

Part 1

Setting the scene

Chapter

1

The origins of psychopharma

Introduction

Drugs figure large in modern society, the stuff of headlines. On the one hand, are the ‘good’ ones, miracles of modern science; on the other, ‘bad’ ones, damned in censorious sound bites as harbingers of social doom.

Drugs figured no less in the lives of our ancestors but while man’s complex relationship with them stretches deep into prehistory, roles and perceptions have reversed. In the past, many compounds were, as today, sought for medicinal purposes, but it was often those who cultivated such ways who were the outcasts – ones whose gifts, whose very allegiances, might just be demonic. On the other hand, for those who could use drugs to open the door on the other world – the world of gods and spirits and all things buried deep within – came real power, for they controlled the religious and social observances, more important than life itself. The fact that certain substances alter human experience probably ranks with fire as one of man’s earliest and most abiding discoveries.

Seen in this context, the discipline we call ‘psychopharmacology’ is young indeed, the term being attributed to the American pharmacologist David Macht in 1920. From a hesitant and empirical start, psychopharmacology blossomed into its ‘Golden Age’ in the 1950s, a decade that saw the explosive birth of virtually all the major categories of psychopharma on which we still depend today (Table 1.1). The consequences were pretty spectacular. Psychiatry, one of the oldest medical specialties,¹ no longer needed to languish secretively behind the impenetrable walls of madhouses or rely on the dubious chic of the analyst’s couch. Disorders of emotion, thought, perception, cognition – of relatedness itself – could be legitimately conceptualised within a *medical* frame of reference and probed using chemical tools to facilitate their management, maybe even lighting the way to cures. And – what a bonus! – to open the curtain on their pathophysiology. From there

it did not seem too great a leap to the ultimate prize – understanding the workings of the human brain itself.

The prize may still be some way from the obtaining, for probing an organ-system of the complexity of the brain comprises multilayers of understanding and exploratory tools of a sophistication beyond what is currently available. At present, brain systems are to some extent only understandable through oversimplified, reductionist concepts built from ‘static’, extracted snapshots of a world that in reality is dynamic and profoundly inter-related. Nonetheless, the explosion of psychopharmacology in the 1950s allowed psychiatry to take its place at the medical top-table. And it must have seemed it would go on forever.

By definition, ‘Golden Ages’ are limited, not just by time but by dulling of the glitter that made them shine – and psychopharmacology was true to the principle. With the exception of anticonvulsants as mood stabilisers, and cognitive enhancers, nothing fundamentally new has entered the ‘psycho-pharmacopoeia’ in the best part of half a century, so there was long enough to contemplate the problems as the lustre dimmed. Long enough, perhaps, for hope to cloud reason?²

This is depressing in itself but when the R&D consequences of this early twenty-first century hangover are viewed through the withdrawal from CNS of a number of large pharmaceutical organisations, the limitations of what we have learned, the barrenness of our theorising, become evident.

The ‘Golden Age’

Chronologically, the modern advance of psychopharmacology actually began in 1949 when the Australian psychiatrist John Cade reported the anti-manic and mood-stabilising properties of lithium salts (Table 1.1). It makes no difference that the theory behind the first clinical application was antediluvian and frankly haywire, or that without monitoring,

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Table 1.1 A chronology of 1950s' psychopharmacology

1949	Cade	Antimanic (and maintenance) action of lithium salts	Cade's views, based on the nineteenth-century idea of 'urate diathesis', crystallised while a prisoner in the notorious Changi Prison, Singapore during WW2
December 1950	Charpentier	Synthesis of chlorpromazine (CPZ)	Charpentier also synthesised promethazine
December 1951	Sigwald/ Bouttier	First solo treatment of a psychotic patient with CPZ	'Mme Gob'
March 1952	Hamon et al.	First publication on the efficacy of CPZ	The patient was bipolar, in a manic phase
May	Delay/ Deniker	First case series demonstrating efficacy of CPZ	
1951/1952	(Various)	Mood-elevating effects of isoniazid/iproniazid	During Sea View Hospital trials of efficacy in TB (Selikoff and Robitzek)
1952	Zeller	Monoamine oxidase inhibiting effects of iproniazid	
1953	Schindler	Carbamazepine	Antiepileptic properties discovered following resynthesis in 1960
1954	Steck/ Thiebaux	First literature reports of parkinsonism with CPZ	Parkinsonism had been noted by Delay as early as 1953
	Kline	Reserpine (as antipsychotic)	Alkaloids of <i>Rauwolfia serpentina</i> used in Ayurvedic medicine for centuries (including 'nervousness'). Purified, dose-standardised reserpine introduced in the West as an antihypertensive (1950)
	Panizzon	Methylphenidate	Actually synthesised 1944 – called 'Ritalin' after Marguerite (i.e. Rita) Panizzon
1955	Berger	Meprobamate	Synthesised by Ludwig and Berger (1950) from myanessin, developed as preservative for penicillin
	Kuhn	First clinical trial of G22355 (imipramine)	Used originally as a potential antipsychotic. Amongst the many who got worse, Kuhn noted 3 with 'vital depression' who improved, stimulating second evaluation in depression
	Delay	Introduction of class name ('neuroleptics')	Coined to persuade analytically orientated profession of a biological mode of action
1956	Ayd	First account of acute dystonias (with CPZ)	
1957		First report (at American Psychiatric Association) of efficacy of anti-tuberculous drugs in individuals without TB	Previous reports suggested mood elevation in TB patients only
	Kuhn	Efficacy of G22355 in 'vital' depression	Imipramine introduced internationally in the spring of 1958
	Randall	Behavioural actions of 1,4-benzodiazepines	Synthesised by Sternberg but not thought interesting on initial evaluation. Retested during a lab 'spring clean', with remarkable findings
1958	(Petersen)	Thioxanthenes	Synthesised at Lundbeck Laboratories: Chairman, P.V. Petersen
	Janssen	Haloperidol	
1959	Sigwald et al.	First report of tardive dyskinesia Synthesis of clozapine	Earlier reports (e.g. Schonecker) unconvincing
1960		Anxiolytic properties of chlordiazepoxide	Cohen and Tobin

