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Introduction

History, to quote Voltaire, is a trick the living play on the dead. One of the general biases of this trick is that we have made progress. Nowhere in history is this seen more clearly than in the history of medicine, where former ages are commonly portrayed as dark ages. Within the history of medicine, nowhere is this truer than in the history of psychiatry and within psychiatry, biological therapeutics before the advent of chlorpromazine and imipramine is seen as particularly benighted. It is widely taken, by current psychiatric practitioners, as all but unquestionable that nothing worked before modern psychotropic agents. To the modern critical eye, therefore, treatment with the available physical therapies must in some sense have constituted an abuse by virtue of the fact that they were either known to be inefficacious or should have been suspected of being so – and yet these treatments were forced on unwilling patients. The period now seems a veritable dark age, from which the discovery of chlorpromazine emerged leading to the sunny uplands of modern psychopharmacotherapy.

Conventional accounts of the physical therapies assume an all but complete discontinuity between the period before and after chlorpromazine.[1] Even revisionist histories such as Shorter's[2] make concessions to this point of view by talking of a First and Second Biological Psychiatry. In very recent years, a challenge to these views has emerged, primarily from historians

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working on the history of physical therapies in psychiatry other than pharmacotherapy, and in particular on the history of psychosurgery.[3,4] This work has provided an increasing body of evidence that, for example, psychosurgery – far from being a – mistake was developed from cutting edge scientific research, that its benefits in individual cases have probably been underestimated and that it and other physical therapies made a contribution to improving asylum morale.

It can also be noted that affective disorders were treated with a treatment (ECT) that had a greater treatment effect size than the commonly used therapies today. ECT clearly worked for melancholic depressions, whereas a majority of modern antidepressants do not (see below). One of the major psychoses (GPI), which accounted for 5–20% of admissions, depending on the region, had been eradicated with fever therapy and subsequently penicillin. And a good case can also be made that, in some countries, the management of opiate addiction was more enlightened or at least more successful than it now is.

Nevertheless, even a substantial challenge to the dominant 'mythology' can be dismissed as involving non-pharmacological therapies, leaving it possible to argue that the discontinuities between pharmacotherapeutic approaches before and after chlorpromazine and imipramine continue to justify designating these periods in terms of a dark age and a scientific period, respectively. A comparative analysis of pharmacotherapeutics before and after chlorpromazine, therefore, is called for and may shed light both on the biases that operate within history and on some of the changes that have accompanied chlorpromazine's introduction.

This paper is neither a comprehensive history of comparative treatment effect sizes nor a history of mentalities, but falls somewhere in between the two. It scrutinizes a series of largely forgotten pharmacotherapies for some of what they reveal about the mentality of therapists and the nature of the conditions they were treating. The analysis focuses on three areas. First, treatments used in 'community' settings for nervousness are discussed. Second, some treatments used within the asylum for psychoses are investigated. Third, the question of the extent to which earlier treatments were evaluated, compared with today, is addressed as answers to this question intersect with any judgements about whether their use was abusive or not. The messages derived from each area will need to be viewed as provisional in that the analysis is hampered by a lack of data. While the major therapies of insulin coma, ECT and leucotomy have been looked at in detail, the full range of pharmacotherapies within asylum settings have rarely been documented, and the availability of community treatments on an over-the-counter basis before 1950 means that good data on the extent of usage are not at present available. The paper focuses largely on treatments that failed, at least in the sense that they have not survived. The paper, however, will succeed if readers are persuaded that these are areas that may repay further investigative efforts.

Community nervousness and anti-nervousness agents

The most striking difference between the pre-chlorpromazine era and the present day lies in the category of drugs now called antidepressants. There were no 'antidepressants'. There wasn't even the concept that there might be such a group of drugs. The word antidepressant was probably coined by Max Lurie in 1952[5] but the coinage took time to take. As late as 1966, *Webster's International Dictionary*[6] did not carry this term and other international dictionaries such *The Random House Dictionary of the English Language* in 1987[7] refer to the fact that the term antidepressant probably emerged sometime in the mid 1960s. Early discoveries of imipramine by Kuhn and iproniazid by Kline did not bring the term antidepressant immediately in their wake. Imipramine was initially termed a thymoleptic and iproniazid a thymerethic or psychic energizer. The term antidepressant possibly only later took hold because imipramine-like drugs appeared effective against hospital or endogenous depressions rather than for community nervous states.

The story, however, is even more complex. Not only were there no antidepressants before imipramine but depression as it is now understood did not exist either. Depressive disorders, at least in Europe, were restricted to the melancholias, with or without delusions, and severe depressive personality disorders that led to admissions to hospital at a rate of approximately 50 per million of the population.[8] These early figures need to be set beside current estimates for depressive disorders which run at 100,000 per million. It follows that conditions currently described as primary care depression or community depressions, and thought to be in some way continuous with hospital depression, before 1950 must have been subsumed within the general pool of community nervousness and as such must have been viewed as discontinuous with melancholia.

