be transformative. Change came from a more conservative science, an activity interested in maintaining research programs even when faced with contradicting empirical data, that was forced to break paradigms. This paradox reflects the precarious balances between conservatism and innovation science is forced to find as an activity that men do together.

During this thesis we have seen the importance of private and public funding in the establishment of the growing industrial-academic complex of psychiatry. Public financing sometimes served national and political interests. The role of the United States Senate in funding research, for example, went beyond national lines showing its capacity and interest in reshaping European post-war scientific community, including psychiatry. But other nations were also invested in their pharmaceutical industry's success, as we have detailed in this thesis when looking at the National Institut Voor Radio-Elementen, in Belgium, who customised the radioactive haloperidol for Philip Seeman, upon a request from Paul Janssen. Beyond the public money, private funding from the pharmaceutical industry growingly penetrated the academic world. We have seen in Liège how universities could become a crossroad of funding sources. Theoretically exclusively publicly financed, the university of Liège had multiple activities explicitly sponsored by Janssen Pharmaceuticals. These included meetings and symposia, publications (*Les feuillets psychiatriques de Liège*), and even staff (André Pinchard worked for both institutions). The hybrid funding certainly created ethical challenges, but were still a far cry from ghostwriting and more pernicious practices developed in the years since (see (E. Shorter, 2021)).

Our research was mostly interested in the main actors in the scientific developments that led to the discovery of haloperidol and the dopamine hypothesis. Those that authored the papers, that occupied institutional positions, those that were portrayed in seminal networking dinner parties. However, we should also say a word about the absentees. The presence of women is rare, both in papers, and scientific meetings. As an example, in the 1969's "Semaine interdisciplinaire des neuroleptiques" a hundred and twenty-one men and three women were invited. Their absence probably followed more general societal barriers for women in public life, but highlights how informal elective affinities may have also contributed to exclude those that didn't belong to the white male privileged position. When

collaborators are chosen in the cafeteria or over drinks, similar social identities may be favoured. In fact, even when women had an important role in the planning of drug trials, history often credits others, as the example of Charmian Elkes shows. Although mostly excluded from the scientific work itself, women sometimes found an important role in networking and funding, as Mary Lasker's impact in the growth of the National Institutes of Health demonstrates. Despite the important Jewish presence, other ethnic minorities were shunned.

During our research we pursued psychiatric knowledge construction through different sceneries. We started at a private pharmaceutical laboratory, perceiving how it flourished into a pharmaceutical empire, through privilege and opportunity. Scientific development was monetised in virtue of a very practical approach to produce new compounds. Almost at the same time, at state funded laboratories, in the United States and in Sweden, both Brodie and Carlson's teams were trying to figure out how these newfound compounds worked. Scientific discovery wasn't directly monetised, but it advanced our actors national and international visibility, it advanced their careers in the academy. Both at Beerse and Bethesda, and at Lund, although understanding schizophrenia was a key part of the research, patients and their illness were completely absent. A product for an exclusively human disease was constructed in a lab with no human subjects and research about the way these drugs work followed the same principle. In both places, objectivity and reproducibility were important goals as methodology was clearly described in published papers. Excluding the human factor helped achieve these goals. Animal models both of schizophrenia and of neuroleptic action were the answer, trying to make a bridge between basic research and clinical practice.

In Belgium we saw the differences between a private clinic and a classical asylum. One seen as a temporary institution with reintegration purposes, the other as a way of reclusion and marginalisation. We have also tracked a psychiatric ward in an American state hospital as it was becoming a psychopharmacological experimental clinic (with successive drug trials), and at the same time trying to transform itself following the ideological principles of "the therapeutic community". Beyond these incredible differences, in the three institutions, cooperation, restraining and silence were still the principal therapeutic objectives during the haloperidol trials.

The dopamine hypothesis was constructed through this interaction - between asylum and laboratory, between the messy power struggles of psychiatric wards, and the clean simple reproducible procedures of the lab. These two distant universes were connected by two common actors: the researchers networks and the drug building processes. As we have described during this thesis, there is a complex process that transforms a substance into a drug. Constructed as compounds in the lab, the substances can be, initially, little more than a chemical identity. Still, some substances, like haloperidol, bring with them an origin story that already suggests therapeutic goals, even if they need to enhance their social characteristics as drugs in order for this to be realised. Processes of clinical validation and promotion - trials- were then developed in the clinics. As compounds increasingly become drugs, affirming therapeutical qualities, changing the asylum's lived experiences and their social organisation, their mechanism of action comes into question. Making their way back to the laboratory, the same drugs were again studied, in order to unravel their newfound mysterious capacities. The laboratories answers would then further enhance the substances therapeutical characteristics. This back and forth between different settings principally served the monetising goals of drug development, but in the process created not only new theory (that would change the understanding of mental illness) but reframe a new structural network of industrials and academics that would rule psychiatry in the decades to follow.

Haloperidol's rich process of becoming a drug was particularly productive in terms of theory building. Only eight years separate Janssen's construction of haloperidol in 1958 with which we started our thesis, and van Rossum's dopamine hypothesis (the latter arguably strongly influenced by Janssen's construction strategy). During this period haloperidol featured in numerous lab experiments, clinical trials, and scientific papers. Its ascension to the role of paradigmatic drug, a drug to which every other neuroleptic was compared, was completed with Seeman's work in the 1970's. Concurrently two major transformative trends were reframing both psychiatry in a wider sense and schizophrenia research more specifically. These changes affect the construct of schizophrenia itself, but also reshape the way we saw and classified the drugs used to manage or treat it. We have shown through this research how haloperidol participates in both these transitions, that together create the conditions for the dopamine hypothesis.

Psychiatric research had a long tradition of identifying symptoms of disordered movement, as we showed through Hans Steck's work, these would be incrementally neglected as neurology and psychiatry consolidated their divorce. Psychiatry would then find an exclusive monopoly in the disordered inner living experience of patients. Schizophrenia would follow a similar path, from a shattered self influencing almost every aspect of human experience, to a list of identifiable symptoms. Kraepelin's conception of dementia praecox had been built from longitudinal observations highlighting a mostly chronic and progressive disease. Bleuler's expansion of the construct kept some of the initial observations. In fact, Bleuler and Kraepelin agreed on a broad, and sometimes heterogeneous, entity that included a pervasive fragmentation of the mind, a loosening of the inner unity, impacting for example judgement, and emotional interest. Delusions and hallucinations were accessory symptoms, they weren't necessarily present. The pessimistic outlook and the low reproducibility made schizophrenia very difficult to operationalise in a drug trial and this diagnostic conundrum is maybe one of the explanations for the non-specific selection of patients included in the first neuroleptic trials.

But a new schizophrenia was emerging as Kurt Schneider's influence grew, namely with the translation of his work into english in 1959. Schneider proposed a Schizophrenia where delusions and hallucinations became paramount, inner experiences could be indexed, and diagnosis could be done transversally, repudiating the classical need for a long observation period. The new concept served the needs of the emerging academic-industrial complex formed around drug trials and neurochemistry. The new schizophrenia, whose influence can be felt, for example, in the haloperidol trials at Dave, was also much more similar to the experimental models of psychosis.

Psychosis produced in the context of amphetamine intoxication, was mainly characterised by exactly these inner experiences of delusions and hallucinations. Paul Janssen's *a posteriori* narrative of anecdotal evidence of amphetamine intoxication provoking psychosis being the starting point for haloperidol's endeavour, shows amphetamine was important to him and is further materialised in his use of amphetamine antagonism in the animal testing of compounds. Both industry and academics would benefit from a schizophrenia that was more closely aligned to experimental models. This process, sometimes called paranoidization, benefitted drug development, drug testing, and clinical

trials. If the model the lab used to simulate or provoke psychosis wasn't similar to schizophrenia, schizophrenia transformed itself as to resemble the experimental psychosis, and was another way of ensuring a bridge between the laboratory and the clinic.

Closely associated to schizophrenia's paranoid tendency was a second trend we have pursued during this thesis. When neuroleptics were first introduced, they had an ample field of action, indications included not only the psychoses but also more neurotic symptoms such as anxiety. They weren't seen as healing specific diseases but mostly as alleviating symptoms despite the nosological categories diagnosed. This was changed by two processes we detailed during this thesis. First the marketing posturing of some neuroleptics, specifically haloperidol, that presented itself since the Dave trial, more and more as anti-schizophrenic. Haloperidol was defining itself as a major hallucinolitic and anti-delusional, and those were becoming more and more accepted as the cardinal symptoms of schizophrenia. Secondly the lab work at, for example, Bethesda and Lund, as it tried to answer questions about neuroleptics' mechanisms, crystallised the idea that they had a specific anti-schizophrenic action. The new schizophrenia (under Schneider's influence) found a specific treatment (anti-psychotics).

The dopamine hypothesis depends profoundly on both these trends- paranoidization of schizophrenia and the redefinition of neuroleptics (or major tranquillisers) as antipsychotics. Its creation rests upon haloperidol's development through anti-amphetamine tests, reinforcing the importance of amphetamine experimental model of psychosis. Furthermore, neuroleptics mechanism of action, namely its capacity to block dopamine receptors, informs us about schizophrenia only if we see them as specifically anti-schizophrenics. The way van Rossum hypothesised about schizophrenia's etiology depends upon this new schizophrenia, and the antipsychotics that accompany it. The hypothesis validation and recognition in the decades following depended on the growth of these major trends during the 1960's and 1970's.

The changes in schizophrenia that we formulated in our research, and are sometimes called paranoidization, implicated three distinct yet strictly interconnected processes of construct transformation that we may call *reification*, *mechanification, cerebralization.*

Reification of schizophrenia addresses the unfathomable concreteness that emerged with the transformation of the multiple etiological narratives into one hegemonic biological

explanation - the dopamine hypothesis. The new schizophrenia diagnosis depended less and less on previous personality, disease course or social disfunction and could therefore dissociate from narratives of familiar or social etiology. Before the nineteen sixties schizophrenia was seen sometimes as inherent to the person itself, frequently determined by the patient's most precocious experiences, often indistinguishable from the patients way of being in the world. The new schizophrenia would then find a role as a more concrete and easily defined disease. It distances itself from the specificity of the case history, from the circumstances of the patients life, from their narratives of distress. Becoming more and more an external entity with autonomous ontology, that can sometimes penetrate a patients mind, to be again expelled by a specific medication. This process changed what was a vague but profoundly pervasive illness, touching almost every aspect of human activity, into a concrete disease that could be declined into a symptoms' list. Before this process, schizophrenia demanded a multilevel understanding, had symbolic and even political overtones, representing what was placed in the margins of society. During the period we studied these shared social aspects were reduced to the physical reality of the patients' body.

Mechanification of schizophrenia refers to the transformation of a complex multilevel interaction into the malfunction of a simple biological pathway. Again, before the emergence of the 1960's, theory construction concerning schizophrenia implicated hybrid languages. As we have seen in many examples during this thesis, researchers used concepts from psychoanalysis, behavioural psychology, medicine, etc. interchangeably, trying to articulate both concrete and symbolic references in the same model. Understanding patients implied not only identifying physical, and behavioural signs of illness, but also giving meaning to symptoms, contextualising them in the family and in the broader community. Psychoanalysis was a spectacular tool for this multilevel articulation and its relevance was indisputable during the 1950's as we have seen, even in the psychopharmacological milieu.

The process we followed during our research reframed the necessity for these symbolic interactions. As neuroleptics (notably haloperidol) emerged clinically, in the asylum, they (almost concomitantly) became a laboratory tool as to construct a biological pathway - chemical neurotransmission, and a causal malfunction – namely, the dopamine hypothesis. Both normal pathway and malfunction worked to reinforce each other. Neurotransmitters (notably dopamine) liberated from pre-synaptic neurones stimulated post-

synaptic receptors, this apparently simple biological mechanism recuperated metaphors of biological reproduction as a substance is liberated and travels trough a gap in order to inseminate a receptor entity: thought and behaviour were born that way. Overactivity of the dopamine neurotransmission is a clear dysfunction in the spatiotemporal continuity of the normal dopamine transmission. Despite these reproductive undertones, the dysfunction reminds us a broken mechanism of a machine built by men. It places the human patient as a subject devoid of intentionality, without guilt or agency. Mental illness and particularly schizophrenia were reduced to a mechanistic malfunction and in such were liberated from moral or normative views of illness. Context including modalities of suffering and political, social and familial interaction became superfluous. They persisted, of course, in theory construction during the following decades but they were no longer needed to explain the disease. This mechanistic explanation underscores the seductive value of simplicity in scientific production, but also in clinical action. Easily explained, it could simplify the communication by industry sales representatives, and would later become a major marketing advantage in antipsychotic proliferation. But its consequences are wider, affecting the clinical encounter, in ways that are beyond the scope of this research. The hybrid language that was so common in our protagonists, would quickly desapear in the next few years after the dopamine hypothesis. Polarising psychiatric discourses, psychoanalytic concepts would quickly disappear from biological psychiatry.

The new schizophrenia would no longer be seen as a negotiated construct, but as independent from the academic capacity to conceptualise it, or even the clinician capacity to recognise it in the patient. If neurotransmission disfunction existed, if dopaminergic transmission was overactive, the disease was present. A reformed Schizophrenia could then become a universal and a-historical diagnosis. This aspiration to understand schizophrenia as a natural type was one of the promises of the dopamine hypothesis, even if it didn't really materialise completely in current psychiatric taxonomy (as the absence of biomarkers and the non-specificity of treatment interventions shows). This categorial demarcation between normal and pathologic is still problematic in psychiatry fifty years later.

Finally, *cerebralisation* is the process by which schizophrenia was finally materialised exclusively in the central nervous system. As we have seen, psychiatric pathology was frequently interpreted in a contextualised manner, exclusively biological approaches were

rare, but even those often weren't solely reduced to the brain. Auto-intoxicating hypothesis had an important clinical and theoretical impact in first decades of the 20th century, and even during the 1950's the human fluids of blood and urine, were extensively studied, as different hypothesis from taraxein to trans-methylation were entertained. The dopamine hypothesis, by contrast, follows a broader movement that sees the brain as one of the central elements of modern identity. Again, neuroleptics, and haloperidol in particular, had an important role in this reduction of the self to the brain. The idea that a drug could change thought content, specifically that a drug could be anti-delusional, was initially faced with resistance from clinicians. Even if somatic treatment for mental disorders long preceded neuroleptics, they were seen as non-specific interventions, and left room, as we have seen, for multiple narratives and hybrid interpretive elements (notably, but not exclusively, somatic and psychoanalytic). During the first years of neuroleptic introduction these ideas persisted, but as specificity was further highlighted by the academic industrial complex, the need for multiple theoretical framing would wane.

Authors like Alain Ehrenberg (2004) and Fernando Vidal (2009) approached this discursive trend proposing concepts like *Brainhood* or *Le sujet cerebral*. In the last century, the brain progressively affirmed itself as the exclusive venue where we can find ourselves. This model includes naturalised ideas about interiority and agency that touch many different sectors of society from law to art. The dopamine hypothesis closely follows this ideological movement and reinforces it. Psychiatric pathology, and notably schizophrenia (seen as the quintessencial disorder of the self), became exclusively entangled in central neurotransmission. The brain turned into the only ground for understanding behavioural disorders in general, more so it became the central object of attention when it comes to searching for answers about the fractured mind, and our sense of selves .

This fracturing of schizophrenia's concept transformation in three different processes - *reification*, *mechanification, cerebralization,* is, of course, reductive and artificial. It is used as a frame for detailing and understanding the way a new schizophrenia came to be but those were dependent and mostly simultaneous phenomena.

There isn't a wish to morally judge this processes in our work. We don't see them as inherently good or bad. Their impact in patients life is so complex we have trouble judging this effect in a normative sense. Narrowing disease mechanisms, and simplifying explanatory

models can certainly reassure patients, give them hope, and maybe even reduce stigma. They can promote research, including pharmacological research, but not exclusively, that may undoubtedly help many patients in the future. Nevertheless schizophrenia's transformations may have come at a cost, creating doubts about construct validity and erasing important contextual and political discourses from the etiological discussion, reshaping research objectives and reorienting resources. The possible consequences of this are beyond the scope of our work. They merit further research and an honest reflection from psychiatry as a discipline, its users/patients, their loved ones and society at large.

