The psychopharmacological era: notes toward a history

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The psychopharmacological era: notes toward a history

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SUMMARY Cultural and economic influences on the psychopharmacological era are reviewed, in an attempt to bring into focus what has been happening in psychopharmacology for the past thirty years. It is argued that the belief that clinical advances are made through the heroic achievements of disinterested scientists is a simplistic view that may militate against future significant discoveries. Such discoveries, it is argued, still come about for the most part serendipitously, despite a widespread belief that psychopharmacology has become a rational science.

Introduction

The earliest histories of any branch of science, just as the histories of anything else, tend to focus on chronologies of who discovered what and when and the recollections of eminent discoverers. This is very much the case in psychopharmacology at present, as the recent volumes on *Discoveries in Pharmacology* (Parnham and Bruinvels 1983) or *Discoveries in Biological Psychiatry* (Ayd and Blackwell, 1970) illustrate. Undoubtedly important as this is, especially for younger generations of workers entering the field, such individual 'heroic' accounts implicitly relegate to roles of minimal importance other influences on development such as economic, or cultural factors. In some respects this is not surprising as medical historians have generally contrived to ignore the history of the drug business, seemingly in the belief that it is irrelevant to medical science, even though the production and use of drugs has increasingly underpinned medical business since the seventeenth century (Liebenau, 1987; Porter and Porter, 1989). Such neglect, however, seems particularly misplaced in psychopharmacology, which is a science that defines itself in terms of drug use and many of whose most eminent practitioners work in or in close association with pharmaceutical companies. This article seeks to offer some notes toward a future history, that will surely locate the dynamic of advance in psychopharmacology other than solely with the insights and oversights of individual scientists.

Science, business and drug development

One of the principal consequences of the introduction of antidepressants and neuroleptics was the development of the monoamine hypotheses of depression and the dopaminergic hypothesis of schizophrenia. However, far from these hypotheses being an unambiguous advance in the scientific understanding of mental illness, I have argued elsewhere (Healy, 1987a) that the monoamine hypotheses in particular were quite simplistic; that they accounted for less of the clinical data and were as unscientific as the psychodynamic hypotheses before them, in that they have been in practice, incapable of disproof. They did, however, legitimize research on the neural substrates of behaviour in a way that earlier hypotheses did not. They also provided opportunities for research, the benefits of which, as regards furthering our knowledge of brain processes and in bringing academic honours and research funding to contemporary neuroscientists and psychiatrists are quite clear. But the benefit in terms of increasing our knowledge of clinical disorders is much less clear.

From the start, drug company research and promotional activity has had a dialectical relationship with academic interests. Initially, it

was the clinical use of reserpine and the laboratory discovery that it depleted amine neurotransmitters that led to the finding that antidepressants blocked the effects of reserpine on mice (see Sulser and Mishra, 1983). This blockade and the notion that antidepressants must in some way increase brain catecholamines became established in company laboratories as a method for screening for antidepressants. While not wishing to deny that some simple screening method was needed to sift through the vast number of compounds which have been synthesized, the disadvantages of this approach only became evident with the essentially serendipitous discoveries of iprindole and mianserin. It then became clear that the reserpine model and too strict an adherence to catecholamine theories was leading to the development of modified tricyclics and MAOIs, rather than to the discovery of new agents, which might in turn lead to development of or replacement of the orthodox academic hypotheses.

The downgrading of the reserpine model and the replacement of the initial formulations of the monoamine theories by amine receptor hypotheses, however, has not led to any change in drug company strategy. In the case of drugs developed during the past decade, it is highly likely that many potential antidepressants have been missed because they did not bring about beta-receptor downregulation as Sulser's 1978 hypothesis suggested they should (Sulser and Mishra, 1983). It also seems quite likely at the moment that drugs failing to bring about potentiation of 5-hydroxytryptamine (5-HT) neurotransmission in line with the proposal of de Montigny (de Montigny, Chaput and Blier, 1988) will not be promoted as vigorously as they otherwise might have been, in the light of the current fashion for sensitizing 5-HT receptors.