These non-hospital nervous conditions were more likely to attract a diagnosis of anxiety or mixed anxiety depressive disorder or 'nerves'. For this group of conditions, there were in fact a large number of treatments before imipramine. Among the first treatments to come to prominence were the opiates.[9, 10, 11] There is a considerable amount of evidence for a substantial use of opiates in the treatment of hospitalized mood disorders, particularly in the German-speaking countries during the nineteenth century, that continued through to the first half of the twentieth century.[12] Justifications for the use of opiates often appealed to a supposed use of laudanum by Paracelsus during the sixteenth century. The widespread availability of opiates, before the 1914 Harrison Narcotics Act in the United States and subsequent acts in the United Kingdom and Europe, probably led to the use of these agents in large amounts for nervous conditions. In the case of the opiates, before 1914, and other cures for community nervousness, thereafter, we are hampered in that through till 1950 the majority of these agents were

available without prescription. As a result, there are few records to document the range of preparations in use or the frequency of their use. Within hospital settings, one of the interesting aspects of opiate use, given the relative absence of modern ideas of specificity in therapeutics, was the recognition that these agents were most likely to be effective in affective disorders.

A second major treatment was with bromides. Bromides were first introduced in the 1860s.[13] Their use was initially in hospital settings where, combined with henbane, digitalis or cannabis,[14] they proved effective sedatives. By the turn of the century the bromides had migrated into primary care, where they had a clear vogue during the 1920s and 30s. By then, there are some estimates that 4 out of 10 scripts in general practice were for bromides.[15] Enthusiasm for the bromides alone, or in combination with other agents, echoed the greetings that were subsequently given to Milltown, Valium and Prozac.[16] There are clear similarities in the rise and later downfall of each of these agents. The toxic effects of overdose with bromides became relatively widely known, making their way into popular literature as in the *Letters of Virginia Woolf* and Evelyn Waugh's account of the *Ordeal of Gilbert Penfold.*

A further group of drugs comprised the agents that were isolated from henbane and other plants in the great period of alkaloid isolation during the mid nineteenth century. Chief among henbane's alkaloids were hyoscine and hyoscyamine, which are now known to have anticholinergic effects. These were introduced in mid century.[17] Hyoscine, and other alkaloids with anticholinergic effects, are among the active principles of Mandragora, which along with henbane had been used for nervousness for millennia. While it is common now to dismiss the anticholinergic effects of modern drugs as side-effects, a series of twentieth-century studies have suggested that what are now called anticholinergic agents have anti-nervousness properties and may be useful for depressive disorders.[18, 19, 20, 21] In fact, the modern clinical trial base is strong enough for anticholinergic agents to suggest that clinicians are likely to have seen beneficial effects from agents of this type. This evidence of efficacy, along with lengthy traditions of employing agents with similar effects, provide good grounds for sustaining the use of these agents through a century of therapy and changing rationales for use.

We know from hospital records that hyoscine was used, very soon after its isolation, alone or in combination with camphor and lupulline.[22] It later had a place in hospital, along with morphine and atropine, in a potent sedative cocktail called Hyoscine Co A.[23] In primary care and office practice in the first half of the twentieth century, it was used in combination with bromides and barbiturates.[24] The ready availability of all these agents makes it highly likely that they would have been used in a widespread manner for nervous conditions, both on prescription and by individuals self-medicating.

Of interest, here, are recent suggestions that current antidepressant agents need to be shown to be superior to 'active placebos', among which

supposedly are the anticholinergic agents.[25, 26] An analysis of antidepressant studies have led Greenberg and colleagues[27] to suggest that antidepressants may, in fact, work largely by virtue of the side-effects they cause, and therefore controls for side-effects need to be introduced into clinical trials. The idea that antidepressants might work because of the side-effects they cause seems almost impossible from the modern point of view, where side-effects have a very distinct meaning in contrast to the specific effects of a magic bullet. But for most of human history, what would now be called side-effects have been taken as indicators that the drug was working and this evidence would almost certainly have contributed to what would now be termed the placebo effect of former treatments.[28]

The use of hyoscine is particularly interesting in this context, in that this agent can induce both euphoria and sedation, both of which have face validity as therapeutic principles that might directly contribute to desired outcomes in nervous conditions. Far from simply providing an 'active placebo', therefore, hysocine sits Janus-faced looking back at an older mentality for administering psychotropic drugs and forward to modern confusions as to when agents can be said to work. Can one appeal to the obviously useful things they do, such as the analgesia produced by morphine, or are they only accepted to work following processes involving controlled trials? The use of hyoscine had its origins in a theoretical framework, the humoral framework. From the middle of the nineteenth through to the middle of the twentieth century its use was probably largely pragmatic. Paradoxically, with the emergence of empirical support for the use of this class of agents, it fell from grace.