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toxicity was there to be interpreted as ‘improvement’. The consequences of lithium’s clinical development³ as a treatment of mood disorders were sufficiently spectacular for these early negatives to be overlooked. Furthermore, with actions focused particularly on mood (Johnstone et al., 1988), lithium continues to offer one of the best tools for unravelling the pathophysiology of human emotion.

The rauwolfia alkaloid reserpine has a long association with Ayurvedic medicine where it was used, amongst other things, in the treatment of insanity but was introduced into Western medicine by Robert Wallace Wilkins as an antihypertensive in 1950. Four years later, in the wake of chlorpromazine, it was recommended in US psychiatric practice as an antipsychotic by Nathan Kline, though with limited success. Because reserpine developed a reputation for promoting depression (in approximately 15% of users), its pharmacology did, however, become a foundation of the Biogenic Amine Hypothesis of mood disorder.⁴ Also in 1954 methylphenidate, a drug synthesised a decade before (and named ‘Ritalin’ after Rita, the wife of the chemist who synthesised it⁵) was patented for its stimulant properties and marketed as a potential treatment for depression, narcolepsy and fatigue.

We have to look elsewhere, however, for the first effective pharmacological strategies against depressive illness (Lopez-Munoz et al., 2007), a concept that barely existed before the mid twentieth century. In 1951, Irving Selikoff (later to establish the dangers of asbestos) and Edward Robitzek noted a strikingly incongruent elation in seriously, if not terminally, ill tuberculous patients participating in the famous isoniazid and iproniazid trials at the Sea View Hospital in New York.⁶ One local reporter described graphically patients “dancing in the halls tho’ there were holes in their lungs”. The following year, this stimulation ‘side-effect’ of isoniazid was specifically employed in treating depression by Jean Delay in Paris and Lurie⁷ and Salzer in the USA. The basis of this mood-elevating action remains unclear but it was the more substantial effects of iproniazid mediated, as shown by Ernst Zeller in 1952, via MAO inhibition, and again viewed by chest physicians as a ‘side-effect’, that really kick-started the antidepressant era. At the American Psychiatric Association meeting in 1957, a number of reports described improved mood in tuberculous patients treated with iproniazid but it was once again Kline who described its use in depression *per se*.

Although it took till the early 1960s to find clinical application, the dibenzazepine carbamazepine (discovered in 1953) was a child of this period in the blossoming of psychopharmacology. Slightly later but starting from the same molecular source, Swiss pharmaceutical giant Geigy investigated a series of iminodibenzyl derivatives for central antihistaminic activity similar to that of chlorpromazine, the goal being cheaper, non-hepatotoxic phenothiazines.⁸ Finding his hospital short of funds in 1955, the Swiss psychiatrist Roland Kuhn asked the company if they had any new antipsychotics they wished to have researched in patients with schizophrenia. Such was the research ‘climate’ of the mid-1950s! The iminodibenzyl analogue of chlorpromazine, code-named G22355, was duly dispatched and tried, with results later described as “in some patients, quite disastrous” (Broadhurst, quoted in Healy, 1996). The drug did little for psychotic symptoms yet, although sedative, paradoxically appeared capable of promoting manic-like behaviour. Kuhn therefore tried it in patients with depression, presenting his highly favourable findings in 1957. Results were, he noted, especially good in ‘vital’ (i.e. ‘endogenous’) types of disorder. These findings were confirmed in Canada by Heinz Lehmann and imipramine was launched as an antidepressant in 1958.

