1

The background

Introduction

It is always comforting to reflect on a 'Golden Age' – a time of optimism and hope when the barriers of ignorance and impotence tumbled before an onslaught of knowledge.

For psychiatry, the decade of the 1950s might now be seen as one such Golden Age, for the 1950s saw the explosive birth of psychopharmacology. Suddenly, those devoted to the medical management of individuals suffering the ravages of psychiatric disorder had at their disposal an ever-expanding array of therapeutic tools whose efficacy could be established by the application of scientific principle, which did not require a lifetime to show their benefits, and which were relatively cheap. No longer was the therapeutic armamentarium restricted to those who were sufficiently intelligent and articulate to utilise what was on offer, or sufficiently well-heeled to afford it. For no longer would psychiatrists need to be pseudo-physicians, misdirecting their medical skills to crude and largely ineffective physical interventions or suffocating them under a welter of unverifiable dogma. Most importantly of all, no longer were those whose misfortune it was to be afflicted by major disorders excluded from the therapeutic possibilities.

It was, of course, necessary to interpret the concept of knowledge in this 'Golden Age' in a somewhat wider than usual manner, for while it may have been clear that the increasing litany of new compounds worked, understanding of *how* they worked was rudimentary. This nonetheless had a bearing on the other exciting prospect on offer – the availability of a series of tools to explore the functionings of the human brain.

Table 1.1. *A chronology of 1950s' psychopharmacology*

	1949	Cade	The antimanic (and maintenance) effects of lithium salts
December	1950	Charpentier	Synthesis of chlorpromazine
December	1951	Sigwald & Bouttier	First treatment with chlorpromazine
March	1952	Hamon et al.	First publication of the efficacy of chlorpromazine
May	1952	Delay & Deniker	First systematic evaluation of chlorpromazine
	1952	Selikoff	Mood-elevating effects of isoniazid
	1954	Steck Thiebaux	First formal accounts of parkinsonism with chlorpromazine
	1954	Kline	Reserpine
	1954		Methylphenidate
	1955		Meprobamate
	1955		First trial of G22355 (Imipramine)
	1955	Delay	'Neuroleptics'
	1956	Ayd	Identification of dystonia with chlorpromazine
	1957	Kline	Introduction of MAOIs
	1957	Kuhn	First report of antidepressant effect of imipramine
	1957	Randall	Behavioural effects of 1,4 Benzodiazepines
	1958	Petersen	Thioxanthenes
	1958	Janssen	Butyrophenones (haloperidol)
	1958	Zeller	MAO inhibition
	1959		Introduction of imipramine
	1959	Sigwald et al.	First report of tardive dyskinesia
	1959		Clozapine
	1960	Cohen Tobin	Anxiolytic effects of chlordiazepoxide

The Golden Age

The onslaught of compounds introduced into clinical practice was relentless (Table 1.1). Chronologically, it actually began in 1949 when the Australian psychiatrist John Cade reported the antimanic and mood-stabilising properties of lithium salts. It has to be

admitted that the theory behind the work which led to these observations was frankly awry, but the consequence was to be enormous when, in other places, the therapeutic potential was brought to clinical fruition.

The rauwolfia alkaloid reserpine, long associated with Ayurvedic medicine, was introduced into Western psychiatry by Nathan Kline in 1954, the same year that the central stimulant methylphenidate became available, though this would have to endure the controversies of several decades before it would find respectability – of sorts.

In the early years of the decade, the inappropriate elation of tuberculous patients receiving antituberculous drugs pointed to the first effective antidepressant strategy through inhibition of the enzyme monoamine oxidase, a strategy applied clinically with the introduction of iproniazid in 1957.

Meanwhile, the search for ever-cheaper, non-hepatotoxic phenothiazines led Geigy to investigate a series of iminodibenzyl derivatives for antihistamine activity similar to that of chlorpromazine. The iminodibenzyl analogue of chlorpromazine, code named G22355, was tested by the Swiss psychiatrist Roland Kuhn but with results later described as 'in some patients, quite disastrous' (Broadhurst, quoted in Healy, 1996) as the drug, although sedative, paradoxically appeared capable of promoting manic-like behaviour. In 1955, Kuhn tried it in depressed patients and in 1957 published results of remarkable effectiveness in 'vital' (endogenous) depression. Imipramine entered use in 1959.