The availability of dexamphetamine since 1935 and methylphenidate since 1954 must also be considered. These agents are now conventionally thought of as stimulants rather than antidepressants. They superseded arsenic and strychnine for the treatment of nervous states in which fatigue was prominent. The discovery of 'proper' antidepressants was notable in that these more sedative agents helped lead to a resolution of hospitalized depressions, where stimulants had not.[29] This was the case, even though the first placebo-controlled treatment trial in medicine involved the administration of dexamphetamine in 1939 to hospital patients in a cross-over fashion by Dub and Lurie, who found that it worked in depression but not in schizophrenia.[30] Against this background, it can be noted that the overwhelming majority of disorders now diagnosed as depressive are not the hospitalized depressions, in which the efficacy of imipramine and other early tricyclic agents was demonstrated. It is not clear that dexamphetamine or methylphenidate would not be as effective for these community conditions as any currently available antidepressant. Indeed, from what studies have been done, the treatment-effect size of dexamphetamine and methylphenidate in community depressive disorders is as great as the treatment-effect of these conditions with any SSRIs.[31] Advertisements for methylphenidate for

depressive and fatigue states can be found in mainstream psychiatric journals, such as the *Archives of General Psychiatry*, through to the mid 1970s.

Conversely, the licence applications for a number of the better-known selective serotonin re-uptake inhibitors (SSRIs) did not contain a single study of hospital depression, owing to a relative inefficacy of these agents for severer depressions. It is highly likely that had the SSRIs been tested clinically in the 1950s they would never have been designated as antidepressants. Many of the seeming discontinuities between pre-1950s' practices as regards the therapy of community nervousness and now, therefore, are more apparent than real. One of the few genuine discontinuities lies in the use of the SSRIs for the treatment of obsessive-compulsive disorder (OCD), where there were no clearly effective treatments before the 1960s. The treatment effect size for the SSRIs is in fact larger for OCD, social phobia and even premature ejaculation than it is for depression. This suggests that the designation of these drugs as antidepressants owes something to the state of the market conditions prevailing when they were launched rather than to something intrinsic to either the nature of the drugs or the conditions they are used to treat.[32] Such a situation should provide fertile ground for a history of psychiatry.

Finally, a range of tonics were also available for centuries. To illustrate the use of these agents and the interface between older and new mentalities, I will take the group of tricyclic antihistamines, produced during the 1950s by a range of different companies, before the term antidepressant had been coined. One of these was cyproheptadine, which is now known to have a receptor profile that is very similar to currently marketed antidepressants such as nefazodone. Cyproheptadine has also been shown in clinical trials to have antidepressant properties. It was, however, initially marketed as a tonic. The significance of this is that tonics – agents that increased appetite, improved sleep, etc. – were in widespread use during the first half of the century for symptoms of fatigue and nervousness and had almost certainly been used for this purpose for centuries. Many of them may have had beneficial effects for the conditions in which they were used. A number of them almost certainly contain what would now be thought of as antidepressant principles. One of them, St John's wort, is at present the best selling 'antidepressant' in Germany. Another, isoniazid, an anti-tubercular treatment, which had prominent tonic properties, was investigated by Jean Delay in Paris as well as Max Lurie in Cincinnati for a possible usefulness in depressive states and was demonstrated to be useful.[33,34]

Regulatory arrangements before 1962 permitted the marketing of apparently non-specific agents such as tonics. Companies were not required to restrict their marketing to specific nosolytic agents. Imipramine was an essentially similar agent to cyproheptadine, which in contrast to cyproheptadine became an antidepressant (in whatever the modern sense of that word means), therefore, in part by virtue of the stroke of a regulatory pen. This, allied with

regulatory requirements to make these agents available on prescription only, may in fact have been a greater driver in the formation of modern psychiatry than either any professional manoeuvres to capture business by psychiatrists or any increase in their ability to ameliorate nervous conditions.

The interface between anxiety and depression

One of the big difficulties in making sense of pharmacotherapy in the first half of the century is the fact that community nervousness is more likely to have been interpreted as anxiety-based rather than mood-based. Accordingly, a range of tranquillizers of one sort or the other would have been used. However, neither the terms anxiolytic nor tranquillizer were available as therapeutic concepts during the first half of the century. The useful agents were generally seen as sedatives. While propanediols had been available as sedatives from the early years of the century, it was not until the advent of the propanediol, meprobamate, in 1955, that the process of distinguishing anxiolytics from sedatives began.[35] Chief among the sedatives before that were the barbiturates. The first in a series of barbiturates were produced in the 1860s.[36] They came into wider use after their sedative properties were discovered and a method of producing a series of barbiturate congeners was discovered by Fischer and von Mering in 1903.[37] The core molecule was almost infinitely manipulable, which made it possible to produce a series of compounds with varying half-lives and other properties. It also made it possible to introduce a series of 'new' agents at regular intervals, which made these compounds appealing to the fledgling pharmaceutical industry.