We have seen how pharmacocentric the dopamine hypothesis is. Its main argument hangs on a proposed mode of action for neuroleptics. Some have extensively criticised this logic (Kendler & Schaffner, 2011). The neuroleptic mode of action hypothesis, if confirmed, could involve a therapeutical activity in pathophysiological pathways distant from schizophrenia's etiology (those authors point, for example, to diuretics acting in the kidney but being used to treat heart failure). Nevertheless, the importance of both psychostimulants and neuroleptics in the dopamine hypothesis conception remains indisputable. Haloperidol specifically was one of the actors transforming schizophrenia's definition and, in the process, gaining a newfound specificity. Our thesis structure reflects this central characteristic. We started our research with the construction of haloperidol. This construction, as we have seen, was already embedded in theory, namely through the initial animal models, but when introduced in the asylum, in the first clinical trials, haloperidol further advanced its social promise of therapeutic action. In a sense, haloperidol was never only a passive substance. From its creation it transported social intentions, and as its use expanded, and its action gained specificity, it contributed to the formulation of hypotheses about the origins of the disease it promised to treat. Going from compound to drug, haloperidol turned into a major actor in the reshaping of schizophrenia. Psychiatric substances became protagonists in the shaping of theory. Chemical identities, patented clinical formulae, would exhibit this incredible power of transforming a whole discipline as a way of becoming drugs. We can now look at substances as becoming capable of intervening, reframing the power relations, the knowledge system, the academic- industrial network. Drugs shape the illnesses they treat as much as the illness shapes drug research. We are then forced to recognise that in the same way artefacts were constructed by theory, they themselves become constructers of theory. Our

example calls for accepting a complex mutual relationship between artefacts and theory, where they become so closely netted that they seem sometimes indistinguishable.

An important limitation to our work is the lack of diversity in our sources. Although our thesis could be said to be about psychiatry, our patients are nowhere to be seen. We chose to hear the men in power, read the articles they published, to reflect on their discourse, to understand better the nature of their connections, to ponder the consequences of their proposals. In doing so, we may be accused of reproducing what neuroleptics first brought into the asylum - the persistent silencing of patients voices. In my defense, I would argue this is an inevitable consequence of our main question. The dopamine hypothesis for schizophrenia is created in the areas of power, probably distant from many patients lived-experiences, discourses and hopes.

Another interesting, and in some ways related, criticism would point to the chronological organisation of our thesis. van Rossum having declared haloperidol's creation as one of the main ideas behind the dopamine hypothesis, we decided to start this thesis at that moment. Furthermore, our thesis dedicates an important part of its attention to van Rossum's other main references in his seminal 1966 paper. To understand an idea we tried to look through the author's own acknowledgements. In doing so, we run the risk of imprisoning ourselves in van Rossum's perspective, and can be accused of an internalistic approach. This was never our intention, on the contrary, we searched through the material looking for connections of a diversified nature including funding, affective relations and ideological background.

There are important problems to the history of psychiatry written by psychiatrists. Andrew Scull (1991) summarises some of these pitfalls. Sometimes projects turn into an historical exercise with the intent of justifying present practice, sometimes an antiquarian approach reproduces official accounts and is deprived of any critical perspective. Unfortunately, the authors of such studies can be unaware of the critical limitations of such approaches. Wishing to escape this fallacy we tried our best to suspend our beliefs and alliances. We hope to have achieved that goal.

We concentrated on schizophrenia research and neglected other pathologies. We concentrated on the dopamine hypothesis for schizophrenia and neglected sister biochemical proposals as the biogenic amine hypothesis for mood disorders. They both share the same

pharmacocentric origins, emerge at the same historical moment and follow a similar path of success within the discipline. We chose a more concentrated approach, trying to mostly keep in sight our principal object of study. Notwithstanding, we believe some of the answers we found in our work may apply to the biogenic amine hypothesis for depression as well – a relationship that would benefit from further exploration. Understanding their common ascension would further advance our knowledge of psychiatry during this key timespan. Detailing their interconnections would be important in future work.

During the 1960's and 1970's, social movements and patient groups were said to be defying psychiatry's authority. Although it is beyond the scope of our research we would find interest in reflecting about this forces at the walls. Questions linger about how society at large was receiving the concepts produced by psychiatry, and of how patients movements both contested and promoted the new psychiatric conformation. Further, what specific changes in the narratives around schizophrenia were brought about by the dopamine hypothesis and how this affected treatment, clinical work and the psychiatric wards hierarchical organisation - all these questions could be useful directions for future work.

One particular consequence of this crisis was the questioning of the power of the psychiatric doctor, as roles of social workers, psychologist, and psychiatric nurses were expanding. The biological turn of the 1960's and 1970's, of which the dopamine hypothesis is a notable example, has arguably be said to occur in the context of defending, or reinforcing, the role of the medical doctor. Work dedicated to studying these power struggles could find interesting sources in clinical case reports, but also patient's diaries, correspondence and other textual or artistic materials.

Our research unveiled the dopamine hypothesis inception, describing the way it was woven within psychiatry's institutional tissue and illustrating how the hypothesis took part in the major theoretical and institutional reforms of the 1950's and 60's. We can now understand more clearly the grip it holds over the discipline, its mostly uncontested role.

When medical hypotheses become motors of major theoretical contributions, structuring clinical activity, conditions are created for they to become entrenched, nesting in a place beyond appraisal. Progressive scientific communities must fight to keep healthy criticism, defend the freedom to ask hard questions, and promote self reflection in order to find fruitful paths.

Bibliography

A) Primary sources

Amin, A. H., Crawford, T. B. B., & Gaddum, J. H. (1954). The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *The Journal of Physiology, 126*(3), 596-618. doi:https://doi.org/10.1113/jphysiol.1954.sp005229

Ancel, P. (1950). *La chimiotératogenèse: réalisation des monstruosités par des substances chimiques par les vertébrés*: G. Doin.

Andén, N. E., Carlsson, A., Dahlström, A., Fuxe, K., Hillarp, N. Å., & Larsson, K. (1964). Demonstration and mapping out of nigro-neostriatal dopamine neurons. *Life Sciences, 3*(6), 523-530. doi:https://doi.org/10.1016/0024-3205(64)90161-4

Andén, N. E., Corrodi, H., Fuxe, K., & Hökfelt, T. (1967). Increased impulse flow in bulbospinal noradrenaline neurons produced by catecholamine receptor blocking agents. *European Journal of Pharmacology, 2*(1), 59-64. doi:10.1016/0014-2999(67)90024-6

Arvid Carlsson. (1999). In L. R. Squire (Ed.), *The History of Neuroscience in Autobiography* (Vol. 2, pp. 28-66): Academic Press.

Azima, H. (1953). Fundamentals of a Neo-Jacksonian conception of psychiatry and neurology: Henri ey's "organo-dynamism". *Arquivos de Neuro-Psiquiatria, 11*, 360-370.

Azima, H. (1955). Prolonged sleep treatment in mental disorders; some new psychopharmacological considerations. *Journal of Mental Science, 101*(424), 593-603. doi:10.1192/bjp.101.424.593

Azima, H. (1956). Official Reports. *American Journal of Psychiatry, 112*(9), 749-750. doi:10.1176/ajp.112.9.749

Azima, H. (1962). *Psilocybin disorganization.* Paper presented at the Recent Advances in Biological Psychiatry, Society of Biological Psychiatry, Toronto.

Azima, H., Durost, H., & Arthurs, D. (1960). The effect of R-1625 (haloperidol) in mental syndromes: A multiblind study. *American Journal of Psychiatry, 117*(6), 546-547. doi:10.1176/ajp.117.6.546

Azima, H., & Ogle, W. (1954). Largactil in Mental Syndromes. *Canadian Medical Association Journal, 71*(2), 116-121. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1824804/

Azima, H., Vispo, R. H., & McKenna, R. (1961). Anaclitic therapy induced by drugs. *Comprehensive psychiatry, 2*(5), 281-293. doi:https://doi.org/10.1016/S0010-440X(61)80034-5

Ban, T. A., & Sulser, F. (2011). *An Oral History of Neuropsychopharmacology: The First Fifty Years, Peer Interviews: Neuropharmacology*: CreateSpace Independent Publishing Platform.

Barbeau, A. (1969). L-dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Canadian Medical Association Journal , 101*(13), 59-68.

Bellak, L. E. (1958). Schizophrenia: A review of the syndrome.

Benzedrine sulfate- a warning. (1938). *Journal of the American Medical Association, 110*(12), 901-902. doi:10.1001/jama.1938.02790120043013

Bertler, Å., & Rosengren, E. (1959). Occurrence and distribution of dopamine in brain and other tissues. *Experientia, 15*(1), 10-11. doi:10.1007/BF02157069

Birkmayer, W., & Horrnykiewicz, O. (1961). Der L-3, 4-Dioxyphenylanine (= DOPA)-Effect bei der Parkinson-Akinese. *Wien. Klin. Wochschr., 45*, 787-788.

Blackstone, H. A. (1931). Postencephalitic parkinsonism.

Bleuler, E. (1937). *Lehrbuch der psychiatrie*. Berlin,: J. Springer.

Bobon, J. (1962). *Psychopathologie de l'expression: rapport de psychiatrie présenté au congrès de psychiatrie et de neurologie de langue française,* LXe session, Anvers, 9-14 Juillet 1962: Masson.

Booth, G. (1951). Basic concepts of psychosomatic medicine. *Pastoral Psychology, 1*(10), 11-18.

Bordeleau, J. M. (1961). Introduction et position du problème. *Système extra-pyramidal et neuroleptiques: extrapyramidal system and neuroleptics*. Editions psychiatriques.

Bowman, R. L., Caulfield, P. A., & Undenfriend, S. (1955). Spectrophotofluorometric assay in the visible and ultraviolet. *Science, 122*(3157), 32-33. doi:10.1126/science.122.3157.32

Brandrup, E., & Kristjansen, P. (1961). A Controlled Clinical Test of a New Psycholeptic Drug (Haloperidol). *Journal of Mental Science, 107*(449), 778-782. doi:10.1192/bjp.107.449.778

Brodie, B. B., Pletscher, A., & Shore, P. A. (1955). Evidence that serotonin has a role in brain function. *Science, 122*(3177), 968. doi:10.1126/science.122.3177.968

Brodie, B. B., & Shore, P. A. (1957). A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. *Annals of the New York Academy of Sciences, 66*(3), 631-642. doi:10.1111/j.1749-6632.1957.tb40753.x

Brodie, B. B., Sulser, F., & Costa, E. (1961). Theories on mechanism of action of psychotherapeutic drugs. *Revue Canadienne de biologie, 20*, 279-285.

Burnham, D. (1960). Schizophrenia: A Review of the Syndrome. *American Journal of Psychiatry, 116*(9), 859-859. doi:10.1176/ajp.116.9.859

Cameron, D. E. (1956). Psychic driving. *American Journal of Psychiatry 112*(7), 502-509. doi:10.1176/ajp.112.7.502

Cantini, C. (1997). Souvenirs d'un ancien infirmier (A Cery, 1954-1989). *L'Ecrit:[bulletin du Service des soins infirmiers du département universitaire de psychiatrie adulte (DUPA)*](4), 1-8.

Carlsson, A. (1990). Early psychopharmacology and the rise of modern brain research. *Journal of Psychopharmacology, 4*(3), 120-126. doi:10.1177/026988119000400304

Carlsson, A. (2000). Biographical. *NobelPrize.org*.

Carlsson, A. (2001). A Half-Century of Neurotransmitter Research: Impact on Neurology and Psychiatry. *Bioscience Reports, 21*(6), 691-710. doi:10.1023/a:1015556204669

Carlsson, A., & Lindqvist, M. (1963). Effect of Chlorpromazine or Haloperidol on Formation of 3-Methoxytyramine and Normetanephrine in Mouse Brain. *Acta Pharmacologica et Toxicologica, 20*(2), 140-144. doi:https://doi.org/10.1111/j.1600-0773.1963.tb01730.x

Carlsson, A., Lindqvist, M., & Magnusson, T. O. R. (1957). 3,4-Dihydroxyphenylalanine and 5-Hydroxytryptophan as Reserpine Antagonists. *Nature, 180*(4596), 1200-1200. doi:10.1038/1801200a0

Carlsson, A., Shore, P. A., & Brodie, B. B. (1957). Release of Serotonin from Blood Platelets by Reserpine. *Journal of Pharmacology and Experimental Therapeutics, 120*(3), 334-339. Retrieved from https://jpet.aspetjournals.org/content/jpet/120/3/334.full.pdf

Charcot, J. M. (1877). *Lectures on the Diseases of the Nervous System*: *Delivered at La Salpêtrière*: New Sydenham Society.

Contributors to this issue. (1958).. *Psychiatric Quarterly, 32*(3), 633-639. doi:10.1007/BF01563530

Cooper, D. (1974). *The Grammar of Living*. Random House

Crane, G. E. (1956a). Further studies on iproniazid phosphate: Isonicotinil-isopropylhydrazine phosphate Marsilid. *The Journal of Nervous and Mental Disease, 124*(3), 322-331. Retrieved from https://journals.lww.com/jonmd/Fulltext/1956/09000/

Crane, G. E. (1956b). The psychiatric side-effects of iproniazid. *American Journal of Psychiatry, 112*(7), 494-501. doi:10.1176/ajp.112.7.494

Crane, G. E. (1960). Some questions concerning the value of psychotherapy in nonhospitalized patients treated with psychopharmacologic agents. *Psychiatric Quarterly, 34*(3), 430-442. doi:10.1007/BF01562424

Crane, G. E. (1968). Tardive dyskinesia in patients treated with major neuroleptics: a review of the literature. *American Journal of Psychiatry, 124*(8), Suppl:40-48. doi:10.1176/ajp.124.8S.40

Crane, G. E. (1968). Tardive dyskinesia in schizophrenic patients treated with psychotropic drugs. *Agressologie*.

De Jong, H., & Baruk, H. (1930). La catatonie expérimentale par la bulbocapnine et le syndrome catatonique chez l'homme. *L'Encéphale: Revue de psychiatrie clinique biologique et thérapeutique*.

Delay, J., & Deniker, P. (1958). États Hysteroides D'Origine Medicamenteuse. *Canadian Psychiatric Association Journal, 3*(3), 132-144. doi:10.1177/070674375800300306

Delay, J., & Deniker, P. (1960). Apport de la Clinique a la Connaissance de L'Action des Neuroleptics. *Système extra-pyramidal et neuroleptiques: extrapyramidal system and neuroleptics*. Editions psychiatriques.

Delay, J., Deniker, P., Azima, H., & Lemperiere, T. (1952). Laureomycine dans le traitement de la paralysie generale- premiers resultats. *Presse Medicale, 60*(60), 1264-1264.

Delay, J., Deniker, P., Green, A., & Mordret, M. (1957). Le syndrome excito-moteur provoqué par les médicaments neuroleptiques. *Presse Medicale, 65*(79), 1771-1774.

Delay, J., Deniker, P., & Harl, J. (1952). Utilisation en therapeutique psychiatrique d'une phenothiazine d'action centrale elective (4560RP). *Annales Médico-psychologiques, 110*, 112-117.

Delay, J., Laine, B., Azima, H., & Puech, J. (1953). [Contribution to the study of homeostasis in schizophrenia and the other psychoses]. *Encephale, 42*(5), 385-406. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/13127835

Delay, J., Pichot, P., Lemperiere, T., & Elissalde, B. (1960). [The action of haloperidol in psychoses]. *Acta neurologica et psychiatrica Belgica, 60*, 21-38. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/13815608

Denber, H. (1958). Ineffectiveness of mepazine (pacatal). *American Journal of Psychiatry, 114*(7), 656. doi:10.1176/ajp.114.7.656

Denber, H. (1961). Psychodynamic effects of the drug-induced extrapyramidal reaction on ward social structure. *Revue canadienne de biologie, 20*, 631-641.

Denber, H. (1972). Psychodynamic Observations of the Research Worker in Psychiatry: Further Considerations. *Canadian Psychiatric Association Journal, 17*(6_suppl2), 83-88.

Denber, H., & Merlis, S. (1954). A note on some therapeutic implications of the mescaline-induced state. *The Psychiatric Quarterly, 28*(1), 635-640. doi:10.1007/BF01567079

Denber, H., Rajotte, P., & Kauffman, D. (1959). Problems in evaluation of R-1625. *American Journal of Psychiatry, 116*(4), 356-357. doi:10.1176/ajp.116.4.356

Denber, H. C. (1963). Group Process in a State Hospital. *American Journal of Orthopsychiatry 33*, 900-911. doi:10.1111/j.1939-0025.1963.tb01053.x

Denber, H. C., & Bird, E. G. (1957). Chlorpromazine in the treatment of mental illness. IV. Final results with analysis of data on 1,523 patients. *American Journal of Psychiatry, 113*(11), 972-978. doi:10.1176/ajp.113.11.972

Denber, H. C., & Collard, J. (1962). Différences de bioréactivité au Haloperidol entre deux groupes de psychothiques, américain et européen. *Acta neurologica et psychiatrica Belgica, 62*, 577-588.