In 1955, the first 'tranquilliser', meprobamate, became available, marketed rather quaintly under the name of the town in which it was manufactured (Miltown), and by 1957 it was the most prescribed drug in the USA. Although safer than barbiturates, it still had a rather unsatisfactory therapeutic index. In 1957, however, Lowell Randall demonstrated the behavioural properties of the 1,4-benzodiazepines, and in 1960, chlordiazepoxide became available in the vanguard of a wave of compounds that appeared to offer, at last, an instant solution to life's worries and the prospect of accommodating the public's concern that anything less than eight hours represents inadequate sleep.

It must have seemed it would go on for ever. But, of course, it did not. For the next quarter of a century or more that would essentially be it – the bubble burst and in the silence after the bang psychiatry was left to ponder, with increasing frustration and some alarm, the inadequacies of the tools with which it had been presented.

This is in no context illustrated better than by the one class of drugs omitted from the above list, and the one that is our major topic of consideration in the present volume – antipsychotics. A brief explanation of how they came to us is of some interest.

The chlorpromazine story

There is no single version of the chlorpromazine story that has percolated through the internecine squabbles about who did what and when and which perhaps inevitably followed such a success involving such disparate players. There are, however, certain indisputable facts in this tale and certain accounts that represent, to use the modern analytical jargon, truth of a more narrative than historical kind. As Mark Twain wrote, 'The older I get, the more vivid is my recollection of things that never happened', and the dramatis personae of this particular production are old men all – or dead. What personal insights can now be offered to resolve the hostilities is unclear.

The following brief account is taken from conventional sources (e.g. Swazey, 1974; Caldwell, 1978; Healy 1996) but to those who, by the revisionist nature of historical endeavour, object to the emphasis, the author presents no defence.

The development of antipsychotics could not have had less to do with the needs of psychiatry. To find their roots, we must first dig in the fertile soil of mid-nineteenth century Victorian commercialism.

The synthesis of mauve from coal tar by William Perkin in 1856 provided the fillip to a whole new industry, commercial dyeing, on the back of which flourished the new specialty of organic chemistry. In 1876, Heinrich Caro, chief chemist of the German company BASF, synthesised a new dye, methylene blue, and in 1883, August Bernthsen, a research chemist, published his analysis of its structure. Bernthsen identified the basic nucleus of methylene blue as 'thiodiphenylamin' or phenothiazine. However, it would take many years and whole new fields of research before this discovery could be brought to its potential.

One area of research was shock, specifically anaphylaxis, which led to the identification of histamine and its actions, while a pertinent strand of pharmacological investigation related to the functioning of the autonomic nervous system. By the 1930s, the existence of acetylcholine and adrenaline had been established. Since antagonists of these naturally occurring amines were known, the pharmacologist Daniel Bovet thought it 'reasonable' to postulate that there might exist substances which interfered with the chemically not dissimilar histamine. In the early 1940s, the French pharmaceutical company Rhone-Poulenc developed a series of synthetic antihistamines, some of which – such as diphenhydramine – are still with us.

Meanwhile, phenothiazine had not been neglected. The antimalarial properties of methylene blue had been established in the 1890s, and subsequently phenothiazine was shown to be an effective insecticide against mosquito larvae. However, the molecule was toxic in humans, though an antihelminthic action against swine ascaria was utilised in

veterinary practice in the 1930s. In the 1940s, the American pharmacologist Alfred Gilman returned to the non-oxidised phenothiazines in search of safe antimalarials, but found these compounds to be ineffective and published his negative results in 1944.

Because of the Second World War, these results did not reach France, where a similar investigation was being undertaken by scientists at Rhone-Poulenc. This investigation succeeded in replicating the negative findings with regard to antimalarial activity, but the French group's interest in the field allowed them to observe what Gilman and Shirley had not – the potent antihistamine activity possessed by a number of these compounds. The most important product of this work was promethazine, produced in 1946.