Within hospital care, the barbiturates became the most commonly used sedatives and their use grounded the development of the sleep therapies. As regards community nervousness, the barbiturates were also used extensively.[38] A combination of dexamphetamine and amylobarbitone, which was traded by Smith Kline & French, under the name of Drinamyl, was extremely popular in the 1950s. Drinamyl had relatively extraordinary properties that have not yet been fully appreciated by modern psychopharmacology. Although the idea behind the combination of treatments had been to counteract the sedative effect of the barbiturate with a mild stimulant effect, the stimulant effect of the combination greatly exceeded the effect of dexamphetamine on its own.[39] Many witnesses of the period have attested to the fact that the combination of the two agents appeared to produce little in the line of dependence and relatively little in the line of toxicity and that, when it was later replaced by more conventional antidepressants, in general, patients appeared to have been less happy with the antidepressants.[40]

There is a notable transcultural twist to the antidepressant story. During the 1960s and 1970s, community nervousness, seen generally in terms of anxiety, led to remarkable sales for the minor tranquillizers. Possible problems with dependence on these agents in the 1980s led to the eclipse of

their use and, indeed, the virtual eclipse of both the terms anxiety and anxiolysis. These were replaced by the notion that community nervousness was essentially mood-based, and antidepressants would be the appropriate treatment.[41] The replacement of anxiolytics by antidepressants has, however, been an almost exclusively Western phenomenon. Benzodiazepines do not appear to produce comparable physical dependence problems in Japan where the minor tranquillizer market remains a vastly greater market than the antidepressant market and where no SSRIs are available as antidepressants.

A recent WHO survey of psychotropic drug use worldwide, in addition, has found that 'mood disorders' were more likely to receive a prescription of a mild tranquillizer, while prescriptions for anxiety were more likely to be for an antidepressant.[42] It can be argued, therefore, that practices prevalent in Western countries before 1960 are more in line with current practices worldwide and that the exception to the rule is the relatively odd set of practices that have grown up in the West in recent years. Recent Western prescribing in this area, in other words, has been culture bound. The factors that have led to the emergence of this culture, which is a source of discontinuity with earlier periods, would doubtless repay further scrutiny.

Finally, as regards the antidepressants, there is an issue to do with the frequency of depression. As of the 1950s estimates of the frequency of depressive disorders were of the order of 50 per million. They now run at estimates of 100,000 per million.[43] There has been a move from seeing certain conditions as problems of living, sometimes inappropriately treated with tranquillizers, to seeing them as diseases appropriately treated with antidepressants, even though the evidence that antidepressant use leads to a resolution of these conditions is meagre. Given that a diagnosis can be disabling in its own right, if the remedies being offered for the condition that has been diagnosed do not produce substantial benefits, it is less than clear that we are not sowing the seeds of an iatrogenic crisis on a grand scale.

Some aspects of the treatment of the psychoses

Within mental hospitals, whatever was done about cures, one of the pressing needs was for sedation. The initial agents used were the opiates, hyoscine and digitalis, and there are good indications that what amounted to sleep therapy was in use.[44] The synthesis of chloral in 1869 in Liebig's laboratory and the discovery of its sedative properties[45] led to its being used widely for this purpose, replacing the opiates in many hospitals and digitalis in almost all. Chloral remained in use in conjunction with, or alongside, paraldehyde, a range of barbiturates, bromides and anticholinergic agents through the latter half of the nineteenth and first half of the twentieth centuries.

Methylene blue

In addition to a pragmatic need for sedation, however, a range of other

treatments were tried for more conceptually-driven reasons. Of note is the use of methylene blue. This had been synthesized in 1868. It was subsequently demonstrated by Paul Ehrlich to stain nerve cells and certain parasites selectively. Its selective effects on parasites led to its therapeutic use for malaria, on the same basis that trypan red was employed with some effect for trypanosomiasis. Methylene blue's effects on nerve cells led Ehrlich himself to try it for neuralgia. This clear action on nerve cells also underpinned its use for psychiatric disorders. As early as 1899, Bodoni reported on its use for psychotic disturbances.[46] Bodoni's study makes three things clear. First, it showed the thinking behind its use – the prior demonstration that it acted on nerve cells. Second, it is clear from his report that methylene blue effectively calmed psychotic agitation. Third, he reported that a number of other physicians apart from the author had been using it. Despite the availability of a theoretical rationale and demonstrations of efficacy, it fell out of use, possibly in part because of the contemporary emergence of the barbiturates, which were more effective sedatives. The birth of the notion that an agent could do something other than sedate lay fifty years in the future.