Denber, H. C., & Merlis, S. (1955). Studies on mescaline. I. Action in schizophrenic patients; clinical observations and brain wave patterns, showing effects before and after electric convulsive treatments.*Psychiatric Quarterly 29*(3), 421-429. doi:10.1007/BF01567467

Denber, H. C., Rajotte, P., & Kauffman, D. (1959). Clinical experiences with a new phenothiazine. *American Journal of Psychiatry, 115*(12), 1116-1117. doi:10.1176/ajp.115.12.1116

Denber, H. C., Teller, D. N., Rajotte, & Kauffman, D. (1962). Studies on mescaline. XIII. The effect of prior administration of various psychotropic drugs on different biochemical parameters: a preliminary report. *Annals of the New York Academy of Sciences, 96*(1), 14-36. doi:10.1111/j.1749-6632.1962.tb50098.x

Denber, H. C. B. (1955). Appraisal of Drug Reactions. *Journal of the American Medical Association, 158*(7), 586-587. doi:10.1001/jama.1955.02960070062021

Denber, H. C. B., Rajotte, P., & Ross, E. (1960). Some observations on the chemotherapy of depression: Results with 'Taractan'. *Comprehensive psychiatry, 1*(5), 308-312. doi:https://doi.org/10.1016/S0010-440X(60)80006-5

Divry, P., Bobon, J., & Collard, J. (1958). Le R1625, nouvelle thérapeutique symptomatique de l'agitation psychomotrice. *Acta neurologica et psychiatrica Belgica, 58*(10), 878-888.

Divry, P., Bobon, J., & Collard, J. (1960). Rapport sur l'activité neuropsychopharmacologique du Halopéridol (R-1625). *Acta neurologica et psychiatrica Belgica, 60*, 7-9.

Discussion (1960). *Acta neurologica et psychiatrica Belgica, 60*, 135-149.

Doshay, L. (1961). Evaluation of medical treatment in Parkinson's disease. *Revue canadienne de biologie, 20*, 321-329.

Dundee, J. W. (1954). A review of chlorpromazine hydrochloride. *British Journal of Anaesthesia, 26*(5), 357-379. doi:10.1093/bja/26.5.357

Eddy, N. B. (1957). The history of the development of narcotics. *Law and Contemporary Problems, 22*(1), 3-8.

Ehringer, H., & Hornykiewicz, O. (1960). Verteilung Von Noradrenalin Und Dopamin (3-Hydroxytyramin) Im Gehirn Des Menschen Und Ihr Verhalten Bei Erkrankungen Des Extrapyramidalen Systems. *Klinische Wochenschrift, 38*(24), 1236-1239. doi:10.1007/BF01485901

Eisleb, O., & Schaumann, O. (1939). Dolantin, ein neuartiges Spasmolytikum und Analgetikum. *Dtsch Med Wochenschr, 65*(24), 967-968.

Elkes, J. (1988). The 5th Congress — Washington 1966. In T. A. Ban & H. Hippius (Eds.), *Thirty Years CINP: A Brief History of the Collegium Internationale Neuro-Psychopharmacologicum* (pp. 17-19). Berlin, Heidelberg: Springer Berlin Heidelberg.

Elkes, J. (1995). Psychopharmacology: finding one's way. *Neuropsychopharmacology, 12*(2), 93-111.

Elkes, J., & Elkes, C. (1954). Effect of chlorpromazine on the behavior of chronically overactive psychotic patients. *British medical journal, 2*(4887), 560-565. doi:10.1136/bmj.2.4887.560

Enoch, M. D., & Robin, A. A. (1960). A Controlled Trial of Haloperidol in Chronic Schizophrenics. *Journal of Mental Science, 106*(445), 1459-1467. doi:10.1192/bjp.106.445.1459

Ey, H., Faure, H., & Rappard, P. (1956). Les réactions d'intolérance vis-à vis de la chlorpromazine. *Encéphale, n°4*, pp. 790-796.

Ey, H., & Sakellaropoulos, P. (1956). L'état primordial du délire et l'action thérapeutique de la chlorpromazine. *Évolution Psychiatrique, XXI*(4), pp. 489-497.

Fabing, H. D. (1958). Biochemistry and Schizophrenia. *Journal of Mental Science, 104*(435), 573-588. doi:10.1192/bjp.104.435.573

Faurbye, A., Rasch, P. J., Petersen, P. B., Brandborg, G., & Pakkenberg, H. (1964). Neurological Symptoms in Pharmacotherapy of Psychoses. *Acta Psychiatrica Scandinavica 40*(1), 10-27. doi:10.1111/j.1600-0447.1964.tb05731.x

Fedoroff, S. (1956). Toxicity of schizophrenics' blood serum in tissue culture. *Translational Research, 48*(1), 55-62. doi:10.5555/uri:pii:0022214356901123

Fischer, R. (1953). Stress and the Toxicity of Schizophrenic Serum. *Science, 118*(3067), 409-410. doi:10.1126/science.118.3067.409

Freud, S. (1957). On narcissism: An introduction. In The Standard Edition of the Complete Psychological Works of Sigmund Freud, Volume XIV (1914-1916): On the History of the Psycho-Analytic Movement, Papers on Metapsychology and Other Works (pp. 67-102).

Gaddum, J. H. (1959). Measurement of epinephrine, norepinephrine and related compounds; bioassay procedures. *Pharmacol Rev, 11*(2, Part 2), 241-249; discussion 249-251. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/13667400

Gaddum, J. H., & Hameed, K. A. (1954). Drugs which antagonize 5-hydroxytryptamine. *British journal of pharmacology and chemotherapy, 9*(2), 240-248. doi:10.1111/j.1476-5381.1954.tb00848.x

Garland, H. G. (1952). Parkinsonism. *British medical journal, 1*(4750), 153-156. doi:10.1136/bmj.1.4750.153

Geburtstage (1997).. *Dtsch Arztebl International, 94*(31-32), 2084-. Retrieved from https://www.aerzteblatt.de/int/article.asp?id=7312

Gefahr im Verzuge. (1962). *Der Spiegel(49/1962)*. Retrieved from https://www.spiegel.de/politik/gefahr-im-verzuge-a-fb571858-0002-0001-0000-000045125108

Gerle, B. (1960). Clinical trials of R 1625. *Acta neurologica et psychiatrica Belgica, 60*, 70-74. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/13827511

Goldstein, B., Clyde, D., & Caldwell, J. (1967). Clinical efficacy of the butyrophenones as antipsychotic drugs. *Psychopharmacology: A review of progress, 1967*, 1085-1091.

Gross, A., & Haase, H. J. (1954). Beitrag zur Psychosomatik extrapyramidaler Motilitätsstörungen. *Archiv für Psychiatrie und Nervenkrankheiten, 192*(3), 268-289. doi:10.1007/BF00341906

Haase, H.-J., & Janssen, P. A. J. (1965). *The Action of Neuroleptic Drugs : a psychiatric, neurologic and pharmacological investigation.* Amsterdam: North-Holland Pub.

Haase, H. J. (1954). Uber Vorkommen und Deutung des psychomotorischen Parkinsonsyndroms bei Megaphen- bzw. Largatil Dauerbehandlung. *Nervenarzt, 25*(12), 486-492. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14356297

Haase, H. J. (1961). Extrapyramidal modification of fine movements: a "conditio sine qua non" of the fundamental therapeutic action of neuroleptic drugs. *Rev Can Biol, 20*, 425-449.

Hall, R. A. (1955). Methodology in medical research; the need for controlled clinical studies. *California medicine, 82*(2), 447-449. Retrieved from https://pubmed.ncbi.nlm.nih.gov/14379057

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1532572/

Hall, R. A., & Dunlap, D. J. (1955). A study of chlorpromazine: methodology and results with chronic semi-disturbed schizophrenics. *Journal of Nervous and Mental Disease, 122*(4), 301-314.

Hall, R. A., Jackson, R. B., & Swain, J. M. (1956). Neurotoxic reactions resulting from chlorpromazine administration. *Journal of the American Medical Association, 161*(3), 214-218. doi:10.1001/jama.1956.02970030032008

Haloperidol (Haldol). (1967). Clinical Pharmacology & Therapeutics, 8(5), 770-774. doi:10.1002/cpt196785770

Healy, D. (1998a). *The psychopharmacologists I : interviews by Dr David Healy.* London: Arnold.

Healy, D. (1998b). *The psychopharmacologists II, interviews by Dr David Healy*, . London and New York: Altman.

Healy, D. (2000). *The Psychopharmacologists III: interviews by Dr David Healy*, Taylor & Francis.

Heath, R., Leach, B., Byers, L., Martens, S., & Feigley, C. (1958). Pharmacological and biological psychotherapy. *American Journal of Psychiatry, 114*(8), 683-689. doi:10.1176/ajp.114.8.683

Heath, R., Martens, S., Leach, B., Cohen, M., & Feigley, C. (1958). Behavioral changes in nonpsychotic volunteers following the administration of taraxein, the substance obtained from serum of schizophrenic patients. *American Journal of Psychiatry, 114*(10), 917-920. doi:10.1176/ajp.114.10.917

Heath, R. G., & Krupp, I. M. (1967). Schizophrenia as an immunologic disorder: I. demonstration of antibrain globulins by fluorescent antibody techniques. *Archives of General Psychiatry, 16*(1), 1-9. doi:10.1001/archpsyc.1967.01730190003001

Hebb, D. O. (1955). Drives and the C.N.S. (conceptual nervous system). *Psychol Rev, 62*(4), 243-254. doi:10.1037/h0041823

Hemminki, E. (1973). The quality of drug advertisements in two finish medical journals. A comparison between psychotropic and other drug advertisements. *Social Science & Medicine (1967), 7*(1), 51-59. doi:https://doi.org/10.1016/0037-7856(73)90135-2

Hemminki, E. (1977). Content analysis of drug-detailing by pharmaceutical representatives. *Medical Education, 11*(3), 210-215. doi:doi:10.1111/j.1365-2923.1977.tb00595.x

Hoch, P. H., Cattell, J. P., & Pennes, H. H. (1952). Effects of mescaline and lysergic acid (d-LSD-25). *American Journal of Psychiatry, 108*(8), 579-584. doi:10.1176/ajp.108.8.579

Hornykiewicz, O. (2006). The discovery of dopamine deficiency in the parkinsonian brain. *Parkinson's Disease and Related Disorders*, 9-15.

Hornykiewicz, O. (2008). Basic research on dopamine in Parkinson's disease and the discovery of the nigrostriatal dopamine pathway: the view of an eyewitness. *Neurodegenerative Diseases, 5*(3-4), 114-117. doi:10.1159/000113678

Hoyt, M. L. (1962). Clinical Psychopathology by Kurt Schneider. *International Journal of Group Psychotherapy, 12*(1), 113-113. doi:10.1080/00207284.1962.11508241

Humbeeck, L. (1960). Étude clinique du R 1625 (Halopéridol). *Acta neurologica et psychiatrica Belgica 601*, 75-86.

In Memoriam.(1967). *Canadian Psychiatric Association Journal, 12*(2), 182-182. doi:10.1177/070674376701200211

Jackson, J. A. (1923). The Psychic Manifestations in Paralysis Agitans. *Archives of Neurology And Psychiatry, 10*(6), 680-684. doi:10.1001/archneurpsyc.1923.02190300077003

Janssen, P. (1992). The "Social Chemistry" of Pharmacological Discovery: The Haloperidol Story. An Interview with Dr. Paul Janssen, January 21, 1986. *International Journal of the Addictions, 27*(3), 331-346. doi:10.3109/10826089209068746

Janssen, P. (2002). The decrease in the number of farmers has led to less common sense. Interview with Kirsten Bett. *ECNP (European College of Neuropsychopharmachology) Newsletter, 2, January*.

Janssen, P., Niemegeers, C., & Schellekens, K. (1965). Is it possible to predict the clinical effects of neuroleptic drugs (major tranquillizers) from animal data? I." Neuroleptic activity spectra" for rats. *Arzneimittel-Forschung, 15*, 104-117.

Janssen, P. (1985). Strategies in pharmaceutical research. *Endeavour, 9*(1), 28-33. doi:10.1016/0160-9327(85)90006-7

Janssen, P., Jageneau, A. H., & Schellekens, K. H. (1960). Chemistry and pharmacology of compounds related to 4-(4-hydroxy-4-phenyl-piperidino)-butyrophenone. IV. Influence of haloperidol (R 1625) and of chlorpromazine on the behaviour of rats in an unfamiliar "open field" situation. *Psychopharmacologia, 1*, 389-392. doi:10.1007/bf00441186

Janssen, P. (1965). The Evolution of The Butyrophenones, Haloperidol and Trifluperidol, From Meperidine-Like 4-Phenylpiperidines. In C. C. Pfeiffer & J. R. Smythies (Eds.), *International Review of Neurobiology* (Vol. 8, pp. 221-263): Academic Press.

Janssen, P. (1967). 2 - Haloperidol and Related Butyrophenones. In M. Gordon (Ed.), *Psychopharmacological Agents* (Vol. 4, pp. 199-248): Academic Press.

Janssen, P., Van De Westeringh, C., Jageneau, A. H. M., Demoen, P. J. A., Hermans, B. K. F., Van Daele, G. H. P., . . . Niemegeers, C. J. E. (1959). Chemistry and Pharmacology of CNS Depressants Related to 4-(4-Hydroxy-4-phenylpiperidino)butyrophenone Part I--Synthesis and screening data in mice. *Journal of Medicinal and Pharmaceutical Chemistry, 1*(3), 281-297. doi:10.1021/jm50004a007

Kline, N. (1968). On the Rarity of "Irreversible" Oral Dyskinesias Following Phenothiazines. *American Journal of Psychiatry, 124*(8S), 48-54. doi:10.1176/ajp.124.8S.48

Kline, N. S. (1964). The Practical Management of Depression. *Journal of the American Medical Association, 190*(8), 732-740. doi:10.1001/jama.1964.03070210038007

Kline, N. S. (1965). Lasker Award: Priority Claim-Reply. *Journal of the American Medical Association, 191*(10), 865-866. doi:10.1001/jama.1965.03080100083032

Kline, N. S., & Mettler, F. A. (1961). The extrapyramidal system and schizophrenia. *Revue canadienne de biologie, 20*, 583-587.

Kopeloff, N., & Cheney, C. O. (1922). Studies in focal infection: its presence and elimination in the functional psychoses. *American Journal of Psychiatry, 79*(2), 139-156.

Kraepelin, E. (1893). *Psychiatrie: ein kurzes Lehrbuch für Studirende und Aerzte*: Ambr. Abel.

Kraepelin, E. (1919). *Dementia praecox and paraphrenia*. [Chicago]: Chicago Medical Book Co.

Kraepelin, E. (1992/1920). Die Erscheinungsformen des Irreseins: (The manifestations of insanity). *History of Psychiatry, 3*(12), 509-529 (originally published 1920).

Kübler-Ross, E. (1998). *The wheel of life: A memoir of living and dying*: Simon and Schuster.

Kuntzman, R. (2018). Special edition, Arvid Carlsson MD., Memories. *American College NeuroPsychopharmacology bulletin, Vol 24*.

Lévy-Bruhl, L. (1922). *Les fonctions mentales dans les sociétés inférieures*: F. Alcan.

Lewis, J., & Van Petten, G. R. (1962). The effect of amphetamine and related compounds on the concentration of adenine nucleotides, inorganic phosphate and creatine phosphate in the rat brain. *Journal of Pharmacology and Experimental Therapeutics, 136*(3), 372-377.

Macdonald, A. D., Woolfe, G., Bergel, F., Morrison, A. L., & Rinderknecht, H. (1946). Analgesic action of pethidine derivatives and related compounds. *British journal of pharmacology and chemotherapy, 1*(1), 4-14.

Macht, D. I. (1949). Phytotoxic Blood Sera in Medicine. *Bulletin of the Torrey Botanical Club, 76*(4), 235-243. doi:10.2307/2482317

Meduna, L., & McCulloch, W. (1945). The modern concept of schizophrenia. *Medical Clinics of North America, 29*(1), 147-164.

Mellor, C. S. (1970). First rank symptoms of schizophrenia. I. The frequnncy in schizophrenics on admission to hospital. II. Differences between individual first rank symptoms. *British Journal of Psychiatryy, 117*(536), 15-23.

Mercier, C. (1925). *Recollections. JH Jackson, Neurological Fragments* Oxford Univ. Press, Oxford.

Mertens, C. (1992). Eloge de feu le Pr Jean Bobon, membre titulaire. Académie royale de Médecine de Belgique. Retrieved from http://old.armb.be/index.php?id=4070

Meszaros, A. F., & Gallagher, D. L. (1958). Measuring indirect effects of treatment on chronic wards. *Dis Nerv Syst, 19*(4), 167-172.

Meurice, E. (1960). Quelques réflexions d'ordre psychopathologique sur le R 1625 et ses effets secondaires. *Acta neurologica et psychiatrica Belgica, 60*, 96.

Meurice, E. (2005). *Le traitement à long terme et la réhabilitation des schizophrènes:* Éditions du Céfal.

Minkowski, E. (1925). La genèse de la notion de schizophrénie et ses caractères essentiels. *L'Évolution psychiatrique, 1*, 193-236.

Montagu, K. A. (1957). Catechol Compounds in Rat Tissues and in Brains of Different Animals. *Nature, 180*(4579), 244-245. doi:10.1038/180244a0

Morel, B.-A. (1860). *Traité des maladies mentales*: V. Masson.