In 1955 the first ‘tranquilliser’, meprobamate,⁹ became available, marketed rather quaintly under a name (‘Miltown’) based on the town in which it was manufactured (Milltown, New Jersey). By 1957, over 36 million prescriptions had been issued in the USA, and meprobamate accounted for one-third of all prescriptions annually. Although less sedative and hence safer than barbiturates, it could still cause waking impairments but its decline was triggered less by safety concerns than by one domestic and one foreign calamity, both commencing in 1960. The domestic one was charges under America’s strict anti-trust laws, resulting in the manufacturer’s enforced loss of patent. The second, far more devastating issue, flowed from Lowell Randall’s discovery in 1957 of the behavioural properties of the 1,4-benzodiazepines,¹⁰ and was Cohen and Tobin’s demonstration, in 1960, of the anxiolytic properties of chlordiazepoxide, the first commercially available benzodiazepine.

Mysteriously, the drug-scape thereafter fell eerily silent. The bubble burst and in the silence that followed the bang, psychiatry was left to ponder, with increasing frustration and some alarm, the inadequacies of

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the tools it had been gifted. This is illustrated nowhere better than by the one class of drug omitted from our list, the one that is the major focus of the present volume – antipsychotics. A brief outline of how they came to us may be of interest.

The chlorpromazine story

There is no single version of the story of chlorpromazine that has percolated through the internecine squabbles about who did what and when, perhaps an inevitability where unanticipated success blossoms from varied ideas sown by disparate players. Some believed a Nobel Prize was there for the taking had the lines of attribution been more generously, less contentiously drawn and certainly in terms of both clinical and theoretical impact, the development of chlorpromazine stands out as perhaps the most striking example of a major medical discovery never rewarded by a Nobel Committee. The present account comes from conventional sources (including Swazey, 1974;¹¹ Caldwell, 1978; Healy, 1996) and one can only apologise to those who, through the revisionist nature of history, accept a different emphasis.

The development of antipsychotics could not have had less to do with the needs of psychiatry. To find its origins, we must dig deep in the fertile soil of Victorian commercialism. A time-traveller back to the first half of the nineteenth century would notice one immediate difference from the world of today – for most, then was a world devoid of colour. Dyes were mainly vegetable- (in some instances animal-) based and unstable, tending to fade in sunlight, while those providing vividness were so expensive as to be the sole preserve of the very rich. Then, in 1856, 18-year-old William Perkin changed everything when, in an attempt to make quinine from the aniline of coal tar, he inadvertently produced a sticky splurge which, when dissolved in alcohol, revealed itself as purple (subsequently termed ‘mauve’). Within a few short years, ‘Perkin’s Purple’ was *the* fashion statement. Perkin’s realisation of the commercial potential of his sticky splurge had two consequences (apart from making him very rich and ultimately titled): firstly, it established the commercial dye industry, and secondly, it spawned the new discipline of organic chemistry to service commercial demand.

In 1876, Heinrich Caro, chief chemist of the German company BASF, synthesised a new dye, methylene blue, which, because of its many applications, became a commercial success, and in 1883, research chemist August

Bernthsen published his analysis of its structure, the basic nucleus of which he identified as ‘thiodiphenylamin’ – or phenothiazine. It would take many years, whole new areas of research, and two Nobel Prizes, before this discovery was brought to its potential.

One of those areas was shock, and specifically anaphylaxis, which led to the identification of histamine, while a second strand of work was into neurotransmission. Henry Dale had suggested that acetylcholine might act as a transmitter as early as 1914 but it took some years for this to be established (by Otto Loewi,¹² with whom Dale shared the first of our Nobel Prizes in 1936). Indeed, whether the process of inter-cell signalling in the nervous system was chemical or electrical was one of the great controversies of early twentieth-century physiology. In the meantime, Swiss pharmacologist Daniel Bovet made a leap of faith in suggesting (in 1937) that if chemical transmission included such things as ‘anticholinergics’ which modified the functionality of acetylcholine, why might that other amine, histamine, not also be modifiable by ‘antihistamines’? As a result of his work in verifying this hypothesis, he became, in 1957, the recipient of our second Nobel Prize. In the early 1940s, the French pharmaceutical company Rhône-Poulenc started development of a series of synthetic antihistamines, some of which (e.g. diphenhydramine) are still with us.

Meanwhile, phenothiazine had not been neglected. The antimalarial properties of methylene blue were established in the 1890s¹³ by, amongst others, Paul Ehrlich. Subsequently, phenothiazine was shown to be an effective insecticide against mosquito larvae but this molecule was too toxic for widespread human use and an anthelmintic action against swine ascaridia utilised in veterinary practice had, by the 1930s, become its only commercial application. The development avenues seemed blocked.