Effective though they were as sedatives, the barbiturates nevertheless left many problems unsolved, in particular the issue of correcting the supposed pathophysiological basis for psychotic disorders. This unmet need provided the matrix for further theoretically-driven efforts. The progress of pharmacology led to the discovery that methylene blue was an oxidative agent. As an oxidative agent, there were theoretical grounds to believe that it might be of benefit in toxic states. In 1938, this led to a further attempt to use it in psychiatry and a further report of its efficacy, in this case specifically for states of dementia praecox.[47] This report apparently had even less impact that that of Bodoni, perhaps because of the contemporary discovery of the convulsive therapies and, soon afterwards, of psychosurgery.

The methylene blue story offers a striking continuity that cuts across the divide marking the introduction of chlorpromazine, in that a conceptual argument, similar to those put forward by Bodoni and Allexsaht, emerged for its use in the 1970s. Based on its capacity to inhibit the transport of vanadium and indicators of disturbed vanadium transport in manic-depressive disorder, it was hypothesized that methylene blue would be useful in the management of manic-depressive disorders. It is. Naylor and colleagues demonstrated that it had clear prophylactic effects in this condition.[48] Needless to say no one uses methylene blue for this purpose today, providing yet another continuity between the pre- and post-chlorpromazine eras. In all three instances, it can be noted that there were competing therapies and competing interest groups likely to make more money out of other therapies than they would from methylene blue. In no case, however, was there any greater theoretical basis for the use of these other therapies.

The above demonstrations of efficacy should not occasion much surprise as methylene blue contains the phenothiazine nucleus.[49] The interest lies in

the contrast between these uses of methylene blue and the introduction of chlorpromazine in the 1950s. Rhône-Poulenc had synthesized a number of phenothiazine antihistamines in the 1940s, some of which found their way immediately into psychiatric practice, because of the utility of their sedative effects. In contrast, chlorpromazine, which was less sedative, appeared to have little clear theoretical rationale to support it. Its use became established on the basis of pragmatic efficacy, linked shortly afterwards with extraordinary commercial support. The conjunction of physician inputs and commercial support, in due course, helped generate a theoretical basis for the use of the drug – the dopamine theory of schizophrenia – but the distinguishing feature of chlorpromazine's early use was the lack of a theoretical basis for that use. Its users were not doing science in accordance with conventional theories of how science is supposed to operate – the use of methylene blue more nearly approximated to these models. It is, therefore, perhaps not so surprising that chlorpromazine's early use was largely in asylum as opposed to university settings,[50, 51, 52] in contrast to methylene blue whose use originated in university settings.

Uric acid and lithium

Lithium is another treatment with a balance between theoretical basis and empirical evidence, not dissimilar to that seen for methylene blue. In the nineteenth century, the notion of a uric acid diathesis achieved widespread support.[53] It was felt that this underpinned a number of disorders from gout through to rheumatism, cardiac disorders and manic depressive disorders, which were seen as a form of gout retroceding to the head. It is easy to see how the notion of a uric acid diathesis would emerge in an era before the advent of X-rays or other methods to assess internal physiology, in that physicians were restricted to inspecting urine, faeces, blood and other secretions. As urates precipitate out in urine, it was all but inevitable that theories would form about their role in a variety of disorders. The discovery that lithium dissolves urate stones set the scene for its use for a wide range of conditions, in much the way that the fact that methylene blue stained nerve cells provided a basis for trying it for nervous disorders. The effects of lithium on urates, later, supported what amounted to an industry in lithium waters in both America and Europe.

The widespread use of lithium, largely fuelled by this understanding, appears to have led to the discovery by Carl Lange that it had prophylactic effects in manic depressive disorders. Carl and his brother Frederick during the years between 1880 and 1900 appear to have treated several hundred patients with mood disorders using lithium salts, reporting generally favourable results.[54, 55] Hammond, in Bellevue Hospital in New York, also used it in mood disorders, for similar reasons it would seem, and reported good results.[56]

In the face of such findings, it is of considerable interest that the use of

lithium died out. While problems with toxicity may have played some part in this, its eclipse appears to have been primarily linked to the eclipse of the uric acid diathesis. As the theoretical rationale, which underpinned treatment, was discredited, so also the treatment, despite apparent efficacy, appears to have lost the confidence of medical practitioners and to have fallen into disuse. The extent to which it fell into disuse, however, is uncertain. A number of British country asylums had large supplies of lithium in stock at the turn of the century.[57] This use of lithium appears to have migrated with some of the doctors from these hospitals to Australia, where lithium could also be found in the pharmacies of a number of Australian mental hospitals during the 1940s, before its use by John Cade.

Lithium was rediscovered by Cade in 1949 by virtue of his observations of its tranquillizing effects on guinea pigs while trying, on the basis of a theoretical rationale, to dissolve urates in their urine. Its subsequent use in manic depressive disorders appeared to bring about all but miraculous recoveries – at least as portrayed by conventional accounts. In fact the results were mixed. A number of the early patients on lithium died. Lithium was clearly toxic and this toxicity had led to its withdrawal by the FDA. A range of investigators worldwide read Cade's reports and a number tried out the new treatment, particularly in France, but the results were disappointing and few persevered with it.