This strategy of following academic dictates persists despite the evidence that academic fashions are just that – fashions. Views are adopted and promoted vigorously with the claim that they account for all the evidence, which they may well appear to do at the time of initial promulgation and for a honeymoon period afterwards. This happens inevitably as contrary evidence which may have existed previously would not have been reported in the absence of any reason to report it. For example, no one would have reported a lack of correlation between CSF 5-HIAA and suicidal behaviour until after claims had been made that such correlations exist. Furthermore, new contrary evidence often receives a poor reception and sometimes initial rejection, *especially* from the most prestigious journals.

Increasingly, however, this strategy, which goes under the name of a 'rational' strategy of drug development, is leading us away from the methods that gave us the original antidepressants iproniazid and imipramine – that is good clinical observation. Perhaps it is thought that the opportunities for such pioneering/primitive research do not now exist. Yet it appears that millions of people worldwide have been on calcium entry blockers for years, which have been entering their brains and bringing about mental state changes unnoticed by clinicians. Nothing was detected it seems until it was fortuitiously noted by Barrow and Childs in 1986, that verapamil appears to be beneficial for tardive dyskinesia. This discovery was delayed, despite academic awareness going back more than a decade that drugs active on calcium fluxes should bring about altered brain functioning (Carlsson – discussion). This state of affairs is not confined to calcium entry blockers. There are some indications that the angiotensin-converting enzyme (ACE) inhibiting antihypertensives (Whalley, 1989) and aspirin (see discussion) have also been entering the brain for years and bringing about mental state changes.

Arguably part of the reason for this neglect is that no investment is being put into fostering clinical observation of the type that discovered that antitubercular agents could also be antidepressant or that some anaesthetics were ataractic. Some reasons why this should be the case are developed in the remainder of this article.

Science, business and drug marketing

One of these reasons stems from drug marketing strategies. A common feature of the accounts of how individual clinicians discover new drugs is the emphasis placed on how they not only recognized the value of the agent but at the same time they recognized a condition it might treat (Kuhn, 1990; Sandler, 1990). It is this act of making visible the invisible that is the truly creative act. But making visible the invisible could also well describe the process of niche marketing as currently practised by drug companies.

Neuroleptic antidepressants

In recent years, flupenthixol has been widely marketed by Lundbeck as both a neuroleptic and an antidepressant. The basis for this marketing strategy stems from a number of uncontrolled studies reported from Denmark in the late 1960s (Sonne, 1966; Reiter, 1969), in which depressed subjects showed a response to flupenthixol, that was comparable to that shown by other antidepressants, that is 60–70% responded. It was noted that this response was brought about by low doses of flupenthixol – lower than doses then in use for the management of schizophrenia.

Further support for this contention has come from a number of double-blind studies of flupenthixol versus placebo (Predescu *et al.*, 1973; Frolund, 1974; Ovhed, 1976) and versus nortriptyline (Rosenberg, Ostensen and Fonnelo, 1976; Johnson, 1979), amitriptyline (Young, Hughes and Lader, 1976) and phenelzine (Razak, 1980). In all these cases flupenthixol proved superior to placebo and at least equivalent to the antidepressants.

Another pointer to the antidepressant effect of flupenthixol that is cited is that when used in schizophrenia it seems less likely to cause 'depression' than fluphenazine (Carney and Sheffield, 1975; Johnson and Malik, 1975). On balance, however, it would appear that the 'depression' induced by neuroleptics in schizophrenia is more an expression of drug-induced toxicity (demotivation and akinesia) rather than a true endogenous mood disorder (Bartels and Drake, 1988). Therefore the decreased likelihood that flupenthixol causes such a syndrome is not strictly speaking evidence that it is an antidepressant.

While accepting that there is sufficient evidence to warrant further investigation of the 'antidepressant' properties of flupenthixol, Robertson and Trimble (1982) note several problems in the way of accepting that this agent is an antidepressant in the conventional sense. In general, the studies cited above were conducted on patients with mixed anxiety-depressive states rather than clearcut cases of endogenomorphic depression. Second, the effect achieved has been clearly present from the first week of treatment. For example, in Johnson's study both flupenthixol and diazepam were as effective as nortriptyline in the longer term (29 days) and more effective in the short term – but few would consider diazepam an antidepressant. In Reiter's study the effect of flupenthixol was most commonly present within 24 h (Reiter, 1969). If not present by the end of the first week, he thought that treatment could be discontinued, as the likelihood of response was then minimal.