It was the Second World War that provided *the* crucial impetus. Because of the traditionally prominent role malaria has played in the morbidity and mortality of fighting men, one of the interests of the military during times of war, apart from battlefield objectives, has long been antimalarial treatments. In the early 1940s the American chemist Henry Gilman¹⁴ returned to the non-oxidised phenothiazines in the constant quest for safe and effective antimalarials that accompanies warfare.¹⁵ His negative findings were published in 1944.¹⁶ However, because of WW2 these studies remained unknown in France, where similar lines of investigation were being explored at Rhône-Poulenc. Equally

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negative findings were accruing but that group's research background made them aware of something Gilman (and his co-researcher, Shirley) overlooked – the potent antihistaminic properties of a number of these compounds. The most significant product of this programme was promethazine, produced in 1946.

It was clear that these new synthetic antihistamines had unusual central actions. In humans, they were sedative yet some appeared to have beneficial effects in parkinsonism. In the autumn of 1950, Paul Koetschet, Rhône-Poulenc's Assistant Scientific Director, proposed a phenothiazine amine development programme, with a view to exploiting central actions irrespective of antihistaminic properties. The evidence to support the proposal was flimsy, even by the standards of the time, and Koetschet admitted that “it was difficult to know” what clinical applications there might be for any products that emerged. The first, he suggested, might be in pre-anaesthesia, while his “hope” was for more active antiparkinson agents. And “finally”, he mused on the possibility of “an application in psychiatry”. Never can a CNS development programme have achieved so much from such speculative beginnings and Koetschet is surely one of those whose central role in our story has been overlooked.

Koetschet's reliance on an outcome of interest to anaesthesia was not, however, without foundation and brings us back to shock. Technical advances in surgery had not been matched by improved survival rates and in the first half of the twentieth century the old adage that the operation was a success but the patient died was not without truth. Haemodynamic, or circulatory, shock all too frequently undermined the accomplishments of even the most technically gifted surgeon but the underlying mechanisms were not understood. So the vacuum was filled with multiple theories of greater or lesser credibility in whose hot air chlorpromazine's rightful Nobel Prize got frazzled!

Henri Laborit would undoubtedly have been surprised to learn at the start of his career that by the end of it the greater part of his legacy would lie within psychiatry. For Laborit was not a psychiatrist, but a military surgeon. His research career started on a topic of interest to navies around the world – seasickness, especially the possible role of cholinergic mechanisms, in pursuance of which he (and a colleague, Morand) developed a cholinesterase assay for plasma estimations. When, in 1946, it was postulated that inhibition of peripheral cholinesterase might underlie shock, Laborit was well placed to shift emphasis.

He did not accept the primacy of capillary changes in initiating shock but was more taken with neural (i.e. autonomic) disturbances. These views, along with the cocktail of drugs he recommended to counteract shock, were, in later years, roundly criticised and became part of the squabbles – irrelevant to us – that damaged his reputation. However, what cannot be denied is Laborit's exceptional powers of clinical observation. In obviating shock, his aim was to dampen or ‘stabilise’ autonomic activity during and after surgery by means of a complex pharmacological regime which latterly included promethazine. This was his so-called lytic cocktail.¹⁷ His accounts of the ‘secondary’ effects of promethazine were impressive, especially in relation to affective and behavioural changes, where he noted patients becoming “calm and somnolent, with a relaxed and detached expression” (1949), an effect he was clearly able to distinguish from that of morphine. Later, he wrote: “although conscious, they felt no pain, no anxiety”, postulating that (these effects) “can reasonably be attributed to a central action” and that “synthetic antihistamines made it possible to disconnect certain brain functions”. (1950). Laborit's acumen is the more impressive when one considers that promethazine had been tried previously in psychiatric patients but only sedation was noted.

Much debate has surrounded the importance of these observations in Rhône-Poulenc's decision to proceed with the development of aminophenothiazine derivatives, and it is unlikely that anything now can resolve the controversies. What is fact, however, is that proceed they did. And success came fast. On 11 December 1950 – only two months after Koetschet's original proposal – Rhône-Poulenc's Chief Chemist, Paul Charpentier, produced from a series of compounds, the most centrally selective – initially called ‘chlorpromazine’. Pharmacologist Simone Courvoisier confirmed, amongst its many actions,¹⁸ a unique property of producing indifference to noxious stimuli in laboratory animals and after three months of basic testing the renamed ‘chlorpromazine’ was deemed ready for clinical trials. Charpentier and Courvoisier then exit our story, their crucial contributions largely and unjustly forgotten. The first samples for psychiatric evaluation (as a potentiator of barbiturate-induced sedation) were dispatched to Dr J. Schneider at the Broussais Hospital in April 1951.