Mormont, C., & Englebert, J. (2019). Un parcours dans la psychologie clinique et la psychiatrie à l'Université de Liège: singularités et originalités. *Une Fabrique des Sciences humaines? L'Université de Liège dans la mêlée (1817-2017)*, 257-264.

Niemegeers, C. J. E., & Janssen, P. A. J. (1960). Influence of Haloperidol (R 1625) and of Haloperidide (R 3201) on Avoidance and Escape Behaviour of Trained Dogs in A "Jumping Box". *Journal of Pharmacy and Pharmacology, 12*(1), 744-753. doi:10.1111/j.2042-7158.1960.tb12741.x

NIMH. (1968). *Who's Who in NIMH*: National Institute of Mental Health.

Norton, W. A. (1967). A Review of Psychiatric Rating Scales. *Canadian Psychiatric Association Journal, 12*(6), 563-574. doi:10.1177/070674376701200606

O'Neil, W. M. (1949). The relation of inner experience and overt behaviour. *Australasian Journal of Philosophy, 27*(1), 27-45. doi:10.1080/00048404908541251

Osmond, H., & Smythies, J. (1952). Schizophrenia: A New Approach. *Journal of Mental Science, 98*(411), 309-315. doi:10.1192/bjp.98.411.309

Paquay, J., Arnould, F., & Burton, P. (1959). Etude clinique de l'action du R 1625 à doses modérées en psychiatrie. *Acta neurologica et psychiatrica Belgica, 59*, 882-891.

Paquay, J., Arnould, F., & Burton, P. (1960). Experimentation clinique du Haloperidol. *Acta neurologica et psychiatrica Belgica, 60*, 108-116.

Paton, W. D. M. (1960). The Principles of Drug Action: President's Address. *Proceedings of the Royal Society of Medicine, 53*(10), 815-820. doi:10.1177/003591576005301002

Pletscher, A., Shore, P. A., & Brodie, B. B. (1955). Serotonin release as a possible mechanism of reserpine action. *Science, 122*(3165), 374-375. doi:10.1126/science.122.3165.374

Rapport, M. M. (1949). Serum vasoconstrictor (serotonin) the presence of creatinine in the complex; a proposed structure of the vasoconstrictor principle. *Journal of Biological Chemistry, 180*(3), 961-969. doi:https://doi.org/10.1016/S0021-9258(19)51208-X

Rosenfeld, H. (1961). Leopold Bellak (Ed.): Schizophrenia: A Review of the Syndrome (Book Review). *The International Journal of Psycho-Analysis, 42*, 126.

Rossum, J.M. van, Janssen, P., Boissier, J., Julou, L., Loew, D., Nielsen, I. M., . . . Tedeschi, D. (1970). Pharmacology. In *The neuroleptics* (Vol. 5, pp. 23-70): Karger Publishers.

Rossum, J. M. van (1958). *Pharmacodynamics of cholinomimetic and cholinolytic drugs: theories on drug-receptor interactions and structure-action relationships of quaternary ammonium salts.*[Doctoral thesis, Radboud University]

Rossum, J. M. van. (1966a). The significance of dopamine-receptor blockade for the action of neuroleptic drugs. In B. H (Ed.), *Neuro-Psycho-Pharmacology* (pp. 321-329). Amsterdam: Excerpta Medica Foundation.

Rossum, J. M. van (1966b). The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Archives internationales de pharmacodynamie et de therapie, 160*(2), 492-494. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/5954044

Rossum, J. M. van, & Hurkmans, J. A. T. M. (1964). Mechanism of action of psychomotor stimulant drugs: Significance of dopamine in locomotor stimulant action. *International Journal of Neuropharmacology, 3*(2), 227-239. doi:https://doi.org/10.1016/0028-3908(64)90012-7

Rossum, J. M. van, Amerom, W. F. H., Daamen, J. L., Hurkmans, J. A. T. M., Megens, G. J. J., & Peters, K. A. (1962). Cumulative record of motor activity. (A new procedure and its use for the study of central stimulant drugs). *Experientia, 18*(2), 93-96. doi:10.1007/BF02138279

Rossum, J. M. van, Schoot, J. B. van der, & Hurkmans, J. A. T. M. (1962). Mechanism of action of cocaine and amphetamine in the brain. *Experientia, 18*(5), 229-231. doi:10.1007/BF02148316

Samuels, A. S. (1961). A controlled study of haloperidol: the effects of small dosages. *American Journal of Psychiatry 118*(3), 253-254. doi:10.1176/ajp.118.3.253

Sanan, S., & Vogt, M. (1962). Effect of drugs on the noradrenaline content of brain and peripheral tissues and its significance. *British journal of pharmacology and chemotherapy, 18*(1), 109-127.

Sano, I., Gamo, T., Kakimoto, Y., Taniguchi, K., Takesada, M., & Nishinuma, K. (1959). Distribution of catechol compounds in human brain. *Biochimica et Biophysica Acta, 32*, 586-587. doi:https://doi.org/10.1016/0006-3002(59)90652-3

Sarwer-Foner, G. (1966). A Note on the Origins and past History of the Nameless Psychiatric Research Group Sometimes Called "The Group-Without-A-Name". *Canadian Psychiatric Association Journal, 11*(1_suppl), 7-8. doi:10.1177/070674376601101s03

Sarwer-Foner, G. (1994). *Gerald Sarwer-Foner,* ACNP, https://acnp.org/videos/gerald-sarwer-foner-by-george-awad/

Saunders, J. C. (1965). Lasker Award: Priority Claim. *Journal of the American Medical Association, 191*(10), 865-865. doi:10.1001/jama.1965.03080100083031

Schneider, K. (2009/1956). *Kraepelin und die gegenwärtige Psychiatrie, Anthology of German Psychiatric Texts:* Wiley. (originally published in 1956)

Sciences, N. A. o. (2003). *Biographical Memoirs: Volume 83*. Washington, DC: The National Academies Press.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry , 20*(1), 11.

Seabra-Dinis, J., & da Silva, M. (1960). L'emploi thérapeutique d'un nouveau médicament non phénothiazinique, le R 1625 ou halopéridol, chez des malades mentaux d'évolution prolongée. *Acta neurologica et psychiatrica Belgica, 60*, 123.

Seeman, M. (2004). Therapy in the gray zone: psychiatry recalled. *Canadian Medical Association Journal, 171*(12), 1477-1479. doi:10.1503/cmaj.1040002

Seeman, M. (2017). The 1960s in North American psychiatry. *Hektoen International*. Retrieved from https://hekint.org/2017/11/16/1960s-north-american-psychiatry/

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 of the United States of America, 72*(11), 4376-4380. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC388724/

Semelaigne, R. (1932). *Les Pionniers de la psychiatrie française avant et après Pinel*, vol. 2, Paris, J. B. Baillière, 243.

Services, U. S. C. S. C. o. A. (1969). Authorization for Military Procurement, Research and Development, Fiscal Year 1970, and Reserve Strength: Hearings, Ninety-first Congress, First Session, on S. 1192 and S. 2407 [and S. 2546]: U.S. Government Printing Office.

Shapiro, A. K. (1959). The placebo effect in the history of medical treatment: implications for psychiatry. *American Journal of Psychiatry 116*(4), 298-304. doi:10.1176/ajp.116.4.298

Shepherd, M., & Watt, D. C. (1956). A controlled clinical study of chlorpromazine and reserpine in chronic schizophrenia. *Journal of Neurology, Neurosurgery, and Psychiatry, 19*(3), 232-235. doi:10.1136/jnnp.19.3.232

Stanley, E. (1992). The "Social Chemistry" of Pharmacological Discovery: The Haloperidol Story. An Interview with Dr. Paul Janssen, January 21, 1986. *International Journal of the Addictions, 27*(3), 331-346. doi:10.3109/10826089209068746

Steck, H. (1926). Les syndromes extrapyramidaux dans les maladies mentales.*Archives Suisses de Neurologie et de Psychiatrie, 19*, 195-233.

Steck, H. (1927). Psychiatrie et Biologie: Leçon inaugurale donnée le 2 mars 1926, à Lausanne. *Schweizerische medizinische Wochenschrift., 57(19):*, 436–441.

Steck, H. (1931). Les syndromes mentaux postencéphalitiques. *Archives Suisses de Neurologie et de Psychiatrie*, 137-173.

Steck, H. (1954). Le syndrome extrapyramidal et diencéphalique au cours des traitements au largactil et au serpasil. *Annales Médico-Psychologiques (Paris), 112*(2), 737-743.

Stein, L. (1966). Psychopharmacological Aspects of Mental Depression. *Canadian Psychiatric Association Journal, 11*(1_suppl), 34-49. doi:10.1177/070674376601101S13

Stengel, E. (1960). Schizophrenia. A Review of the Syndrome. Ed. by Leopold Bellak. Logos Press, New York, 1958. Pp. 1010. $14.75. *Journal of Mental Science, 106*(443), 780-781. doi:10.1192/bjp.106.443.780-b

Stertz, G. (1921). Der extrapyramidale Symptomenkomplex (das dystonische Syndrom) und seine Bedeutung in der Neurologie: Karger Publishers.

Stewart, P. (1909). Paralysis Agitans. *The Hospital, 46*(1201), 511.

Strom-Olsen, R. (1965). The importance of the orbital cortex in psychiatry. *Acta Psychiatrica Scandinavica, 41*(3), 274-285. doi:10.1111/j.1600-0447.1965.tb04987.x

Strom-Olsen, R., & Tow, P. M. (1949). Late social results of prefrontal leucotomy. *Lancet, 1*(6542), 87-90. doi:10.1016/s0140-6736(49)90293-7

Udenfriend, S. (1995). Development of the spectrophotofluorometer and its commercialization. *Protein science : a publication of the Protein Society, 4*(3), 542-551. doi:10.1002/pro.5560040321

Uhrbrand, L., & Faurbye, A. (1960). Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine and electroconvulsive therapy. *Psychopharmacologia, 1*(5), 408-418. doi:10.1007/BF00441188

Venning, G. R. (1963). A Hypothesis Concerning a Site of Action of Tranquilizing Drugs and the Significance Of Associated Extrapyramidal Motor Phenomena. *The Journal of New Drugs, 3*(6), 351-355. doi:doi:10.1002/j.1552-4604.1963.tb00090.x

Venning, G. R. (1983). Identification Of Adverse Reactions To New Drugs. II (Continued): How Were 18 Important Adverse Reactions Discovered And With What Delays? *British Medical Journal (Clinical Research Edition), 286*(6362), 365-368. Retrieved from http://www.jstor.org/stable/29509541

Vialli, M., & Erspamer, V. (1937). Ricerche sul secreto delle cellule enterocromaffini. *Zeitschrift für Zellforschung und Mikroskopische Anatomie, 27*(1), 81-99. doi:10.1007/BF00391792

Vint, F. (1934). The brain of the Kenya native. *Journal of Anatomy, 68*(Pt 2), 216.

Vogt, M. (1969). Release from brain tissue of compounds with possible transmitter function: interaction of drugs with these substances. *British journal of pharmacology, 37*(2), 325.

Waelkens, J. (1960). Etude clinique du R 1625 (Halopéridol). *Acta neurologica et psychiatrica Belgica, 60*, 128.

William Beecher Scoville obituary. (1984). *Hartford Courant,* p. 68.

Willis, R. A. (1958). *The borderland of embryology and pathology*. London: Butterworth.

Wittenborn, J. R. (1986). The Wittenborn Psychiatric Rating Scale. In N. Sartorius & T. A. Ban (Eds.), *Assessment of Depression* (pp. 249-258). Berlin, Heidelberg: Springer Berlin Heidelberg.

Woolley, D. W., & Shaw, E. (1954). A Biochemical and Pharmacological Suggestion About Certain Mental Disorders. *Proceedings of the National Academy of Sciences of the United States of America, 40*(4), 228-231. doi:10.1073/pnas.40.4.228

Wortis, J. (1962). Physiological treatment. *American Journal of Psychiatry, 118*, 595-599. doi:10.1176/ajp.118.7.595

Young, D., & Scoville, W. B. (1938). Paranoid Psychosis in Narcolepsy and the Possible Danger of Benzedrine Treatment. *Medical Clinics of North America, 22*(3), 637-646. doi:https://doi.org/10.1016/S0025-7125(16)37027-4

B) Secondary sources

American Psychiatric Association . (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.)

Awouters, F. H. L., & Lewi, P. J. (2007). Forty Years of Antipsychotic Drug Research – from Haloperidol to Paliperidone – with Dr. Paul Janssen. *Arzneimittelforschung, 57*(10), 625-632. doi:10.1055/s-0031-1296660

Ban, T. A. (2007). Fifty years chlorpromazine: a historical perspective. *Neuropsychiatric Disease and Treatment, 3*(4), 495-500.

Ban, T. A., & Hippius, H. (2012). *Thirty Years CINP: A Brief History of the Collegium Internationale Neuro-Psychopharmacologicum:* Springer Science & Business Media.

Barras, V. (2001).[Review of A history of psychiatry from the era of the asylum to the age of Prozac by Edward Shorter] *Journal of History of The Behavioral Sciences*. 37:95-96 .https://doi.org/10.1002/1520-6696(200124)37:1<95::AID-JHBS26>3.0.CO;2-3.

Barrett, R. J. (1998a). Conceptual foundations of schizophrenia: I. Degeneration. *Australian and New Zealand Journal of Psychiatry, 32*(5), 617-626. doi:10.3109/00048679809113113

Barrett, R. J. (1998b). Conceptual Foundations of Schizophrenia: II. Disintegration and Division. *Australian & New Zealand Journal of Psychiatry, 32*(5), 627-634. doi:10.3109/00048679809113114

Baumeister, A. (2000). The Tulane Electrical Brain Stimulation Program A Historical Case Study in Medical Ethics. *Journal of the History of the Neurosciences, 9*(3), 262-278. doi:10.1076/jhin.9.3.262.1787

Baumeister, A. (2011). The Search for an Endogenous Schizogen: The Strange Case of Taraxein. *Journal of the History of the Neurosciences, 20*(2), 106-122. doi:10.1080/0964704X.2010.487427

Baumeister, A. A. (2013). The chlorpromazine enigma. *Journal of the History of the Neurosciences, 22*(1), 14-29. doi:10.1080/0964704x.2012.664087

Baumeister, A. A., & Francis, J. L. (2002). Historical Development of the Dopamine Hypothesis of Schizophrenia. *Journal of the History of the Neurosciences, 11*(3), 265-277. doi:10.1076/jhin.11.3.265.10391

Baumeister, A. A., Hawkins, M. F., & Uzelac, S. M. (2003). The Myth of Reserpine-Induced Depression: Role in the Historical Development of the Monoamine Hypothesis. *Journal of the History of the Neurosciences, 12*(2), 207-220. doi:10.1076/jhin.12.2.207.15535

Berrios, G. E. (1985). Positive and Negative Symptoms and Jackson: A Conceptual History. *Archives of General Psychiatry, 42*(1), 95-97. doi:10.1001/archpsyc.1985.01790240097011

Berrios, G. E. (1996). *The History of Mental Symptoms: Descriptive Psychopathology since the Nineteenth Century*. Cambridge: Cambridge University Press.

Berrios, G. E. (2018). Historical epistemology of the body-mind interaction in psychiatry. *Dialogues Clin Neurosci, 20*(1), 5-13. doi:10.31887/DCNS.2018.20.1/gberrios

Berrios, G. E., & Beer, D. (1994). The notion of unitary psychosis: a conceptual history. *History of Psychiatry, 5*(17), 013-036. doi:10.1177/0957154x9400501702

Berrios, G. E., Luque, R., & Villagrán, J. M. (2003). Schizophrenia: a conceptual history. *International journal of psychology and psychological therapy, 3*(2), 111-140.

Beveridge, A. (1997). [Review of A history of psychiatry from the era of the asylum to the age of Prozac by Edward Shorter] *The British Journal of Psychiatry, 171*(4), 397-397.

Beveridge, A. (2014). The history of psychiatry: personal reflections. *J R Coll Physicians Edinb, 44*(1), 77-84. doi:10.4997/jrcpe.2014.118

Bovet, E. (2012). *Biographie du diencéphale. Revisiter l'histoire de la psychiatrie à travers le parcours d'une zone cérébrale.*[Doctoral thesis, Université de Lausanne]

Bovet, E. (2015). Biography of a brain structure: studying the diencephalon as an epistemic object. In K. S. Kendler & J. Parnas (Eds.), *Philosophical Issues in Psychiatry III: The Nature and Sources of Historical Change*: Oxford University Press.

Buchenau, S. (2002). Trieb, Antrieb, Triebfeder dans la philosophie morale prékantienne. *Revue germanique internationale*(18), 11-24.