It was clear that these new synthetic antihistamine compounds had unusual central actions. In humans they were clearly sedative, while some appeared to have beneficial effects in Parkinson's disease. In the autumn of 1950, Paul Koetschet, Rhone-Poulenc's Assistant Scientific Director, proposed a phenothiazine amine development programme, with a view to exploiting central actions irrespective of antihistamine 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 whatever products emerged. The first he suggested might lie in pre-anaesthesia, while his 'hope' was for more active antiparkinson agents. 'Finally' he mused on the possibility of 'an application in psychiatry'!

Koetschet's reliance on an outcome of interest to anaesthesia was not without foundation, and brings us back to shock. For the first half of the century, the old adage that the operation was a success but the patient died was based on more than gallows humour. Haemodynamic and traumatic shock all too frequently undermined the accomplishments of even the most technically skilled surgeon. Despite a number of explanatory hypotheses, the mechanisms remained arcane. Working within this general framework was a young naval surgeon, Henri Laborit.

Laborit began his research career on a topic of concern to navies the world over – seasickness. His interest was in the possible role of cholinergic mechanisms, and in pursuit of this he and a colleague (Morand) developed a cholinesterase assay for plasma estimations. When, in 1946, it was postulated that inhibition of peripheral cholinesterase may underlie shock, Laborit was well placed to shift his emphasis. He did not accept the primacy of capillary changes in initiating shock, but was more taken with neural (i.e. autonomic) disturbances that might underlie the problem.

Laborit's views on the mechanism of shock and the cocktail of drugs he recommended to counteract it were roundly criticised in later years, but none of this is of relevance to our interest. For what cannot be denied

is that Laborit was possessed of 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 (i.e. sympatho-parasympatho-lytic) cocktail'.

His observations of the 'secondary' effects of promethazine were impressive, especially in relation to the affective and behavioural changes. He noted that patients became 'calm and somnolent, with a relaxed and detached expression', an effect he was clearly able to distinguish from that of morphine. Laborit's acumen is highlighted by the fact that promethazine had been tried previously in psychiatric patients but only sedation had been noticed.

Much effort has been expended in debating just how pivotal these observations were in Rhone-Poulenc's decision to proceed with the development of aminophenothiazine derivatives, and nothing can be provided here – or perhaps anywhere now – to resolve this controversy. What is fact is that proceed they did; and success came fast. Chloropromazine was synthesised by Rhone-Poulenc's chief chemist, Paul Charpentier, in December 1950, only two months after Koetschet's original proposal, and, after only three months of laboratory study, was deemed ready for clinical trial. The first samples for psychiatric evaluation, as a potentiator of barbiturate-induced sedation, were dispatched to Dr J. Schneider of the Broussais Hospital in April of 1951.

At this time, Laborit was working in the Val de Grace military hospital outside Paris on the development of artificial hibernation as an anaesthetic technique, and he apparantly had no knowledge of the development of the renamed chlorpromazine. When he approached Rhone-Poulenc about the possibility of producing a more effective phenothiazine derivative than promethazine to add to his 'lytic cocktail', he was surprised to learn that one already existed. He received his first samples, as the twelfth investigator, in late June of 1951. In October of that year he was able to report 'the twilight state' that patients entered after receiving his cocktail containing chlorpromazine, and at a meeting the following December he could quote a colleague as observing that the drug 'may produce a veritable medicinal lobotomy'!

Laborit began urging his psychiatric colleagues to try it clinically, although, as the 'urging' was from a surgeon, it is perhaps not surprising that he was met with a fair degree of indifference. In early November 1951, he participated in the first administration of chlorpromazine to a normal subject – his friend Dr C. Quatri, herself a psychiatrist! Quatri described an initial period of discomfiture, supplanted later by 'an extreme feeling of detachment' in which perception was 'filtered, muted'.

In January of 1952, psychiatrists at the Val de Grace finally tried the

drug, although their decision was 'without much conviction'. The patient was a young manic man with several previous admissions. The favourable results were presented orally the following month and published (by Hamon and colleagues) in March. Perhaps because of the origins of their inspiration, the authors of this first published report on the efficacy of chlorpromazine were grudging in their praise, making it clear that 'naturally' they were 'not presenting a new therapy for treating mania'!