At this time, Laborit was working at the Val de Grace military hospital outside Paris on another novel way to advance anaesthesia, artificial hibernation, a

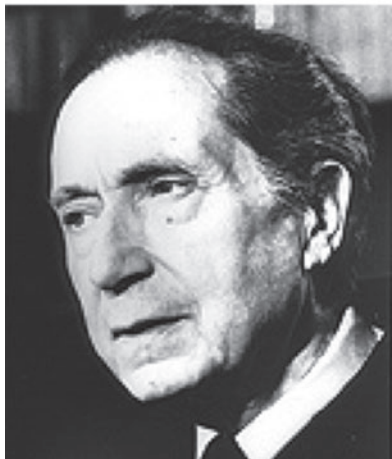
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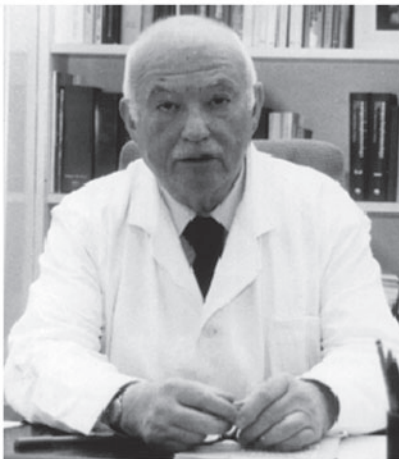
The chemist
Paul Charpentier



The surgeon/anaesthetist
Henri Laborit



The psychopharmacologist
Jean Delay



The clinician
Pierre Deniker

Figure 1.1 Four key figures in the history of antipsychotics.

now important idea that was revolutionary then and that was later to return to Laborit some respectability.¹⁹ He apparently had no knowledge of the development of chlorpromazine, so when he approached Rhône-Poulenc about the possibility of producing a more effective (i.e. centrally selective) phenothiazine derivative than promethazine to add to his ‘lytic cocktail’, he was surprised to learn that one already existed. He received his samples, as the twelfth investigator, in late June 1951.

The novel characteristics of what he had been given were evident to him immediately, and by October he could describe the “twilight state” recipients entered after taking his chlorpromazine-based lytic cocktail. Two months later he quoted a colleague who stated

that this new drug “may produce a veritable chemical lobotomy”.

Laborit realised that chlorpromazine’s real potential might lie beyond anaesthesia. The effect he was seeing was not, as the psychiatrists again thought, simply sedation or from a drug whose value might lie only in potentiation. This was something new – and it was Laborit who spotted it. So he began urging psychiatric colleagues to try it, though with little success. Perhaps the fact that the ‘urging’ came from a surgeon had something to do with it but more likely was the entrenched indifference to pharmacology of a profession that still felt its expertise lay in opposite directions. However, Laborit continued to study the drug’s unique actions and, in early November 1951, participated in its

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first administration to a normal volunteer – and its first solo ‘psychiatric’ outing. The ‘volunteer’, Dr Cornelio Quatri, was a psychiatrist! Quatri noted an initial period of discomfort but this soon evolved:

At 1.00pm, an intense affective change appeared that the group noticed immediately: the painful feeling of imminent death disappeared to make room for a euphoric relaxation ... This new state left me indifferent ... Although very much in touch with my surroundings, I was more and more overcome by an extreme feeling of detachment from myself and from others. My perceptions were normal, but their tone had changed; everything was filtered, muted. (Dr C. Quatri, 9 November 1951)

These striking subjective effects were obtained after a small dose (50 mg), though the drug was still given parenterally (usually IV) and Quatri collapsed with postural hypotension on going to the toilet. In a foretaste of what was to become the history of antipsychotic pharmacology, normal volunteer studies were suspended.

Eventually, in January 1952, psychiatrists at the Val de Grace were persuaded to try the drug, although their decision was “without much conviction” as can be seen by the fact that the regime also involved potentiation and ECT. The patient (‘Jacques Lh’) was not schizophrenic but a 24-year-old bipolar patient with several previous admissions, who was then manic. The remarkably favourable results – improvement within three weeks – were presented orally in February and published (by Hamon and colleagues) in March. Despite the impressive results, the authors of this first published report on the efficacy of chlorpromazine were grudging in their praise – “naturally” they stated sniffily, they were “not presenting a new therapy for treating mania”!

It is, however, Jean Delay and Pierre Deniker who are most associated with the introduction of chlorpromazine, though even here Laborit played a role. Deniker’s brother-in-law was a surgeon at the Val de Grace and a colleague of Laborit’s and prior to Sunday lunch one day, told Deniker of Laborit’s assertions concerning this new drug, about which he was talking constantly. Deniker thought this interesting²⁰ and mentioned it to Professor Jean Delay, head of L’Hôpital St Anne where Deniker worked. Delay, a pioneering clinical psychopharmacologist and one of the most distinguished French psychiatrists of his day,²¹ was also interested and the two men acquired samples. Their results from a series of 38 patients were presented in May 1952, at the prestigious centennial meeting of the Société Médico-Psychologique in Paris.