Buckman, J. (1977). Brainwashing, Lsd, and Cia: Historical and Ethical Perspective. *International Journal of Social Psychiatry, 23*(1), 8-19. doi:10.1177/002076407702300103

Burnham, J. C. (2011). Transnational history of medicine after 1950: framing and interrogation from psychiatric journals. *Medical history, 55*(1), 3-26. doi:10.1017/s0025727300006025

Caroff, S. N., Ungvari, G. S., & Cunningham Owens, D. G. (2018). Historical perspectives on tardive dyskinesia. *Journal of the Neurological Sciences, 389*, 4-9. doi:10.1016/j.jns.2018.02.015

Carpenter, D. (2014). *Reputation and power: Organizational image and pharmaceutical regulation at the FDA* (Vol. 137): Princeton University Press.

Castel, R. (1971). L'institution psychiatrique en question. *Revue française de sociologie*, 57-92. Retrieved from https://www.persee.fr/doc/rfsoc_0035-2969_1971_num_12_1_1949

Charland, L. (2013). Why psychiatry should fear medicalization. *The Oxford handbook of philosophy and psychiatry*.

Chlorpromazine for treating schizophrenia. (2020). Retrieved from https://laskerfoundation.org/winners/chlorpromazine-for-treating-schizophrenia/

Choquard, F. (2012). *Le regard d'un psychiatre sur les écrits de la folie: la carrière de Hans Steck à l'Asile psychiatrique de Cery (1920-1960).*[Doctoral thesis, Université de Lausanne]

Costa, E., Karczmar, A. G., & Vesell, E. S. (1989). Bernard B. Brodie and the rise of chemical pharmacology. *Annual Review of Pharmacology and Toxicology, 29*(1), 1-21. doi:10.1146/annurev.pa.29.040189.000245

Costall, B., Domeney, A. M., Kelly, M. E., & Naylor, R. J. (1991). Pharmacological Models in the Development of Antipsychotic Drugs — New Strategies. In B. Olivier, J. Mos, & J. L. Slangen (Eds.), *Animal Models in Psychopharmacology* (pp. 253-263). Basel: Birkhäuser Basel.

CountyAsylums. (n. d.). Runwell Hospital. Retrieved from https://www.countyasylums.co.uk/runwell-chelmsford/

Crow, T. J. (1980). Positive and Negative Schizophrenic Symptoms and the Role of Dopamine. *British Journal of Psychiatry, 137*(4), 383-386. doi:10.1192/S0007125000071919

Curzon, G. (1990). How reserpine and chlorpromazine act: the impact of key discoveries on the history of psychopharmacology. *Trends in Pharmacological Sciences, 11*(2), 61-63. doi:https://doi.org/10.1016/0165-6147(90)90318-3

Czech, H., & Zeidman, L. A. (2014). Walther Birkmayer, Co-describer of L-Dopa, and His Nazi Connections: Victim or Perpetrator? *Journal of the History of the Neurosciences, 23*(2), 160-191. doi:10.1080/0964704X.2013.865427

Daemmrich, A. (2002). A Tale of Two Experts: Thalidomide and Political Engagement in the United States and West Germany. *Social History of Medicine, 15*(1), 137-158. doi:10.1093/shm/15.1.137

Danziger, K. (1997). *Naming the Mind: How Psychology Found Its Language*: SAGE Publications.

Demetriades, A. K. (2012). From encephalitis lethargica to cerebral cytoarchitectonics: the polymath talent of Constantin von Economo (1876-1931), pioneer neuroanatomist, neurophysiologist and military aviator. *Scottish Medical Journal, 57*(4), 232-236. doi:10.1258/smj.2012.012108

Dickman, M. S. (2001). von Economo encephalitis. *Archives of neurology, 58*(10), 1696-1698. doi:10.1001/archneur.58.10.1696

Dunn, L. B., Candilis, P. J., & Roberts, L. W. (2006). Emerging Empirical Evidence on the Ethics of Schizophrenia Research. *Schizophrenia Bulletin, 32*(1), 47-68.

Ehrenberg, A. (2004). Le sujet cérébral. *Esprit (1940-)*(309 (11)), 130-155. Retrieved from http://www.jstor.org/stable/24249872

Ellenbroek, B. A., & Cools, A. R. (2003). Animal Models for Schizophrenia. *Biological Psychiatry*. Retrieved from https://doi.org/10.1002/0470854871.chxvii1

Enoch, D., Puri, B. K., & Ball, H. (2020). *Uncommon psychiatric syndromes*: Routledge.

Enoch, M. D., & Irving, G. (1962). The Ganser Syndrome. *Acta Psychiatrica Scandinavica, 38*(3), 213-222. doi:10.1111/j.1600-0447.1962.tb01795.x

Erhardt, L. R. (2003). Women – a Neglected Risk Group for Atherosclerosis and Vascular Disease. *Scandinavian Cardiovascular Journal, 37*(1), 3-12. doi:10.1080/14017430310006965

Eyal, S. (2018). The Fever Tree: from Malaria to Neurological Diseases. *Toxins, 10*(12), 491. Retrieved from https://www.mdpi.com/2072-6651/10/12/491

Faden, R. R., Beauchamp, T. L., & King, N. M. P. (1986). *A History and Theory of Informed Consent*: Oxford University Press.

Foer, J. (2005). The Adderall Me. *Slate.* Retrieved from https://slate.com/technology/2005/05/my-romance-with-adhd-meds.html

Foley, P. (2000). *The L-DOPA story revisited. Further surprises to be expected?* Paper presented at the Advances in Research on Neurodegeneration, Vienna.

Foley, P. (2018). *Encephalitis Lethargica: The Mind and Brain* Virus: Springer New York.

Foucault, M. (1961). *Folie et Déraison: Histoire de la Folie à l'age classique*. Gallimard

Fulford, B., Thornton, T., & Graham, G. (2006). *Oxford Textbook of Philosophy and Psychiatry*: OUP Oxford.

Gauchet, M., & Swain, G. (2012). *Madness and Democracy*: Princeton University Press.

Gaunt, R. (1977). Animal models in drug development: historical aspects. *Oncology, 34*(3), 94-95. doi:10.1159/000225197

Geyer, M. A., & Markou, A. (1995). Animal models of psychiatric disorders. *Psychopharmacology: the fourth generation of progress*, 787-798.

Geyer, M. A., & Moghaddam, B. (2002). Animal models relevant to schizophrenia disorders. In *Neuropsychopharmacology: The Fifth Generation of Progress* (Kenneth L. Davis, ed.).

Gilman, S. L. (1985). *Difference and pathology : stereotypes of sexuality, race, and madness*. Ithaca: Cornell University Press.

Goetz, C. G. (2011). The history of Parkinson's disease: early clinical descriptions and neurological therapies. *Cold Spring Harbor Perspectives in Medicine , 1*(1), a008862. doi:10.1101/cshperspect.a008862

Goffman, E. (1961). *Asylums: Essays on the social situation of mental patients and other inmates*: AldineTransaction.

Gold, I., & Stoljar, D. (1999). A neuron doctrine in the philosophy of neuroscience. *Behavioral and Brain Sciences, 22*(5), 809-830; discussion 831-869.Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11301571

Goulet, D (n. d.). Capsules historiques. Retrieved from https://medecine.umontreal.ca/faculte/histoire/capsules-historiques/

Granger, B., & Albu, S. (2005). The Haloperidol Story. *Annals of Clinical Psychiatry, 17*(3), 137-140. doi:10.3109/10401230591002048

Green, A. R. (2008). Gaddum and LSD: the birth and growth of experimental and clinical neuropharmacology research on 5-HT in the UK. *British journal of pharmacology, 154*(8), 1583-1599. doi:10.1038/bjp.2008.207

Gründer, G., & Cumming, P. (2016). Chapter 7 - The Dopamine Hypothesis of Schizophrenia: Current Status. In T. Abel & T. Nickl-Jockschat (Eds.), *The Neurobiology of Schizophrenia* (pp. 109-124). San Diego: Academic Press.

Hargittai, I., & Hargittai, M. (2015). *Budapest Scientific: A Guidebook*: Oxford University Press.

Harrow, M., Adler, D., & Hanf, E. (1974). Abstract and Concrete Thinking in Schizophrenia During the Prechronic Phases. *Archives of General Psychiatry, 31*(1), 27-33. doi:10.1001/archpsyc.1974.01760130013002

Healy, D. (1997). *The Antidepressant Era*: Harvard University Press.

Healy, D. (1997). [Review of A history of psychiatry from the era of the asylum to the age of Prozac by Edward Shorter] *Journal of psychopharmacology*.

Healy, D. (2002). *The creation of psychopharmacology*. Cambridge, MA: Harvard University Press.

Healy, D. (2008). The Intersection of Psychopharmacology and Psychiatry in the Second Half of the Twentieth Century. In E. R. Wallace & J. Gach (Eds.), *History of Psychiatry and Medical Psychology: With an Epilogue on Psychiatry and the Mind-Body Relation* (pp. 419-437). Boston, MA: Springer US.

Healy, D. (2008). *Mania: A Short History of Bipolar Disorder*: Johns Hopkins University Press.

Healy, D. (2012). *Pharmageddon*: Univ of California Press.

Healy, D., Mangin, D., & Applbaum, K. (2014). The shipwreck of the singular. *Social studies of science, 44*(4), 518-523.

Hirshbein, L. (2010). Sex and gender in psychiatry: a view from history. *J Med Humanit, 31*(2), 155-170. doi:10.1007/s10912-010-9105-5

Hockstader, L. (1988). Victims of 1950s' Mind-control experiments settle with CIA. *The Washington Post*.

Hoff, P. (2008). Kraepelin and degeneration theory. *European archives of psychiatry and clinical neuroscience,* 258(2), 12-17.

Hornykiewicz, O. (2010). A brief history of levodopa. *Journal of Neurology, 257*(2), 249-252. doi:10.1007/s00415-010-5741-y

Howes, O. D., & Kapur, S. (2009). The Dopamine Hypothesis of Schizophrenia: Version III —The Final Common Pathway. *Schizophrenia Bulletin, 35*(3), 549-562. doi:10.1093/schbul/sbp006

Huertas, R. (1992). Madness and degeneration, Part I. From 'fallen angel' to mentally ill. *History of Psychiatry, 3*(12), 391-411. doi:10.1177/0957154X9200301201

Huertas, R. (2001). Historia de la psiquiatría,¿ por qué?,¿ para qué? *Frenia. Revista de historia de la psiquiatría, 1*(1), 9-36.

Iproniazid for the treatment of severe depression. (2020). Retrieved from https://laskerfoundation.org/winners/iproniazid-for-the-treatment-of-severe-depression/

Jacobs, A. (2012). The Lost World of Benzedrine. Retrieved from https://www.theatlantic.com/health/archive/2012/04/the-lost-world-of-benzedrine/255904/

Janzarik, W. (1985). Present-Day German-Speaking Psychiatry. In P. Pichot, P. Berner, R. Wolf, & K. Thau (Eds.), *Psychiatry The State of the Art: Volume 8 History of Psychiatry, National Schools, Education, and Transcultural Psychiatry* (pp. 189-194). Boston, MA: Springer US.

Javitt, D., & Laruelle, M. (2006). Neurochemical Theories. In *The American Psychiatric Publishing textbook of schizophrenia*. Washington, DC: American Psychiatric Pub.

Jones, A. H. (2005). The cautionary tale of psychiatrist Henry Aloysius Cotton. *The Lancet, 366*(9483), 361-362.

Katschnig, H. (2018). Psychiatry's contribution to the public stereotype of schizophrenia: Historical considerations. *Journal of Evaluation in Clinical Practice, 24*(5), 1093-1100. doi:10.1111/jep.13011

Kendler, K. S. (2014). The dopamine hypothesis of schizophrenia: an updated perspective. In Kendler & J. Parnas (Eds.), *Philosophical issues in psychiatry III: The Nature and Sources of Historical Change* (pp. 283-294).

Kendler, K. S. (2020). The Development of Kraepelin's Concept of Dementia Praecox: A Close Reading of Relevant Texts. *Journal of the American Medical Association Psychiatry, 77*(11), 1181-1187. doi:10.1001/jamapsychiatry.2020.1266

Kendler, K. S., & Schaffner, K. F. (2011). The Dopamine Hypothesis of Schizophrenia: An Historical and Philosophical Analysis. *Philosophy, Psychiatry, and Psychology, 18*(1), 41-63.

Kety, S. S. (1980). The Syndrome of Schizophrenia: Unresolved Questions and Opportunities for Research: The Fifty-second Maudsley Lecture, delivered before the Royal College of Psychiatrists in London, 17 November, 1978. *The British Journal of Psychiatry, 136*(5), 421-436.

Keynejad, R. (2015). Profile: Morgan David Enoch. *BJPsych Bulletin, 39*(3), 145-147. doi:10.1192/pb.bp.114.048066

Kim, M. (2019, February 18). Brainwashed. *Foreign policy.* Retrieved from https://foreignpolicy.com/2019/02/18/brainwashed-north-korea-prisoners-of-war-monica-kim/

Klein, D. F. (2007). Commentary by a Clinical Scientist in Psychopharmacological Research. *Journal of Child and Adolescent Psychopharmacology, 17*(3), 284-287. doi:10.1089/cap.2007.0032

Kroll, J. (1979). Philosophical foundations of French and U.S. nosology. *American Journal of Psychiatry, 136*(9), 1135-1138. doi:10.1176/ajp.136.9.1135

Kuhn, R. (2004). Eugen Bleuler's Concepts of Psychopathology. *History of Psychiatry, 15*(3), 361-366. doi:10.1177/0957154X04044603

Lakoff, A. (2006). P*harmaceutical reason: Knowledge and value in global psychiatry*: Cambridge University Press.

Lanteri-Laura, G. (1972). La chronicité dans la psychiatrie moderne française. Note d'histoire théorique et sociale. *Annales*, 548-568. Retrieved from https://www.persee.fr/doc/ahess_0395-2649_1972_num_27_3_422522

Latour, B. (1994). On technical mediation. *Common knowledge, 3*(2).

Lau, C.-I., Wang, H.-C., Hsu, J.-L., & Liu, M.-E. (2013). Does the dopamine hypothesis explain schizophrenia? In *Reviews in the Neurosciences* (Vol. 24, pp. 389).

Lees, A. J., Tolosa, E., & Olanow, C. W. (2015). Four pioneers of L-dopa treatment: Arvid Carlsson, Oleh Hornykiewicz, George Cotzias, and Melvin Yahr. *Movement Disorders, 30*(1), 19-36. doi:https://doi.org/10.1002/mds.26120

Lehmann, H. E. (1993). Before They Called It Psychopharmacology. *Neuropsychopharmacology, 8*(4), 291-303. doi:10.1038/npp.1993.69

Lenz, W. (1988). A short history of thalidomide embryopathy. *Teratology, 38*(3), 203-215. doi:10.1002/tera.1420380303

Lewi, P. J. (2008). The conductor and his orchestra. *Drug Discovery Today, 13*(7–8), 281-284. doi:http://dx.doi.org/10.1016/j.drudis.2008.02.008

Lewi, P. J., & Smith, A. (2007). Successful pharmaceutical discovery: Paul Janssen's concept of drug research. *R&D Management, 37*(4), 355-362. doi:doi:10.1111/j.1467-9310.2007.00481.x

Lichterman, B. (2009). Henry Molaison. *British medical journal, 338*, b968. doi:10.1136/bmj.b968

Liégeois, A. (1991). Hidden philosophy and theology in Morel's theory of degeneration and nosology. *History of Psychiatry, 2*(8), 419-427. doi:10.1177/0957154X9100200805

López-Muñoz, F., & Alamo, C. (2009). The consolidation of neuroleptic therapy: Janssen, the discovery of haloperidol and its introduction into clinical practice. *Brain Research Bulletin, 79*(2), 130-141. doi:http://dx.doi.org/10.1016/j.brainresbull.2009.01.005

López-Muñoz, F., Alamo, C., cuenca, E., Shen, W. W., Clervoy, P., & Rubio, G. (2005). History of the Discovery and Clinical Introduction of Chlorpromazine. *Annals of Clinical Psychiatry, 17*(3), 113-135. doi:10.3109/10401230591002002

Madras, B. K. (2013). History of the Discovery of the Antipsychotic Dopamine D2 Receptor: A Basis for the Dopamine Hypothesis of Schizophrenia. *Journal of the History of the Neurosciences, 22*(1), 62-78. doi:10.1080/0964704X.2012.678199

Majerus, B. (2011). La baignoire, le lit et la porte. La vie sociale des objets de la psychiatrie. *Genèses, 82*(1), 95-119. doi:10.3917/gen.082.0095

Majerus, B. (2013). *Parmi les fous. Une histoire sociale de la psychiatrie au XX e siècle*, Rennes, PUR.

Mason, P. H. (2010). Degeneracy at multiple levels of complexity. *Biological Theory, 5*(3), 277-288.

Matthysse, S. (1986). *Animal Models in Psychiatric Research.* In J. M. Van Ree & S. Matthysse (Eds.), *Progress in Brain Research* (Vol. 65, pp. 259-270): Elsevier.