However, it was the work of Delay and Deniker that provided the fuel for chlorpromazine's 'lift-off' through a series of reports beginning in May of 1952, although even here it seems that Laborit played a role. According to Swazey, Delay and Deniker heard of chlorpromazine from Deniker's brother-in-law, himself a surgeon, who had utilised Laborit's method.

It is hard to appreciate now how opposed the psychiatry of the time, especially in Continental Europe, was to the idea of pharmacological agents, which were seen as the antithesis of clinical science (Healy, 1996). The 'science' was in unravelling the 'tangled threads' of Bleuler's metaphor. In this context, it is not at all hard to appreciate how frostily the intrusions of a surgeon would be viewed and how, when the trophies were to be awarded, his role would become a source of controversy. But the historical record is clear that it was Henri Laborit, the surgeon, who first identified the psychotropic properties of chlorpromazine. For those offended by the suggestion that he also played a crucial role in providing an impetus for the development of the drug, it is worth recalling that when Rhone-Poulenc came to license the drug to a US manufacturer, 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' (Swazey, 1974) – not the recognition conventionally afforded to other than a key player.

As a footnote, however, if we are looking to priority in relation to the start of the modern era of clinical psychopharmacology, this probably belongs to J. Sigwald, who, on the 28th December 1951, started solo chlorpromazine treatment in a 57-year-old chronic psychotic lady – the memorably named Madame Gob!

What, the reader 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 may cause, and who may even acknowledge the possibility that without them their chosen career might well have been different, may have some interest in the story. It is also presented to dispel the notion, still perpetrated in texts on the subject, that the introduction of chlorpromazine into psychiatric practice was pure 'serendipity'. The drug's development was, no matter

how loosely, a result of the convergence of a number of strands of basic and clinical research with long and honourable scientific credentials, while its eventual home was built on the foundations of astute clinical observation. Its introduction may well have been empirical, but it cannot be considered serendipitous.

There is one final point to highlight from this story – perhaps one of the great ironies of medical history. August Bernthsen, the research chemist who first identified the phenothiazine ring, did so in Heidelberg, only a stone's throw from where Emil Kraepelin would soon formulate his concept of dementia praecox! It would be almost three-quarters of a century before these two powerful developments would find 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 series of phenothiazines was soon available. These were, at the end of the day, essentially derivative, with similar modes of action and, as would later emerge, similar sets of problems associated with their use.

The same judgement would apply to the two other drug types that emerged at this time. In 1958, P.V. Petersen, working at the Lundbeck laboratories in Copenhagen, produced the first thioxanthene. This chemical type was characterised by a carbon substitution at position 10 (the R2 position) instead of the nitrogen of the phenothiazines, the effect of which was that side-chains attached by way of a double bond. Thus, these compounds exhibited stereoisomerism, a property that profoundly affected their pharmacology.

Also in 1958, the Belgian chemist Paul Janssen synthesised haloperidol, the first of an entirely new chemical type, the phenylbutylpiperidines or butyrophenones. This was to some extent a fortuitous event as Janssen had been interested in the pharmacological properties of pethidine (meperidine) analogues modified by simple chemical reactions. Haloperidol was the first drug with relatively selective receptor actions, and hence, in terms of general side-effects, had one of the best tolerability profiles. Haloperidol was to go on to become the 'market leader' antipsychotic in terms of volume usage around the world.

Following Kuhn's demonstration of the antidepressant properties of G22355 (imipramine), other heterotricyclic compounds became of interest, and in 1958 the Swiss company Wander began a development

programme of compounds which, like imipramine, comprised a seven-membered central ring structure. One of these, a dibenzodiazepine with an N-methyl-piperazine side-chain, was HF1854, registered in 1960 as clozapine.