It is hard now to appreciate how entrenched European psychiatry was at this time and how opposed to the idea of pharmacological agents. Then, the ‘science’ was seen to lie in the methods for identifying then reconstituting the ‘interrupted’ or ‘torn threads’ of Bleuler’s metaphor, not in a pill. Even Deniker came up against resistance from his own. He described (to Swazey) how at one meeting in Luxembourg in late 1952, the morning session over-ran and he presented during the lunch break – to an audience of 6! In this context, it is not hard to see how frostily the intrusions of a surgeon would have been viewed and how, when the trophies came to be awarded, his role would become a source of controversy. But the record is clear that it was the surgeon Henri Laborit who first established the *mental state* actions of chlorpromazine. Furthermore, when Rhône-Poulenc came to license the drug to a US manufacturer (Smith Kline & French),²² they made it clear that they were “very interested” in ensuring that “the name and investigations of Dr Laborit ... are mentioned in every scientific publication and also in the popular articles” – not the sort of recognition usually afforded to other than a key player.

If, however, we are looking for priority in the use of chlorpromazine as a solo treatment for psychotic illness, this – and hence the honour of truly starting the modern era of psychopharmacology – probably belongs to Dr Jean Sigwald who, on 28 December 1951, started the drug in a 57-year-old retired psychotic civil servant – the memorably named, Mme Gob!

What, one might ask, is the point of all this? It is presented in the belief that those who prescribe chlorpromazine and its successors, who live with their impact and the problems they can cause, and who may even acknowledge that without them their chosen career path might well have been different, may find some interest in an infrequently recounted tale. It is also presented to dispel the notion, still prevalent in some texts, that the introduction of chlorpromazine into psychiatric practice was pure ‘serendipity’ – i.e. a ‘fluke’! Empirical it may have been but the drug’s development grew, no matter how loosely, from the convergence of a number of strands of basic and clinical research with long, and in some cases very honourable, scientific credentials, while its eventual home was built on the foundation of astute clinical observation. Indeed, perhaps these observations are worth recalling precisely because they belong to an era before standardised assessment, where reliability was a distant dream but where, in the hands of a ‘master’,

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validity, once captured, could be assured. As a result, they may still have something to tell us.

There is one final irony in this story. August Bernthsen, the research chemist who unravelled the chemical structure of the phenothiazine ring, did so in Heidelberg, only a stone's throw and five years from where Emil Kraepelin would formulate his concept of 'dementia praecox'. It would be almost three-quarters of a century before these two powerful developments came to conjunction – years during which psychiatry was dragged through one theoretical quagmire after another and up countless therapeutic blind alleys.

In the wake of chlorpromazine

The pharmaceutical industry was not slow to capitalise on the chlorpromazine story and a steady stream of phenothiazine derivatives started to flow from industry's (notably Rhône-Poulenc's) laboratories. The operative word here is 'derivative', for while there may have been a perception of activity, in terms of core action one substituted phenothiazine was much the same as another – and, as would later emerge, so too were their many problems.

The same judgement would apply to the two other drug types that emerged at this time – both in 1958. Poul Viggo Petersen,²³ heading up a team at Lundbeck Laboratories in Copenhagen, produced the first thioxanthene, chlorprothixene, introduced the following year. This chemical type represents only a relatively minor modification of the phenothiazine molecule but one that has profound effects on pharmacology. By substituting carbon for the nitrogen at position 10 (the 'R2' substitution position on the central ring) side-chains can then attach in mirror-image fashion – that is, these molecules demonstrate *stereoisomerism*. The impact on pharmacology comes from the fact that with the thioxanthenes, only one of the isomers has significant antidopaminergic – and hence, 'antipsychosis' – potential.

A more significant event the same year occurred in Belgium. Paul Janssen, working out of a rented garage, was not interested in creating an antipsychotic, far less a global empire. His interest lay in the effects of simple physical properties on complex organic molecules, in pursuance of which he submitted pethidine (meperidine) to heat. This resulted in nor- (or desmethyl-) pethidine which, when itself heated, resulted in the first butyrophenone. Residual morphine-like actions were readily eliminated by substituting an ester moiety with a tertiary alcohol, while potency and relative

selectivity were ensured by minor modifications to the two aromatic rings (Bennett, 1998). This process, in its essence astonishingly simple, produced in the butyrophenones²⁴ (or 'phenylbutylpiperidines') the first relatively D2 selective drugs and as a result, the best tolerated in terms of their general adverse effect profile, a combination that turned out to have a definite downside, as we shall see. Haloperidol would go on to become the world market-leader antipsychotic in sales terms and to dominate psychiatric practice, especially in the United States, yet it remains a drug whose clinical pharmacology is poorly delineated.²⁵

Following Kuhn's demonstration of the antidepressant action of imipramine, other heterotricyclic compounds became of interest in what was seen as an exciting new field of therapy and one that had proved resistant to innovation – the drug treatment of depression. In collaboration with the Munich group under Professor Hans Hippius, Swiss company Wander began a development programme of compounds that, like imipramine, comprised a 7-membered central ring. One of these, a dibenzodiazepine with an *N*-methyl-piperazine side-chain, was registered as research compound HF1854 in 1960. We know it today as clozapine.