May, E. L., & Jacobson, A. E. (1989). The Committee on Problems of Drug Dependence: a legacy of the National Academy of Sciences. A historical account. *Drug Alcohol Depend, 23*(3), 183-218. doi:10.1016/0376-8716(89)90083-5

McCook, A. (2004). Sune K Bergström. *The Lancet, 364*(9438), 930.

McKenna, P. J., Lund, C. E., Mortimer, A. M., & Biggins, C. A. (1991). Motor, volitional and behavioural disorders in schizophrenia. 2: The 'conflict of paradigms' hypothesis. *British Journal of Psychiatry, 158*, 328-336. doi:10.1192/bjp.158.3.328

Metzl, J. M. (2010). *The protest psychosis: How schizophrenia became a black disease*: Beacon Press.

Minor, J. (2015). The History and Components of Informed Consent. In *Informed Consent in Predictive Genetic Testing: A Revised Model* (pp. 57-107). Cham: Springer International Publishing.

Missa, J.-N. (2006). *Naissance de la psychiatrie biologique: Histoire des traitements des maladies mentales* (1920-1960).

Missa, J.-N. (2008). La psychopharmacologie et la naissance de la psychiatrie biologique. *Les Cahiers du Centre Georges Canguilhem, 2*(1), 131-145. doi:10.3917/ccgc.002.0131

Missa, J.-N. (2010). Peut-on parler de militantisme psychopharmacologique chez les pionniers de la psychiatrie biologique (1952-1960) ? *Sud/Nord, 25*(1), 105-120. doi:10.3917/sn.025.0105

Moncrieff, J. (2009). A Critique of the Dopamine Hypothesis of Schizophrenia and Psychosis. *Harvard Review of Psychiatry, 17*(3), 214-225. doi:10.1080/10673220902979896

Moncrieff, J. (2013). *The bitterest pills: The troubling story of antipsychotic drugs:* Springer.

Moncrieff, J. (2013). Magic bullets for mental disorders: the emergence of the concept of an "antipsychotic" drug. *Journal of the History of the Neurosciences, 22*(1), 30-46. doi:10.1080/0964704x.2012.664847

Mora, G. (1970). The history of psychiatry: its relevance for the psychiatrist. *American Journal of Psychiatry, 126*(7), 957-967. doi:10.1176/ajp.126.7.957

Morrison, H. (2016). Constructing Patient Stories: 'Dynamic' Case Notes and Clinical Encounters at Glasgow's Gartnavel Mental Hospital, 1921-32. *Medical history, 60*(1), 67-86. doi:10.1017/mdh.2015.69

Moskowitz, A., & Heim, G. (2011). Eugen Bleuler's Dementia praecox or the group of schizophrenias (1911): a centenary appreciation and reconsideration. *Schizophrenia Bulletin, 37*(3), 471-479. doi:10.1093/schbul/sbr016

Noll, R. (2004). Historical review: Autointoxication and focal infection theories of dementia praecox. *World Journal of Biological Psychiatry, 5*(2), 66-72. doi:10.1080/15622970410029914

Noll, R. (2012). Dementia praecox, 1886: a new turning point? *History of Psychiatry, 23*(2), 255.

Okasha, A. (2000). Ethics of psychiatry practice: consent, compulsion, and confidentiality. *Current Opinion in Psychiatry, 13*(6). Retrieved from https://journals.lww.com/co-psychiatry/Fulltext/2000/11000/Ethics_of_psychiatry_practice__consent,.38.aspx

Paccioni, J.-P. (2002). Le terme «Trieb» et l'homme comme fin dernière et ultime. *Revue germanique internationale*(18), 25-44.

Packard, R. M. (2021). *The making of a tropical disease: a short history of malaria:* JHU Press.

Parnas, J. (2014). Introduction to" dopamine hypothesis of schizophrenia: An updated perspective". In K. Kendler & J. Parnas (Eds.), *Philosophical issues in psychiatry III: The Nature and Sources of Historical Change*.

Pavan, I. (2021). Neither citizens nor Jews: Jewish property rights after the Holocaust, a tentative survey. *European Review of History: Revue européenne d'histoire, 28*(2), 301-322. doi:10.1080/13507486.2020.1865279

Pichot, P. (1985). The French Psychiatric Tradition. In P. Pichot, P. Berner, R. Wolf, & K. Thau (Eds.), *Psychiatry The State of the Art: Volume 8 History of Psychiatry, National Schools, Education, and Transcultural Psychiatry* (pp. 183-188). Boston, MA: Springer US.

Pichot, P. (1986). The concept of 'bouffée délirante' with special reference to the Scandinavian concept of reactive psychosis. *Psychopathology, 19*(1-2), 35-43. doi:10.1159/000284427

Pichot, P. J. (1984). The French approach to psychiatric classification. *British Journal of Psychiatry, 144*, 113-118. doi:10.1192/bjp.144.2.113

Pieters, T., & Majerus, B. (2011). The introduction of chlorpromazine in Belgium and the Netherlands (1951–1968); tango between old and new treatment features. *Studies in History and Philosophy of Biological and Biomedical Sciences, 42*(4), 443-452. doi:https://doi.org/10.1016/j.shpsc.2011.05.003

Pignarre, P. (1997). *Qu'est-ce qu'un médicament, un objet étrange, entre science*. Marché et société: La Découverte Paris.

Prange, S., Pagonabarraga, J., Krack, P., Kulisevsky, J., Sgambato, V., Tremblay, L., . . . Broussolle, E. (2018). Historical crossroads in the conceptual delineation of apathy in Parkinson's disease. *Brain, 141*(2), 613-619. doi:10.1093/brain/awx362

Prüll, C., Maehle, A., & Halliwell, R. (2009). *A Short History of the Drug Receptor Concept*: Palgrave Macmillan UK.

Ramos, M. A. (2013). Drugs in Context: A Historical Perspective on Theories of Psychopharmaceutical Efficacy. *The Journal of Nervous and Mental Disease, 201*(11), 926-933. doi:10.1097/nmd.0000000000000062

Rasmussen, N. (2006). Making the first anti-depressant: amphetamine in American medicine, 1929-1950. *Journal of the History of Medicine and Allied Sciences, 61*(3), 288-323. doi:10.1093/jhmas/jrj039

Ravina, E. (2011). *The Evolution of Drug Discovery: From Traditional Medicines to Modern Drugs*: Wiley.

Raz, M. (2010). Anaclitic therapy in North America psychoanalytic and psychiatric practice in the 1950s-1960s. *Psychoanalysis and History, 12*(1), 55-68. doi:10.3366/e1460823509000543

Reed, C. (2004, August 31). Elisabeth Kubler-Ross. *The Guardian*.

Rettig, R. A. (2002). The Politics Of Science. *Health Affairs, 21*(3), 274-276. doi:10.1377/hlthaff.21.3.274

Richa, S., Masson, M., & Tawil, S. P. (2019). The dissemination of the French School of Psychiatry and its impact in the world. *L'Encephale, 45*(3), 276-278. doi:https://doi.org/10.1016/j.encep.2018.03.001

Roberts, L. W., Geppert, C. M., & Brody, J. L. (2001). A framework for considering the ethical aspects of psychiatric research protocols. *Comprehensive psychiatry, 42*(5), 351-363.

Rogers, D. (1986). Bradyphrenia in parkinsonism: a historical review. *Psychological Medicine, 16*(2), 257-265. doi:10.1017/s0033291700009077

Rogers, D. (1992). Neuropsychiatry of movement disorders. *Current Opinion in Psychiatry, 5*(1), 84-87. Retrieved from https://journals.lww.com/co-psychiatry/Fulltext/1992/02000/Neuropsychiatry_of_movement_disorders.19.aspx

Rosenberg, C. E. (2002). The tyranny of diagnosis: specific entities and individual experience. *Milbank Q, 80*(2), 237-260. doi:10.1111/1468-0009.t01-1-00003

Roy, Pradipto. Global Pharma and Local Science: The Untold Tale of Reserpine. *Indian Journal of Psychiatry*: February 2018 - Volume 60 - Issue Suppl 2 - p S277-S283 doi: 10.4103/psychiatry.IndianJPsychiatry_444_17

Sacks, O. (1999). *Awakenings*: Vintage Books.

Sandler, M. (1990). Monoamine Oxidase Inhibitors in Depression: History and Mythology. *Journal of Psychopharmacology, 4*(3), 136-139. doi:10.1177/026988119000400307

Sartorius, V., & Sartorius, N. (2020). The WPA celebrates its 70th birthday. World psychiatry : *official journal of the World Psychiatric Association (WPA)*, 19(3), 403-404. doi:10.1002/wps.20787

Saumade, F. (2018). Lévy-Bruhl, Lucien (1857–1939). In *The International Encyclopedia of Anthropology* (pp. 1-4).

Scarfone, D. (2004). Introduction. In *Les pulsions* (pp. 5-12). Paris cedex 14: Presses Universitaires de France.

Schäfer, A. (2016). Graphology in German psychiatry (1870–1930). *History of Psychiatry, 27*(3), 307-319. doi:10.1177/0957154x16646531

Schwartz, H. (1989). *Breakthrough: The Discovery of Modern Medicines at Janssen*: Skyline Publishing Group.

Scull, A. (1991). Psychiatry and its historians. *History of Psychiatry, 2*(7), 239-250.

Scull, A. (2005). *Madhouse: A tragic tale of megalomania and modern medicine:* Yale University Press.

Scull, A. T. (1977). Madness and Segregative Control: The Rise of the Insane Asylum. *Social Problems, 24*(3), 337-351. doi:10.2307/800085

Seeman, M. V. (2019). Does Gender Influence Outcome in Schizophrenia? *Psychiatric Quarterly, 90*(1), 173-184. doi:10.1007/s11126-018-9619-y

Seeman, M. V. (2022). Philip Seeman's contributions to the story of schizophrenia. *Psychological Medicine*, 1-3. doi:10.1017/S0033291721004803

Seeman, P. (2010). Historical Overview: Introduction to the Dopamine Receptors. In K. A. Neve (Ed.), *The Dopamine Receptors* (pp. 1-21). Totowa, NJ: Humana Press.

Seeman, P. (2013). Schizophrenia and dopamine receptors. *European Neuropsychopharmacology, 23*(9), 999-1009. doi:10.1016/j.euroneuro.2013.06.005

Shepherd, M. (1995). Two Faces of Emil Kraepelin. *British Journal of Psychiatry, 167*(2), 174-183. doi:10.1192/bjp.167.2.174

Shorter, E. (1997). *A history of psychiatry : from the era of the asylum to the age of Prozac.* New York: John Wiley & Sons.

Shorter, E. (2005). *A historical dictionary of psychiatry:* Oxford University Press.

Shorter, E. (2011). A brief history of placebos and clinical trials in psychiatry. *Can J Psychiatry, 56*(4), 193-197. doi:10.1177/070674371105600402

Shorter, E. (2021). *The Rise and Fall of the Age of Psychopharmacology*: Oxford University Press, Incorporated.

Shorter, E., & Healy, D. (2007). *Shock Therapy: A History of Electroconvulsive Treatment in Mental Illness*: Rutgers University Press.

Simoni, R. D., Hill, R. L., Vaughan, M., & Tabor, H. (2003). A classic instrument: The Beckman DU spectrophotometer and its inventor, Arnold O. Beckman. *Journal of Biological Chemistry, 278*(49), 79-81.

Slater, L. B. (2004). Malaria Chemotherapy and the "Kaleidoscopic" Organisation of Biomedical Research during World War II. *Ambix, 51*(2), 107-134. doi:10.1179/amb.2004.51.2.107

Sneader, W. (2005). *Drug Discovery: A History*: Wiley.

Stanley, T. H., Egan, T. D., & Van Aken, H. (2008). A tribute to Dr. Paul A. J. Janssen: entrepreneur extraordinaire, innovative scientist, and significant contributor to anesthesiology. *Anesthesia & Analgesia, 106*(2), 451-462, table of contents. doi:10.1213/ane.0b013e3181605add

Starke, K. (1998). A History of Naunyn-Schmiedeberg's Archives of Pharmacology. *Naunyn-Schmiedeberg's Archives of Pharmacology, 358*(1), 1-109. doi:10.1007/PL00005229

Stern, V. (2010). Drugs from D2. *The scientist.* Retrieved from https://www.the-scientist.com/uncategorized/drugs-from-d2-43570

Stompe, T., Ortwein-Swoboda, G., Ritter, K., Marquart, B., & Schanda, H. (2005). The impact of diagnostic criteria on the prevalence of schizophrenic subtypes. *Comprehensive psychiatry, 46*(6), 433-439. doi:https://doi.org/10.1016/j.comppsych.2005.03.003

Strous, R. D., Opler, A. A., & Opler, L. A. (2016). Reflections on "Emil Kraepelin: Icon and Reality". *American Journal of Psychiatry, 173*(3), 300-301. doi:10.1176/appi.ajp.2016.15111414

Swazey, J. P. (1974). *Chlorpromazine in psychiatry: a study of therapeutic innovation.* MIT Press.

Valenstein, E. S. (1998). *Blaming the brain : the truth about drugs and mental health*. New York: Free Press.

Valenstein, E. S. (2007). *The War of the Soups and the Sparks: The Discovery of Neurotransmitters and the Dispute Over How Nerves Communicate:* Columbia University Press.

van der Heijden, F. M., Tuinier, S., Arts, N. J., Hoogendoorn, M. L., Kahn, R. S., & Verhoeven, W. M. (2005). Catatonia: disappeared or under-diagnosed? *Psychopathology, 38*(1), 3-8. doi:10.1159/000083964

van der Veer, R. (2003). Primitive Mentality Reconsidered. *Culture & Psychology, 9*(2), 179-184. doi:10.1177/1354067x0392005

van Gestel, S., & Schuermans, V. (1986). Thirty-three years of drug discovery and research with Dr. Paul Janssen. *Drug Development Research, 8*(1-4), 1-13. doi:10.1002/ddr.430080103

Vargesson, N. (2015). Thalidomide-induced teratogenesis: history and mechanisms. *Birth Defects Res C Embryo Today, 105*(2), 140-156. doi:10.1002/bdrc.21096

Vidal, F. (2009). Brainhood, anthropological figure of modernity. *History of the Human Sciences, 22*(1), 5-36. doi:10.1177/0952695108099133

Vilensky, J. (2010). *Encephalitis Lethargica: During and After the Epidemic:* Oxford University Press.

Walker, C. (2013). Form and content in Jaspers' psychopathology. In G. Stanghellini & T. Fuchs (Eds.), *One Century of Karl Jaspers' General Psychopathology* (pp. 0): Oxford University Press.

Walker, E. F., & Lewine, R. R. (1993). Sampling biases in studies of gender and schizophrenia. *Schizophrenia Bulletin, 19*(1), 1-7.

Wallace, E. R., & Gach, J. (2010). *History of Psychiatry and Medical Psychology: With an Epilogue on Psychiatry and the Mind-Body Relation:* Springer US.

Warnes, H. (2014). Hassan Azima. Retrieved from https://inhn.org/biographies/hassan-azima-by-hector-warnes.html

Warnes, H. (2016). Hector Warnes's complementary comment. Retrieved from https://inhn.org/biographies/hassan-azima-by-hector-warnes/hector-warnes-complementary-comment.html

Washington, H. A. (2006). *Medical apartheid: The dark history of medical experimentation on Black Americans from colonial times to the present:* Doubleday Books.

Whiteley, S. (2004). The Evolution of the Therapeutic Community. *Psychiatric Quarterly, 75*(3), 233-248. doi:10.1023/B:PSAQ.0000031794.82674.e8

Winograd, M., & Davidovich, M. (2014). Freudian Psychoanalysis and Epistemology. Political Disputes. *Recherches en psychanalyse, 17*(1), 73a-88a. doi:10.3917/rep.017.0073

Wolf, M.-A., Yassa, R., & Llorca, P.-M. (1996). Neuroleptic-induced movement disorders: historical perspective. In D. V. Jeste, N. P. V. Nair, & R. Yassa (Eds.), *Neuroleptic-induced Movement Disorders: A Comprehensive Survey* (pp. 3-10). Cambridge: Cambridge University Press.

Wyss, S. (1997). *Evolution du traitement psychiatrique à Cery, 1*900-1969,. Lausanne.