It was arguably the efforts of a single man, Mogens Schou, that made the difference. He established its efficacy for mania on the basis of one of the first randomized, controlled trials in psychiatry.[58] He, and colleagues, worked on methods to determine the serum levels of the drug and on recommendations for safe treatment. A series of bitter disputes between Michael Shepherd and Mogens Schou, regarding the prophylactic effects of lithium, may also have fuelled the imagination of clinicians and sustained awareness of this treatment. Without Schou, there must really be a question mark as to whether lithium would have survived long after its rebirth in the 1950s. As with chlorpromazine, practitioners only had the evidence of successful use and data from clinical trials to support them – there was no theoretical basis for lithium's use; no mythology that could be used to sell it. Its use may well fade away when Schou dies. If it does so, it will probably be because another agent, perhaps of lesser efficacy, displaces it by virtue of marketing that will depend on offering some 'biological rationale'. Commercial support is attracted to the artistic verisimilitude offered by a theoretical rationale, when this is accompanied by patent possibilities.

One of the most obvious differences between the science base of the physical therapies before 1950 and the modern day has been the rise of neuroscience. We now know more about the workings of the brain. Until the 1960s, even basic questions on the mechanism of neurotransmission had not been settled. As of the turn of the millenium, however, the impact of neuroscience on current therapeutics remains aspirational rather than of clinical

utility. Nevertheless, the emergence of modern psychotropic drugs led very quickly to the emergence of 'biochemical' theories to account for their effectiveness. This has given rise to a surprising continuity between pre- and post-chlorpromazine eras. One of the most striking things about the interface between clinical practice and currently dominant theories on the underpinnings of psychiatric disorders is that these theories differ little from the uric acid diathesis in the nineteenth century. Modern drugs are postulated to deliver their therapeutic effect through actions on systems that they can be seen to work on, exactly in line with lithium in the 1840s. The primitive technologies that were available through to the mid 1990s restricted investigation to assays of blood, urine and other bodily fluids and deductions based on the content of these fluids – just as with lithium. In addition, as a direct consequence of these drug effects, in the 1960s it was proposed that the illnesses stemmed from lesions of these same systems, just as it was once proposed that manic-depressive disorder stemmed from a disorder of uric acid metabolism.

Treatment abuse

The common portrayal of the physical therapies before chlorpromazine is coloured by descriptions of treatment abuse. Procedures such as insulin coma, lobotomy and ECT are portrayed as having been inflicted on patients, without their consent and often as leaving a shattered hulk behind. The archetypal treatment of this sort was prefrontal leucotomy, as practised by Walter Freeman.[59] The increasing specificity and effectiveness of modern therapies and a more enlightened therapeutic climate have supposedly made such practices all but inconceivable.

There are two aspects of this that deserve notice. The first is that while Walter Freeman seems to have been a zealot, not all the psychosurgery or the physical therapies that were practised were as indiscriminate or without effect as that championed by him and inflicted on many patients.[60, 61] Joel Braslow,[62] looking at patient hospital records from the period before and after the introduction of malaria therapy for GPI, records a convincing story of increased therapeutic optimism leading to more humane conditions in the asylums of the time. Witnessing cures brought about by physical means in very difficult circumstances appears to have done a considerable amount, in some circumstances, for both staff and patient morale.

It is likely to have been perceptions of small benefits such as these, as well as the need to make some impression on what appeared to be a mountain of human misery, that led to a range of non-specific physical procedures designed to treat infections or promote immune reactions of some sort. These included the removal of tonsils, gonads, stomachs, intestines, spleens, uteri and teeth, the drainage of sinuses and other sites of possible focal sepsis, injections of colloidal calcium and other manoeuvres.[63, 64] The clear

benefits of ECT led to the development of range of other shock therapies such as amphetamine[65] and acetylcholine shock.[66, 67, 68]

In contrast, recent years have seen the use of megadose regimes of neuroleptics. Narcosis with haloperidol, an agent not supposed to have sedative properties, was common practice in the 1970s and 80s. Young women, many of whom will not have had schizophrenia, a proportion of whom will have been abused, will have received haloperidol 10mgs IV hourly for several days on end. It has been standard to have initial regimes of haloperidol 10mgs qds, when research evidence suggests that the optimal doses were between 1 and 5mgs per day.[69, 70, 71] Regimes of flupenthixol of 1000mgs per day have been given to youngsters in their teens.[72] Several oral neuroleptics have been combined together, without pharmacological rationale, and these in turn have been combined with depot neuroleptics, again with little or no rationale.[73] These regimens may have inflicted permanent neurological damage on far greater numbers of individuals than were ever mutilated by psychosurgery. This damage continued over decades, in contrast to the relatively brief period of time during which psychosurgical excesses took place. And far greater numbers of people were exposed to these 'treatments'.