Clozapine's 'success' is a story of survival against the odds. Not only were anticipated antidepressant actions not evident in patients, laboratory animals did not produce the responses predictive of an antipsychotic. After years in the doldrums,²⁶ the US Multicenter Clozapine study (Kane et al., 1988a) established value in a circumscribed population (operationally defined 'treatment-resistant' schizophrenia) which led to a degree of exploitation as unjustified as it was blinkered. So the parentheses around 'success' must stay when alluding to clozapine's place in treatment for, it might be argued, this has turned out to be a double-edged sword. This is a difficult drug for doctors to use and an even more difficult one for patients to take; despite being bombarded by 'opinion leaders' telling us it is under-used, the drug's trial-established benefits, while welcome, are in fact slight; and what advantages there are probably do not, as will be discussed, accrue for enhanced efficacy, as has been repeatedly claimed. Its final legacy is perhaps its most negative, for the majority of new antipsychotics released since 1993 owe their conception to one particular aspect of clozapine's complex pharmacology – one that has led drug development to a second age of derivation and a rather barren anti-climax (see Chapter 12).

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There were two positive consequences of clozapine’s gestation, however. The first was the revival as never before of comparative antipsychotic psychopharmacology. Suddenly the quality literature was full of head-to-head studies comparing different antipsychotics. Many of the possibilities of this endeavour were squandered by the fact that virtually everything was ‘against haloperidol’ and by the more important revelation that we did not know as much about the clinical pharmacology of older antipsychotics as we thought. However, the commercial need for licensed approval stimulated a field that had for too long remained fallow – and which should not be allowed to run feral again.

The second ray of positivity clozapine brought was the challenge it represented to ‘single system’ pharmacology – the notion that the way forward with ‘antipsychosis’ lay with ever more D2 selectivity. This idea held sway for many years and, in the mid-1960s, found what in effect was its realisation in sulpiride. This is a modification of the substituted 2-methoxy-benzamide, metoclopramide,²⁷ and like so many antipsychotics was developed in France. It was not until its wider launch in the late 1970s that its ‘novelty’ was first suggested, though this was not a claim that stood for sulpiride any more than it did for those of its peers similarly targeted as being different (see Chapter 12). Sulpiride was also associated with the concept of site ‘selectivity’ – a preference for mesolimbic over nigrostriatal sites – though as a theory of pharmacodynamic ‘difference’, this again has tended to fade.

From mid-1993, a series of antipsychotic launches on the international market again created an impression of energy and optimism. The age of ‘atypicality’ (Mark II) had dawned. With 10 launches in the UK alone between 1990 and 2008, psychosis seemed more blessed than any other treatment area in medicine. CNS was *the* area to be in! But the image was illusion – fact distorted by sleight-of-hand and slick marketing to which, ironically, industry itself fell victim. Rather than novelty, we were presented with another wave of essentially derivative compounds, reincarnations of old theories and old modes of action²⁸ (Table 1.2). Most followed a particular theory (greater serotonin, especially 5HT_{2A}, antagonism than D2) extracted from the many possible ones presented by clozapine (e.g. olanzapine, risperidone); some gave new legs to single-system pharmacology, and again impressed with their validation of the Dopamine Hypothesis (e.g. amisulpride); some had been floating around the pages of the experimental pharmacology literature for years and were too ancient to be considered

Table 1.2 The ‘seven ages of atypicality’: antipsychotics to which the term has been attached (after Owens, 2008)

<i>Fetal ‘atypicals’</i>	lloperidone Lurasidone
<i>Infant ‘atypicals’</i>	Aripiprazole
<i>Youthful ‘atypicals’</i>	Risperidone Olanzapine Sertindole Quetiapine Ziprazidone
<i>Middle-aged ‘atypicals’</i>	Loxapine Molindone Methotrimeprazine (levomepromazine)
<i>Middle-aged posing as youthful ‘atypicals’</i>	Zotepine Amisulpride Asenapine
<i>Elderly ‘atypicals’</i>	Clozapine (Thioridazine) Pimozide Sulpiride
<i>Deceased ‘atypicals’</i>	Remoxipride Thioridazine

‘new’ (e.g. zotepine). Yet this hotch-potch of drugs of differing pharmacologies, backgrounds and even generations apparently possessed something wondrous in common. Our present focus of interest provides a crucial context to any critique of the concept of antipsychotic ‘atypicality’ and, having read the substance of the present work, the reader will be invited to consider its merits in greater detail in Chapter 12.