Zhang, S. (2016). The Untold Story of Neuroscience's Most Famous Brain. *Wired.* Retrieved from https://www.wired.com/2016/08/untold-story-neurosciences-famous-brain/

Appendix A- Tables

Table 1- *Symposium international sur le halopéridol* Setember 15, 1959 , Beerse, Belgium

Authors	City	Number of patients	Daily dosage	Diagnostics
Divry, Bobon, Collard	Liège, Belgica	94	7,5-30mg	Diverse diagnostic
Delay, Pichot	Paris, França	40	2-24 mg average dose-8mg	Diverse diagnostic
Boissier	Paris, França	n.a. (toxicologic study in animals)	n. a.	n. a.
Chantraine	Lierneux, Belgica	55	4-10mg	Diverse diagnostic
De Haene	Saint-Michel-les-Bruges, Belgica	58	3-10mg	Diverse diagnostic
von Eiff	Bonn, Alemanha	28	4mg	n. a. (Healthy subjects)
Bo Gerle	Lund, Suécia	34	7,5-20mg	Diverse diagnostic
Humbeeck	Rekem, Belgica	81	5-15mg	Diverse diagnostic
Kristjansen	Roskilde, Dinamarca	40	7-25 mg	Diverse diagnostic
Loret	Henri-Chapelle, Belgica	52	?	Diverse diagnostic
Meurice	Lierneux, Belgica	n.a. (theoretical contribution)	n. a.	n. a.
von Oles	Neuss, Alemanha	116	6-16mg	Diverse diagnostic
Paquay	Dave, Belgica	70	3-7mg	Schizophrenia
Scarlato	Milan, Italia	49	3-10mg	Diverse diagnostic
Seabra Dinis	Lisboa, portugal	39	2-12mg	Diverse diagnostic
Wealkens	Rekem, Belgica	160	1,5-3mg	Diverse diagnostic

(1960) *Acta Neurol Psychiatr Belgica,* Vol 60, 7-135

Table 2

Herman Denber's studies at the Manhattan State Hospital until 1959 (excluding chlorpromazine)			
Trade name	Pacatal	RP 7843 (Majeptil)	R 1625 (Haldol / Serenace)
Generic name	Mepazine	Thioproperazina	Haloperidol
Pharmaceutical Company	Warner-Chilcott laboratories	Smith, Kline and French	Janssen (Searle)
Date of publication	January 1958	June 1959	October 1959
Number of patients	47	23	30
Substancial improvement	9%	17%	13%
Improvement	25%	52%	17%
No improvement	66%	26%	70%
Worsening	0%	4%	0%

Appendix B - Illustrations

Figure 1

Photo prise lors de l'inauguration du cycle des séminaires Paul Janssen sur la Réhabilitation des schizophrènes.

On y voit de gauche à droite : le Professeur Marc Ansseau, le Dr Paul Janssen, le Dr Emile Meurice et le Professeur Jacques Boniver

(Meurice, 2005, p. 5)

Figure 2

FIG. 1 *Advertisements for the antipsychotic drug Haldol from the 1970s depicted black men with clenched fists, under the headline "Assaultive and belligerent?"* (Archives of General Psychiatry *31, no. 5 (1974): 732-33.)*

(Metzl, 2010, p XIV)

Figure 3

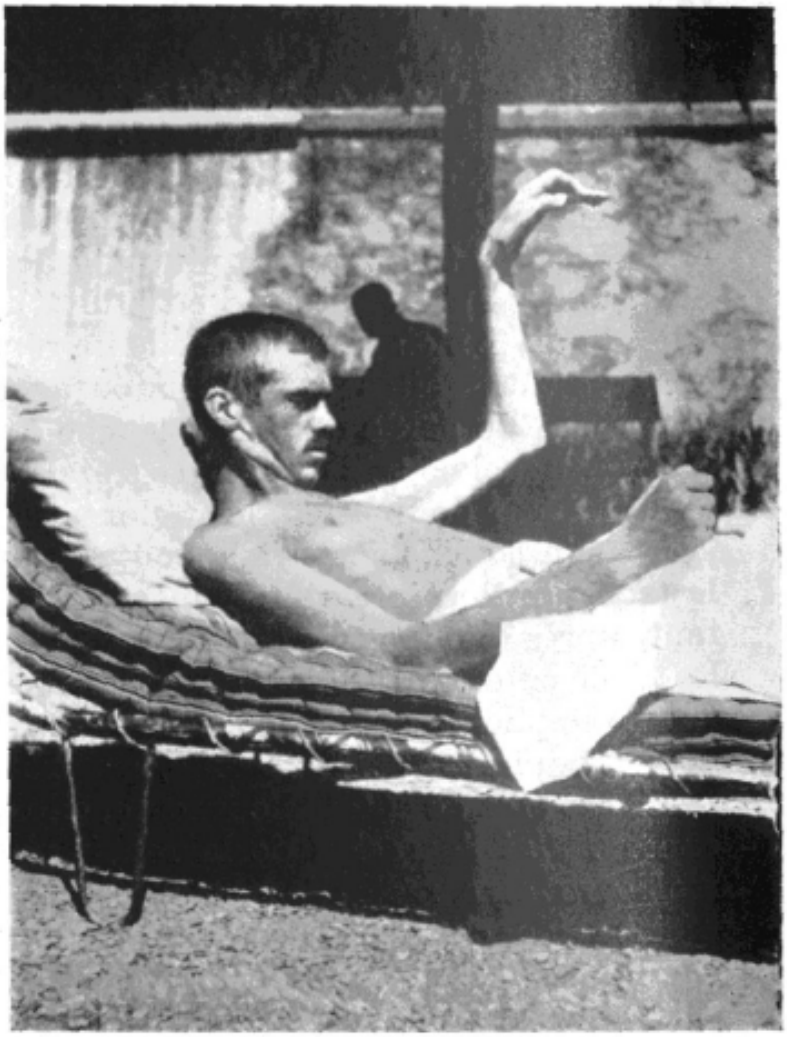
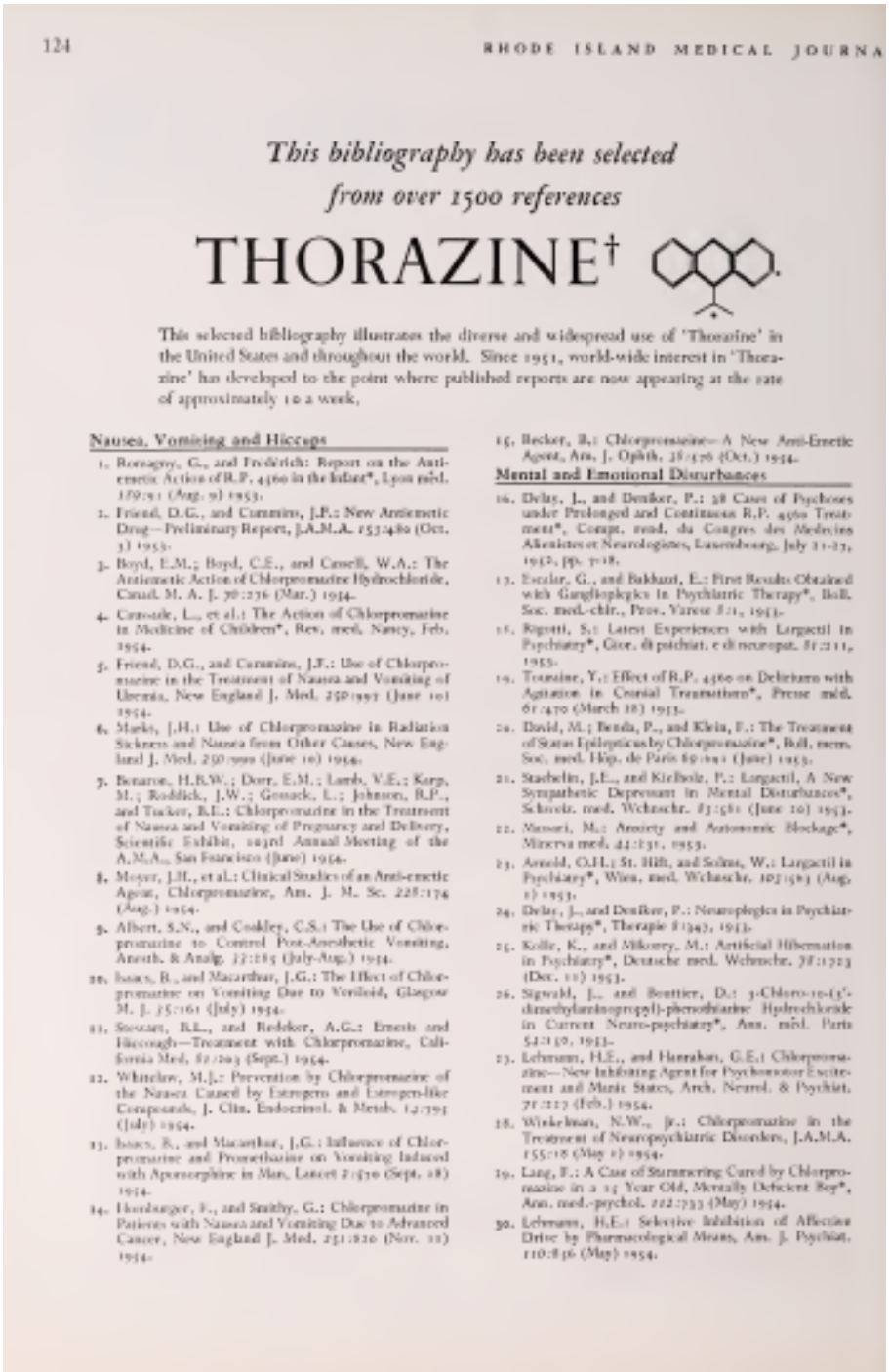


Fig. 14.
Couché: oreiller psychique et catalepsie.

(Steck, 1926)

Figure 4



This bibliography has been selected from over 1500 references

THORAZINE†

This selected bibliography illustrates the diverse and widespread use of 'Thorazine' in the United States and throughout the world. Since 1951, world-wide interest in 'Thorazine' has developed to the point where published reports are now appearing at the rate of approximately 10 a week.

Nausea, Vomiting and Hiccups

1. Ronagny, G., and Frédérich: Report on the Antiemetic Action of R.P. 4560 in the Infant*, Lyon méd. 189:91 (Aug. 9) 1953.
2. Friend, D.G., and Cammins, J.F.: New Antiemetic Drug—Preliminary Report, J.A.M.A. 153:480 (Oct. 3) 1953.
3. Boyd, E.M.; Boyd, C.E., and Cassell, W.A.: The Antiemetic Action of Chlorpromazine Hydrochloride, Canad. M. A. J. 70:276 (Mar.) 1954.
4. Cornade, L., et al.: The Action of Chlorpromazine in Medicine of Children*, Rev. med. Nancy, Feb. 1954.
5. Friend, D.G., and Cammins, J.F.: Use of Chlorpromazine in the Treatment of Nausea and Vomiting of Uremia, New England J. Med. 250:1007 (June 10) 1954.
6. Markt, J.H.: Use of Chlorpromazine in Radiation Sickness and Nausea from Other Causes, New England J. Med. 250:999 (June 10) 1954.
7. Benaron, H.B.W.; Dorr, E.M.; Lamb, V.E.; Karp, M.; Roddick, J.W.; Gonsack, L.; Johnson, R.P., and Tucker, B.E.: Chlorpromazine in the Treatment of Nausea and Vomiting of Pregnancy and Delivery, Scientific Exhibit, 123rd Annual Meeting of the A.M.A., San Francisco (June) 1954.
8. Moyer, J.H., et al.: Clinical Studies of an Anti-emetic Agent, Chlorpromazine, Am. J. M. Sc. 228:174 (Aug.) 1954.
9. Albert, S.N., and Coakley, C.S.: The Use of Chlorpromazine to Control Post-Anesthetic Vomiting, Anesth. & Analg. 33:285 (July-Aug.) 1954.
10. Isaacs, B., and Macarthur, J.G.: The Effect of Chlorpromazine on Vomiting Due to Vertigo, Glasgow M. J. 35:161 (July) 1954.
11. Stewart, B.E., and Redeker, A.G.: Emesis and Hiccough—Treatment with Chlorpromazine, California Med. 81:203 (Sept.) 1954.
12. Whitelaw, M.J.: Prevention by Chlorpromazine of the Nausea Caused by Estrogens and Estrogen-like Compounds, J. Clin. Endocrinol. & Metab. 14:795 (July) 1954.
13. Isaacs, B., and Macarthur, J.G.: Influence of Chlorpromazine and Promethazine on Vomiting Induced with Apomorphine in Man, Lancet 2:530 (Sept. 18) 1954.
14. Hardanger, F., and Smithy, G.: Chlorpromazine in Patients with Nausea and Vomiting Due to Advanced Cancer, New England J. Med. 251:820 (Nov. 11) 1954.
15. Becker, B.: Chlorpromazine—A New Anti-Emetic Agent, Am. J. Ophth. 38:576 (Oct.) 1954.

Mental and Emotional Disturbances

16. Delay, J., and Deniker, P.: 38 Cases of Psychoses under Prolonged and Continuous R.P. 4560 Treatment*, Compt. rend. du Congres des Medecins Aliénistes et Neurologistes, Luxembourg, July 21-23, 1952, pp. 7-18.
17. Escalar, G., and Baldauf, E.: First Results Obtained with Ganglioplegics in Psychiatric Therapy*, Bull. Soc. med.-chir., Prov. Varese 2:1, 1953.
18. Rigetti, S.: Latest Experiences with Largactil in Psychiatry*, Gior. di psichiat. e di neuropat. 81:211, 1953.
19. Teuscher, Y.: Effect of R.P. 4560 on Delirium with Agitation in Cranial Traumatism*, Presse méd. 61:470 (March 28) 1953.
20. David, M.; Benda, P., and Klein, F.: The Treatment of Status Epilepticus by Chlorpromazine*, Bull. mem. Soc. med. Hôp. de Paris 69:691 (June) 1953.
21. Staehelin, J.E., and Kielholz, P.: Largactil, A New Sympathetic Depressant in Mental Disturbances*, Schweiz. med. Wchnschr. 83:581 (June 20) 1953.
22. Nissari, M.: Anxiety and Autonomic Blockage*, Minerva med. 44:231, 1953.
23. Arnold, O.H.; St. Hilt, and Solms, W.: Largactil in Psychiatry*, Wien. med. Wchnschr. 103:583 (Aug. 1) 1953.
24. Delay, J., and Deniker, P.: Neuroplegics in Psychiatric Therapy*, Therapie 8:343, 1953.
25. Kolle, K., and Mikorey, M.: Artificial Hibernation in Psychiatry*, Deutsche med. Wchnschr. 78:1723 (Dec. 11) 1953.
26. Sigwald, J., and Bouttier, D.: 3-Chloro-10-(3'-dimethylaminopropyl)-phenothiazine Hydrochloride in Current Neuro-psychiatry*, Ann. méd. Paris 54:150, 1953.
27. Lehmann, H.E., and Hanrahan, G.E.: Chlorpromazine—New Inhibiting Agent for Psychomotor Excitement and Manic States, Arch. Neurol. & Psychiat. 71:227 (Feb.) 1954.
28. Winkelman, N.W., Jr.: Chlorpromazine in the Treatment of Neuropsychiatric Disorders, J.A.M.A. 155:18 (May 1) 1954.
29. Lang, F.: A Case of Stammering Cured by Chlorpromazine in a 14 Year Old, Mentally Deficient Boy*, Ann. med.-psychol. 112:733 (May) 1954.
30. Lehmann, H.E.: Selective Inhibition of Affective Drive by Pharmacological Means, Am. J. Psychiat. 110:836 (May) 1954.

THORAZINE† BIBLIOGRAPHY (continued)

31. Garmany, G.; May, A.R., and Folkoff, A.: The Use and Action of Chlorpromazine in Psychoneuroses, Brit. M. J. *2*:450 (Aug. 21) 1954.
32. Lancaster, N.P., and Jones, D.H.: Chlorpromazine and Insulin in Psychiatry, Brit. M. J. *2*:565 (Sept. 4) 1954.
33. Elkes, J., and Elkes, C.: Effect of Chlorpromazine on the Behavior of Chronically Overactive Psychotic Patients, Brit. M. J. *2*:560 (Sept. 4) 1954.
34. Kinross-Wright, V.: Chlorpromazine—A Major Advance in Psychiatric Treatment, Postgrad. Med. *16*:293 (Oct.) 1954.
35. Tatlow, W.F.T.; Fisher, C.M., and Dobkin, A.B.: The Clinical Effects of Chlorpromazine on Dyskinesia, Canad. M.A.J. *71*:380 (Oct.) 1954.
36. Bower, W.H.: Chlorpromazine in Psychiatric Illness, New England J. Med. *251*:684 (Oct. 21) 1954.
37. Leon, C.A.: The Use of 'Thorazine' as an Adjunct in the Treatment of Schizophrenia, Bull. Tulane M. Fac. *14*:13 (Nov.) 1954.

Intractable Pain

38. Cahn, J.; Dubousset, M., and Melon, J.M.: The Effect of Potentialized Anesthesia and Hibernation on Experimentally Produced Myocardial Infarction*, Anesth. et analg. *30*:89 (Feb.) 1953.
39. Lucas, J., et al.: Thorazine as an Aid in Management of Cancer Patients, Proc. Am. A. Cancer Research *1*:50 (April) 1954.
40. Sadove, M.S., et al.: Chlorpromazine and Narcotics in the Management of Pain of Malignant Lesions, J.A.M.A. *155*:1626 (June 12) 1954.