The impulses that give rise to megadose regimens of neuroleptic agents as well as to psychosurgery, it must be recognized, are not all bad. They are underpinned by a heroic ethic, according to which it would be a greater sin not to intervene as vigorously as possible than it would be to do no harm, if by doing no harm the patient is left to suffer grievously. Crucially from this point of view, the potential for abuse is not inherent in the treatment, it lies in clinical practice and in particular, it would seem, in clinical practice informed by a scientific rationale. Megadose regimens only emerged following the elaboration of the dopamine hypothesis of schizophrenia, which provided the siren call, which justified ignoring obvious clinical deterioration. In the 'bad old days', the numbers of people who could conceivably have been exposed to this heroic/scientific ethic were relatively few. With de-institutionalization and the growth of the psychiatric profession, it is probable that the numbers of those potentially exposed to abusive treatment regimes has increased a hundred-fold.

The capacity for abuse in psychiatry was linked to the committal system, whereby individuals could be involuntarily detained in hospital and treatments inflicted upon them whether they wished them or not. It was this dilemma that gave rise to the *One Flew Over the Cuckoo's Nest* scenario, where heroic treatments were inflicted not on a patient, who by virtue of an all but chronic vegetative state and lack of responsiveness to all other interventions had nothing else to lose by one last heroic effort, but rather were inflicted on a clearly unwilling individual. Anti-psychiatrists railed against the dangers of these arrangements. Lobbying by many influential figures, by pressure groups of patients and by others has led to a reform of

mental health legislation and greatly reduced the likelihood that abuses on the scale of what happened in the past could stem from this source today.

But to think that we have moved thereby from an era of greater control to one of more openness and lesser control in which the capacity for treatment abuse has been reduced would be misleading. In fact, control has been extended and the capacity for abuse has arguably been increased by virtue of being more concealed and exercised in a more subtle form. Before the 1950s the various therapies, including the barbiturates, anti-cholinergics and other agents were available without the need for a prescription. Prescriptions had been introduced in 1914 in the United States, as a means of controlling the supply of heroin and cocaine to addicts. Subsequent legislation introduced similar arrangements in European countries. But these other drugs, while available on prescription, could also be obtained without prescription. In the 1950s with the introduction of a wide range of new, safer and more effective agents, there was also the introduction of greater regulatory control. The system of prescription only, which had been introduced for addicts, was extended to the entire population.

The rationale for this was that, in a population that was not health conscious, the need to consult a medical practitioner in order to obtain medicines would ensure that the medicines were given for the correct purposes and that the potential pitfalls of treatment would be explained to the patients.[74] This clearly never happened. The system, however, has not been revised, even though it has failed in its primary purpose, nor have its drawbacks been explored. I will touch on two. Essentially in order to prescribe psychotropic drugs today, diseases have to be prescribed to people in a way they didn't have to be prescribed in the 1950s and 1960s. The prescription of a disease does not happen today for over-the-counter medicines, such as St John's wort, for instance. This can be taken as a tonic for problems of living. Its use does not stigmatize as much as the use of an antidepressant would. From this perspective the recent explosion in the apparent incidence of depressive, obsessive and other diseases is unremarkable; companies market disease recognition.[75]

Secondly, many patients get locked into treatments delivered by prescription out of the fear that, should they go against their doctors wishes, when they really need help they will not get it if they haven't done what they are told. This leads to an enormous burden of iatrogenic illness.[76] It should be recognized that iatrogenic deaths and injuries on the scale currently reported are a modern phenomenon and the mechanism of making medicines available on prescription only is one that drives the process forward and will continue to do so as long as it remains in place. The megadose use of neuroleptic agents happened in community settings; it was not hidden behind the walls of the asylum. It is unlikely that patients would inflict similar regimens on themselves if left to access these medicines.

The evaluation of therapies

Finally, the capacity for treatment abuse is popularly thought of as being linked to our capacity for evaluating treatments. Unevaluated treatments, it is thought, have a greater potential for abuse, whereas those which have been evaluated and shown to 'work' clearly cannot be abusive in the same way. The fact that our capacities for evaluation, by means of randomized controlled trials, for instance, emerged at the same time and on the back of the new treatments, is a further factor in arguments for an absolute divide between the pre- and post-chlorpromazine eras. Several cautionary notes are in order here. First, it is clear that claims for treatments such as the eradication of focal infection[77] had been tested rapidly after they were first made and it had been shown that there was no scientific basis for the claim.[78] The continuing use of this approach, therefore, owes something to factors other than our capacity to evaluate treatment efficacy. Second, the first placebo-controlled treatment trial in medicine was Dub and Luries's dexamphetamine study, which suggests that psychiatry was at least as open to the need for evaluative methods in the pre-chlorpromazine era as any other branch of medicine.