What’s in a name? Practice, theory and class terminologies

Jean Delay and Pierre Deniker began their investigations of chlorpromazine in February 1952, unaware of those of Sigwald and Bouttier or the Val de Grace group. Like most early evaluators, their approach was initially towards the drug’s use in ‘excited’ states, regardless of diagnosis. Thus they, like others, first tried it in mania, although they soon extended it to disturbed patients of other diagnostic types. While they were enthusiastic and found some results that were “spectacular”, they knew they would need firm evidence to challenge a wider psychiatric community that was far from ready to be impressed.

In fact, initial results were varied. This was, of course, before the primacy of the randomised controlled trial and standardised dose-finding studies, so

Part 1: Setting the scene

application was of the ‘try and see’ variety – and cautious. The recommended dose from the manufacturer was up to 100 mg/day orally or a maximum of 25 mg for the first intramuscular injection.²⁹ Delay and Deniker opted for a “very high” dose of 75–100 mg IM daily plus the same orally if required, a regimen they themselves were apprehensive about. Compared to the present, Europeans were in those early days generally conservative with regard to dosage but, as was to be repeated time and again with different drugs, when chlorpromazine crossed the Atlantic, ‘megadoses’ entered practice. By the mid-1950s, doses of 1000–2000 mg/day were being used in the USA.

The first British study, reported by Anton-Stevens in the *Journal of Mental Science* in April 1954, was also of the ‘try and see’ variety but the major British contribution at this time came from the work of Joel and Charmian Elkes at the pioneering Department of Experimental Psychiatry, in Birmingham.³⁰ Their study, reported in the *British Medical Journal* in September 1954, was the first controlled trial of chlorpromazine and one of the first such trials in psychopharmacology. Although providing a qualified confirmation of chlorpromazine’s value, they pointed out what Sigwald and Bouttier had also emphasised: that the new drug was not ‘curative’ but rather produced symptomatic benefits that could be all too quickly lost on discontinuation. The seeds of maintenance were sown early!

Within two years of its announcement to an indifferent, if not frankly hostile profession, chlorpromazine had achieved international acclaim. If this was in the vanguard of something new, a new name would be necessary for the class it and its successors represented. Laborit’s influence was again evident in the early suggestions – ‘ganglioplegics’ from himself; ‘neuroplegics’ and ‘neurolytics’, with Delay and Deniker. Another popular pre-1955 term was ‘psycholeptics’. By 1955, however, two principal effects of the drug had been established – extrapyramidal dysfunction and ‘psychic indifference’, either of which could provide a basis for classification.

The first published report of extrapyramidal dysfunction appeared in 1954 (Steck, 1954), though the issue had been aired since, shortly after chlorpromazine’s introduction to human use. As early as 1953, Delay stated that parkinsonian effects were dose-related and as doses embarked on their relentless march upwards, these effects – unsurprisingly – appeared universal. From such an observation it was a short leap of intellect to view them as *essential* to the therapeutic process. The

tendency to produce parkinsonism became an increasing source of interest – not concern – because it seemed to offer a pointer to mode of action.

Within the briefest period, therefore, extrapyramidal disorder shifted from a perception of adverse to one of necessary effect, without which improvement in mental state would not occur. This perception was enshrined in the term ‘neuroleptic’, coined by Jean Delay in 1955, which literally means ‘seizing’ or ‘grasping’ nerves, implying a more forceful and fundamental action than ‘neurotropic’, which was also considered. The emphasis was accordingly very much on the *neurological* component of action.

Laborit’s experience, however, stimulated his interest in a different aspect – the apparently *affective* changes he had witnessed in surgical patients and in Dr Quatri. The word that recurs throughout the earliest writings is ‘detachment’. Chlorpromazine did not dull perception per se but rather diminished emotional response to experience – especially, in the context in which it was largely administered (premedication), noxious experience. This was the so-called ‘psychic indifference’ that translated behaviourally into observed composure and, it could be argued, was *the* unique mental state change the drug (and its successors) produced.

Also in 1955, neurologist Howard Fabing and classicist Alister Cameron proposed an alternative name for this new class of compounds that enshrined this mental state effect – ‘ataraxy’, meaning literally ‘without anxiety’³¹ or, as Caldwell more figuratively suggested, “a state of equanimity”. Drugs promoting this state as their core action would then be ‘ataraxics’ (or ‘ataractics’).

One can find echoes of ‘ataraxy’ in the concept of ‘specific sedation’ still sometimes used in European psychiatry (Lewander, 1994), but in general the term did not catch on, especially in English-language practice. This must remain a source of regret, for wrapping the new class entirely in a neurological blanket allowed fundamental actions to become muddled with adverse ones and sowed the seeds of lasting misunderstanding, a crucial point to which we shall return.

In the 1970s, the Dopamine Hypothesis of Schizophrenia was the most fertile source of research-testable hypotheses within what was becoming known as ‘biological psychiatry’. For some, the drugs from which this theory drew much of its empirical strength became known as ‘anti-schizophrenics’. This was an elementary error by those removed too far and too long from their clinical roots. Half a century of research and