Alcoholism

41. Sangiorgi, L., and Laricchia, R.: Six Cases of Delirium Tremens Resolved by a Method of "Neuro-autonomic Blockage" Derived from Techniques of Artificial Hibernation*, Minerva med. *44*:1469 (Nov. 13) 1953.
42. Kinnaurer, T., and Ehlinger, R.: R.P. 4560 (Largactil) in the Treatment of Delirium Tremens*, Ann. méd.-psychol. *112*:102 (Jan.) 1954.
43. Albert, S.N.; Rea, E.L.; Duvernoy, C.A.; Shea, J., and Fazekas, J.F.: The Use of Chlorpromazine in the Treatment of Acute Alcoholism, Med. Ann. District of Columbia *23*:243 (May) 1954.
44. Cummins, J.F., and Friend, D.G.: Use of Chlorpromazine in Chronic Alcoholics, Am. J. M. Sc. *227*:561 (May) 1954.

Surgery and Obstetrics

45. Liberti, H.: Ganglioplegics in Obstetrical Pathology*, Presse méd. *60*:140 (Feb. 1) 1952.
46. Scrigue, J.; Roux, M., and Hagueruel, P.: Reflections on 43 Cases of Anesthesia with Controlled Hypotension*, Mem. Acad. de chir. *78*:333 (Mar. 19) 1952.
47. Forster, S.; Forster, E., et al.: Potentialized Anesthesia in Thoracic Surgery*, Anesth. et analg. *9*:150 (June) 1952.
48. Perazzo, L.: R.P. 4560, a Potentiator of Anesthesia*, Gior. ital. anest. *18*:404 (July-Aug.) 1952.
49. Heitz, J., and Regent, M.: Potentialized Anesthesia*, Lyon chir. *47*:875 (Oct.) 1952.
50. Laborit, H., and Jaulmes, C.: From Potentiated Anesthesia to Artificial Hibernation*, Toulouse med. *50*:821 (Nov.) 1952.
51. Jentzer, A.: Hibernation, Potentiated Anesthesia, Post-Operative Shock Excluding Controlled Hypotension*, Schweiz. med. Wchnschr. *82*:1215 (Nov. 22) 1952.
52. Lacarrieu, G., and Campos, L.: Hibernotherapy and Neurosurgery—Reflections on 71 Cases*, Mem. Acad. de chir. *79*:386 (May 23) 1953.
53. Smith, A., and Fairer, J.G.: Hibernation Anesthesia in Major Surgery—A Report of 30 Cases, Brit. M. J. *2*:1243 (Dec. 5) 1953.
54. Dundee, J.W., et al.: Hypothermia with Autonomic Block in Man, Brit. M. J. *2*:1237 (Dec. 5) 1953.
55. Decherie, J.-P.: Largactil (R.P. 4560) in Pulmonary Surgery*, Lavel méd. *19*:1203 (Feb.) 1954.
56. Dobkin, A.B.; Gilbert, R.G.B., and Lamoureux, L.: Physiological Effects of Chlorpromazine, Anaesthesia *9*:157 (July) 1954.
57. Hershenson, B.B.; Isaac, S.J., et al.: A New Sedative (Antipsychomotor) Drug Useful in Labor—Preliminary Report, New England J. Med. *251*:1016 (Aug. 5) 1954.
58. Ricci, R.: R.P. 4560 (Largactil) as a Narcotic Potentiator*, Der Anaesthesist *3*:58 (Feb.) 1954.
59. Martin, E.M., et al.: A Preliminary Clinical Report on Largactil (Chlorpromazine), Bull. Acad. Med., Toronto *27*:175 (June) 1954.
60. Bienvre, M.P.: Chlorpromazine in Ophthalmology*, Presse méd. *62*:1213 (Sept. 11) 1954.
61. Golden, A.A.: Nitrous Oxide-Oxygen Potentiation—A Clinical Study, J. Am. Osteopathic A. *54*:102 (Oct.) 1954.

Miscellaneous

62. Moyer, J.H., et al.: Laboratory and Clinical Observations on Chlorpromazine (SKF-2620-A)—Hemodynamic and Toxicological Studies, Am. J. M. Sc. *227*:283 (Mar.) 1954.
63. Chaptal, J., et al.: Effect of Chlorpromazine (Largactil) on the Chorea Syndrome in Children*, Presse méd. *62*:764 (May 19) 1954.
64. Robinson, K.C., and Zuck, D.: (Letter to Editor), Chlorpromazine in Status Asthmaticus, Lancet *2*:1549 (June 26) 1954.
65. Dobkin, A.B.; Lamoureux, L., and Gilbert, R.G.B.: Conservative Therapy of Peripheral Vascular Disease and the Use of Largactil (R.P. 4560, M & B 2376 and 2620A S.K.F.), Treat. Serv. Bull. *9*:524 (June) 1954.
66. Chesney, W.M.: Chlorpromazine and Jaundice, Brit. M. J. *2*:591 (Sept. 4) 1954.
67. Foster, C.A.; O'Mullane, E.J., et al.: Chlorpromazine—a Study of Its Action on the Circulation in Man, Lancet *2*:614 (Sept. 25) 1954.
68. Geiger, H., and Finkelstein, B.A.: Largactil in the Treatment of Tuberculosis*, Schweiz. med. Wchnschr. *84*:1063 (Sept. 11) 1954.
69. Rea, E.L.; Shea, J., and Fazekas, J.F.: Hypotensive Action of Chlorpromazine, J.A.M.A. *156*:1344 (Nov. 27) 1954.

Chlorpromazine is known as 'Largactil' in Canada, England, France and Italy; as 'Megaphen' in Germany; as 'Amplictil' in Argentina; as 'Arapletil' in Brazil; and as 'Hibernal' in Sweden.

*Translation

†Trademark for S.K.F.'s brand of chlorpromazine.

Smith, Kline & French Laboratories
Philadelphia 1

Rhode Island Medical Journal, January 1955, p 124

Figure 5

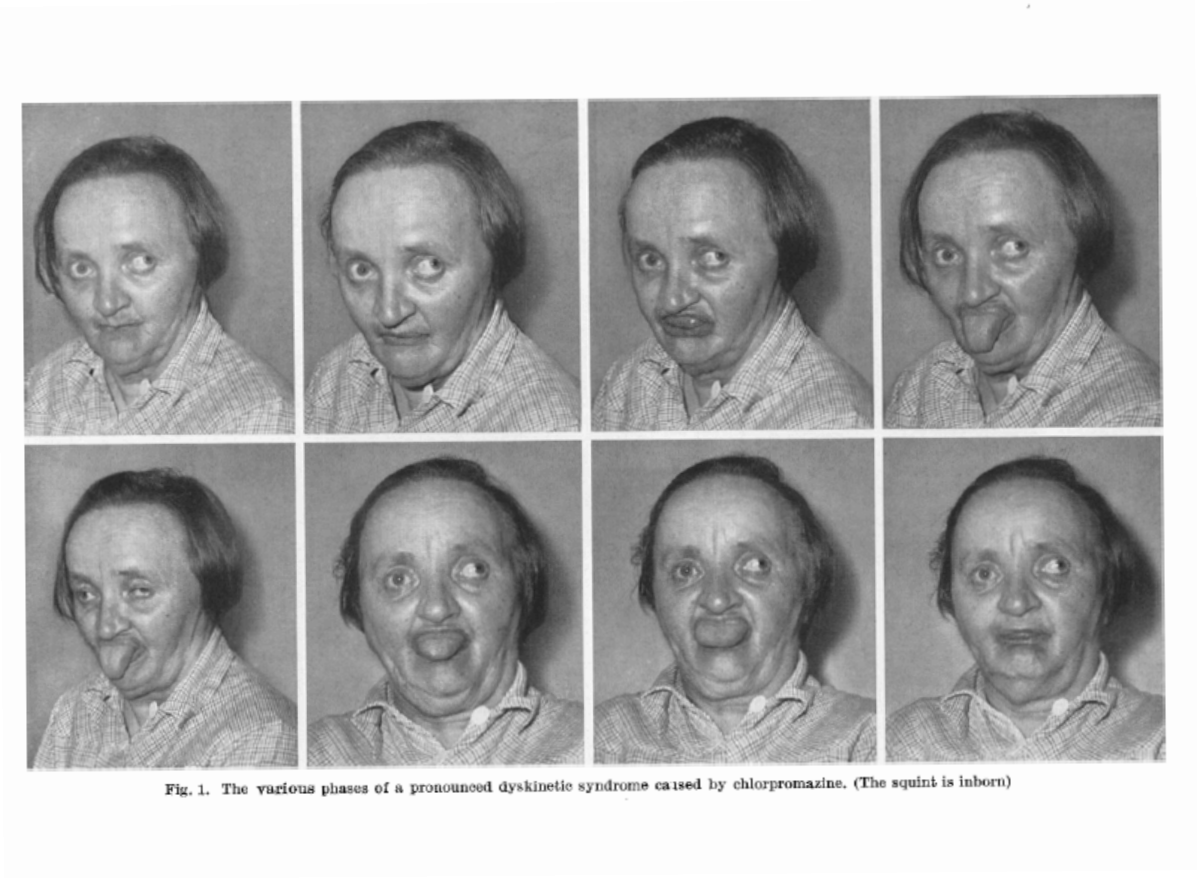
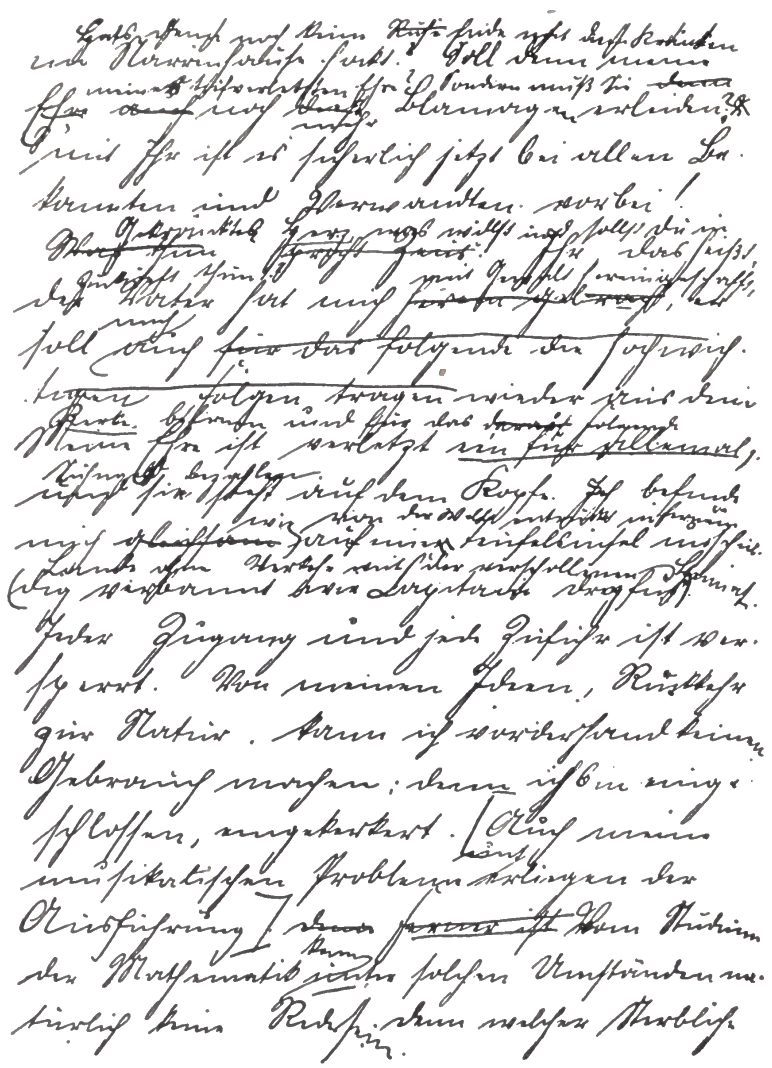


Fig. 1. The various phases of a pronounced dyskinetic syndrome caused by chlorpromazine. (The squint is inborn)

(in Uhrbrand & Faurbye, 1960)

Figure 6



Specimen of writing 4. Letter of a Hebephrenic.

(Kraepelin, 1919, p.100)

Figure 7

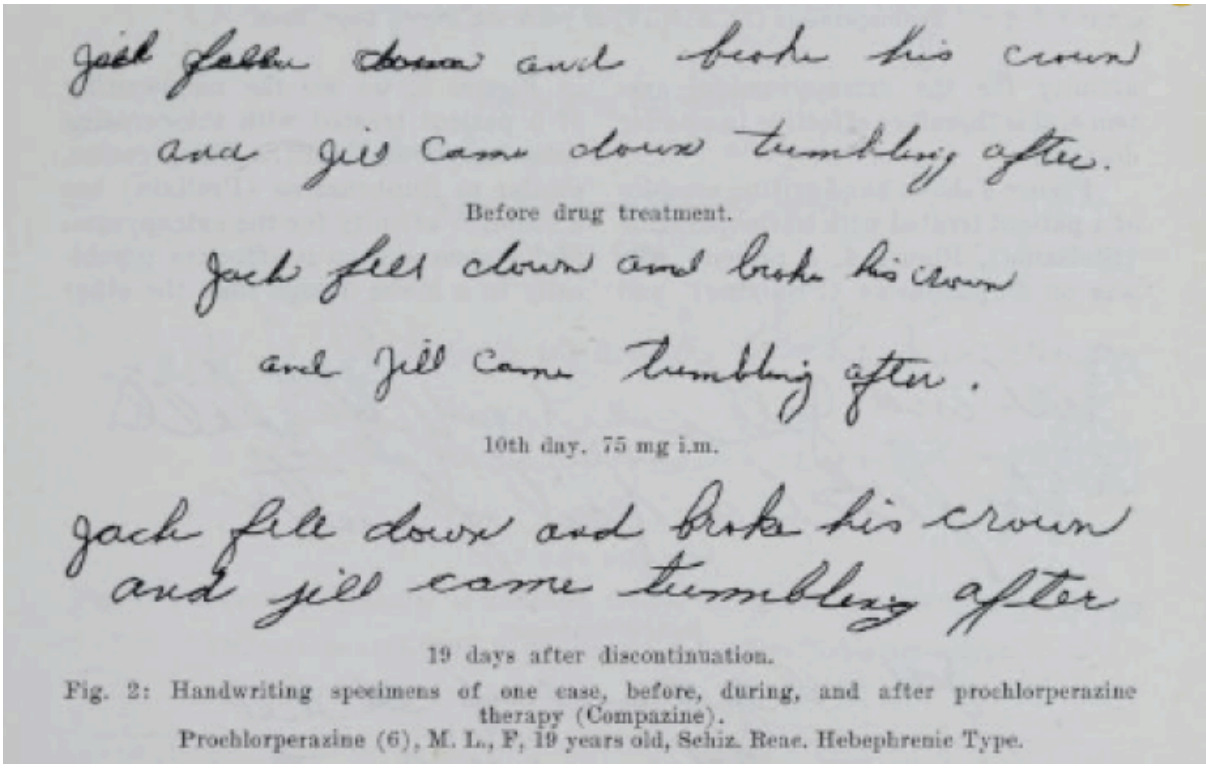


Fig. 2: Handwriting specimens of one case, before, during, and after prochlorperazine therapy (Compazine).
Prochlorperazine (6), M. L., F, 19 years old, Schiz. Reac. Hebephrenic Type.

(Haase, 1961)

Figure 8

Fifth international congress CINP

Figure 8 was gracefully granted by Toine Pieters

Figure 9

Reception a Beerse a propos de la Semaine Interdisciplinaire des Neuroleptiques, 11-16 May 1969

Figure 10

Figure 11

Jean Bobon, Dora Janssen, Pierre Pichot

Figure 12

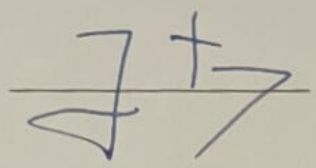
Jean Bobon, Dora Janssen, Pierre Pichot, Mme Bobon, Paul Janssen, (?) ,José Leme Lopes(?), Jackie Collard

Figures 9-12 were gracefully granted by. Christian Mormont.

[DECLARAÇÕES]

Declaro que esta tese é o resultado da minha investigação pessoal e independente. O seu conteúdo é original e todas as fontes consultadas estão devidamente mencionadas no texto, nas notas e na bibliografia.

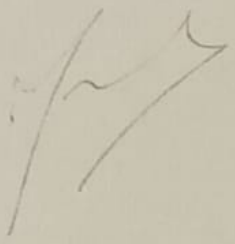
O candidato,



Lisboa, 9 de setembro de 2022

Declaro que esta tese se encontra em condições de ser apreciada pelo júri a designar.

O orientador,



(João Luís Lisboa)

Lisboa, 9 de setembro de 2022