Clozapine's success is a story of survival against the odds. Not only were its expected antidepressant actions not evident, but in laboratory animals it did not produce the responses anticipated of an antipsychotic. However, increasing concern about its adverse effects on the granulocyte cell line culminated in 1975 with reports from Finland of a cluster of 13 cases of agranulocytosis, eight of which were fatal. This effectively terminated its development in most countries, but a lingering impression that this drug was something different led to sponsorship of a large multicentre American study of its efficacy and tolerability in a circumscribed patient group resistant to standard drugs. This study (Kane et al, 1988) has become one of the most influential trials in the history of psychopharmacology, and clozapine was the first antipsychotic to which superior efficacy was attributed – albeit in a specific patient population. Furthermore, this and subsequent work pointed to remarkably favourable neurological tolerability.

Clozapine has radically altered perceptions of the mechanisms whereby antipsychotics bring about not only their therapeutic benefits but also their extrapyramidal effects. It has allowed us to break out of the straightjacket of single system psychopharmacology that was the inevitable lure of the classical dopamine hypothesis, and has returned us to something approaching a more realistic appreciation of neurophysiology and brain therapeutics. Clinically useful drugs that were previously denounced as pharmacologically 'dirty' are now rightly viewed as pharmacologically 'rich', and the race to find a 'safe' clozapine has promoted antipsychotic psychopharmacology once again to the first division. This may ultimately come to be seen as clozapine's lasting legacy.

Single system psychopharmacology has not left the scene entirely, however. In the mid-1960s, modification of the substituted 2-methoxybenzamide, metoclopramide, produced sulpiride, which is chemically distinct from other antipsychotics. Although licensed in France in the late 1960s, the efficacy and especially the central pharmacology of sulpiride only came under scrutiny a decade later. It was the first highly selective dopamine D_2 antagonist and hence in effect represented the realisation of the classical dopamine hypothesis as it relates to antipsychotic action. Furthermore, it appeared to demonstrate a dose-dependent separation of effects thought to be predictive of nigrostriatal antagonism (i.e. motor side-effects) compared to those thought to result from dopamine antagonism at mesolimbic sites (i.e. therapeutic effects). This seemed to fit with clinical observations that sulpiride might

possess a lower liability to promote extrapyramidal dysfunction. Accordingly, sulpiride appeared somewhat different from other classes of antipsychotics in both its clinical and pharmacological characteristics, and hence it was the first drug to be referred to as '*atypical*'.

A range of benzamides with a range of indications is now available worldwide. What will become of the antipsychotic benzamides remains to be seen. The 6-methoxy-benzamide, remoxipride, only managed a couple of years before a reported association with aplastic anaemia curtailed its availability, but amisulpride has been available in France for some time, and raclopride has also been reported on favourably. Although enthusiasm for the highly (dopamine D_2) selective approach to antipsychotic development has waned dramatically in recent years, it may be premature to write its obituary just yet. Even 'science' has its fashions!

A new generation of antipsychotic compounds is now emerging. Thus far, all are based on a model extracted from *one* particular aspect of clozapine's 'rich' pharmacology, namely its relatively potent antiserotonergic – specifically 5-hydroxytryptamine-$_{2A}$ (5-HT_{2A}) – actions. These, in combination with a lower affinity for dopamine D_2 receptors, are behind the designation of these compounds as 'serotonin–dopamine antagonists' (SDAs), although, as with standard drugs, this must not blind one to the fact that they also have many points of pharmacological difference.

This interest in the manipulation of serotonin as a therapeutic aim in psychotic disorders is *re*-newed rather than new, and revives interest of over 40 years ago. These new generation compounds are proving commercially very successful, but it may be that when their place in the armamentarium comes to be more fully established, they will be found to represent relative rather than absolute advances. It is certainly important that we do not substitute one blinkered theory for another and again condemn antipsychotic psychopharmacology to decades of derivative drugs. There are certainly other actions of clozapine awaiting investigation, such as its intriguing and complex effects on noradrenergic systems. There was once a popular theory of that in relation to schizophrenia too, which may one day again see the light of day.

Practice, theory and names

The work of Jean Delay and Pierre Deniker was instrumental in establishing chlorpromazine's therapeutic credentials in psychiatry. They began their investigations 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'