Third, far from providing conclusive answers, a good case can be made that randomized controlled trials as currently practised in psychiatry provide a sophisticated means to override the patient's voice. Just as psychiatrists could once see the outcomes of prefrontal leucotomy as good, a variety of rating scales now offer the possibility of proving the outcome is good. The randomized controlled trial, complete with the use of operational criteria and standardized rating scales has been a triumph that permits a demonstration of efficacy in conditions subject to considerable natural variability and against a background of diverse constitutional types and psychosocial settings. It is also expensive, so that ordinarily only multinational corporations can mount these exercises. These corporations can and do fail to publish the results of many trials and even systematically fail to publish the results from all trials on some measures – such as quality of life measures in antidepressant trials which reflect the patients perceptions of clinical efficacy.[79] Against a background of bland reassurance from company sources on the safety and desirability of the latest product, any natural caution that physicians may have about the therapies they deliver will often have been jettisoned and the capacity for abuse will have been magnified accordingly. There are few grounds for sanguinity and no grounds for thinking that a firewall has been put in place between the abuses of the past and modern clinical practice.

Paradoxically, perhaps, one of the true discontinuities between the pre-chlorpromazine era and now lies in the discovery of the placebo. It is commonplace to hear that almost all therapies available before the revolution in therapeutics that took place during and after the Second World War were

not effective and, therefore, any benefits they produced were in a placebo capacity.[80] While clearly there is some truth to this contention, in other important respects it is misleading. Placebos as we now understand them are treatments which lack intrinsic efficacy but yet their use embodied in a therapeutic act can be demonstrated to be efficacious. Before the widespread adoption of RCTs, there was no understanding that this might be the case. All previous 'placebos', like methylene blue, came complete with a therapeutic rationale (quite apart from a good deal of unrecognized intrinsic efficacy). Modern placebos don't. One of our most grievous failures has been the failure to explore the significance of this.

Finally, as regards evaluative technologies, the ultimate outcome measures are whether patients leave hospital and their rates of readmission. To date there has been little systematic comparison between pre-1950 rates of recovery and thereafter. We are presently analysing data of direct relevance to this question and find that rates of recovery for major affective psychoses were at least as good as now, and rates of readmission were considerably lower before 1950. Recovery and readmission rates for schizophrenia were the same as now.[81] There were far fewer non-psychotic nervous conditions hospitalized before 1950 compared with now, and overall psychiatric bed usage has risen 15-fold.[82] This throws open the question of how much recovery or readmission rates were due to pharmacotherapeutic or other physical approaches before 1950 and equally how much current rates are influenced one way or the other by modern pharmacotherapies. A 15-fold increase in bed usage suggests that modern evaluative technologies which tell us that modern treatments are increasingly efficacious may have something wrong with them or may be misapplied.

In summary, in line with recent arguments from the historiography of psychosurgery,[83, 84] the pharmacotherapies outlined here appear to have been largely therapies with a considerable theoretical underpinning. They had pragmatic evidence of efficacy as well as, in all probability, outcome data that were not as different from modern therapies as modern therapists might like to think. Before 1950, furthermore, the majority of people with nervous problems had considerably more control than they now have over which treatment they would take and for how long. This is an advantage that arguably counts for something in an era when patients appear to feel increasingly alienated from modern medicine, despite being presented with a burgeoning amount of material attesting to the increasing efficacy of modern pharmacotherapies.

Coda

There are many debates about the origins of the psychiatric profession. Some commentators point to the interests of medical people to promote their own profession, to obtain status.[85] These views tend to downplay factors inherent

in the treatment of mental disorders themselves. In contrast, others have pointed to the fact that psychiatry derives legitimacy from the existence of mental illness, the concern to alleviate the condition of those who are ill and an increasing ability to do so.[86] In all probability both factors have contributed.

There is a third, rarely advocated, possibility, however, which is that psychiatry has in part arisen by accident. The growth in the number of psychiatrists in recent years must owe something to the fact of psychiatric treatments being available on prescription only. If the new treatments really do work, their use should otherwise have led to minimal expansion in the number of psychiatrists. If this is the case, then it must be recognized that prescription-only status came about by virtue of a series of accidents that happened elsewhere in medicine. It was not engineered by psychiatrists and bears no relation to the management of mental illnesses *per se*. It is one of the major discontinuities in the field. This development was also initially resisted by the pharmaceutical industry. But one of the biggest differences between 1950 and now is the capacity of the pharmaceutical industry to extract a commercial advantage from preparations which, for the most part, have no compelling evidence of greater efficacy than many older agents. The extent to which this is made possible by prescription-only arrangements is deserving of further scrutiny.

If it is conceded that an 'accident' of this type could play a part in contributing to the growth of psychiatry in recent years, this opens up the possibility that similar contributory factors played a part in the nineteenth century also.

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