Such rapidity of onset is characteristic of a neuroleptic but not of an antidepressant. Whether one has schizophrenia, depression or is simply a control subject, all neuroleptics produce an identifiable state of indifference within a few hours of having had them (Kalinowsky and Hoch, 1961; Swazey, 1974; Healy, 1989). Agitation is the target clinical feature across clinical categories (Baldessarini, 1980). The fact that schizophrenic illnesses typically do not substantially improve for several weeks after therapy has been instituted has tended to obscure this fact (Healy, 1990a, 1990b).

Another problem emerges from Robertson and Trimble's 1982 review. These authors also assessed the antidepressant potential of other neuroleptics based on clinical reports. It would appear that all other neuroleptics possess comparable 'antidepressant' properties to those of flupenthixol. At least as convincing a case can be made for thioridazine, chlorpromazine, perphenazine, thiothixene and sulpiride. In the case of all of these it would seem that their clinical benefits are apparent within the first few days of treatment and that they are best in groups of mixed anxiety-depressive states. Similar findings had also been reported, as early as 1955, for the very first neuroleptic – reserpine (Davies and Shepherd, 1955). (To a historian the subsequent lack of citation of this Davies and Shepherd article, despite the eminence of its authors and its reporting of a controlled clinical trial, in contrast to the widely reported uncontrolled observations of reserpine's propensity to cause depression is interesting – see Healy, 1987a).

Recent basic research on dopamine receptors may offer a rationale for an activating effect of low dose neuroleptics. There is some evidence that dopamine autoreceptors are more sensitive to the effects of dopamine blocking agents than are postsynaptic receptors (Leonard, 1984). Therefore low doses of a neuroleptic might be expected to activate dopamine systems rather than inhibit neurotransmission, in much the way that L-dopa does. It can be noted that L-dopa has been reported to have a similar 'activating' effect in some cases of depression, but it would appear that this is clearly not an antidepressant

effect (Zis and Goodwin, 1982). While all neuroleptics can be expected to do this, some of them, like chlorpromazine and thioridazine also sedate by virtue of an action on alpha$_1$ receptors. In contrast the activating effects of flupenthixol are not obscured by sedative side-effects.

A further basis for a difference between flupenthixol and other neuroleptics lies in its differential binding to dopaminergic receptors. Most neuroleptics bind predominantly to D_2 receptors. Recent neuroleptics have been designed to bind as specifically as possible to these receptors as clinical efficacy appears to correlate with the ability to bind to D_2 receptors (Waddington, 1989). However, thioxanthenes such as flupenthixol also bind significantly to D_1 receptors (Waddington and O'Boyle 1989). Unfortunately, however, recent PET scan studies suggest that whatever the *in vitro* ability of flupenthixol to bind to D_1 receptors, *in vivo* there is negligible binding (Waddington, 1989).

Whether or not any of these neurobiological possibilities grounds an antidepressant action for flupenthixol, it remains clear that the marketing of flupenthixol as an antidepressant preceded the development of any neurobiological rationale for such marketing. The question, therefore, is whether the primary difference between flupenthixol and other neuroleptics lies in marketing strategy rather than in anything else? A market strategy that derives legitimacy from the ability of flupenthixol to lower Hamilton rating scores in a substantial number of depressed subjects.

This lowering of Hamilton rating scores without taking into account other aspects of the clinical picture is the critical issue. Max Hamilton himself did not see his scale as an instrument for measuring the severity of or changes in a depressive illness (Hamilton, 1967). Rather he saw it initially as a checklist of questions clinicians should be asking and observations they should be making. A great number of these questions and observations concern anxiety. A consequence of this is that any treatments or procedures which reduce anxiety may bring about relatively large and relatively rapid changes in overall scores on the Hamilton scale. Despite this – or perhaps because of it – this scale has become the supreme instrument of antidepressant clinical trials and the supposedly objective results that stem from its use are given greater weight than clinical judgements unbolstered by rating scale support.

It would appear that a version of the flupenthixol story is being replayed at the present time with the marketing of amoxapine in the United Kingdom. Amoxapine is being marketed as an antidepressant, with a particularly rapid onset of action. Again there is clinical trial evidence in the shape of reductions in Hamilton rating scores to support this early onset of action (McNair, Rizley and Kahn, 1986). What is not being marketed is its ability to cause a neuroleptic malignant syndrome and akathisia (Cocarro and Siever, 1985). An alternative story might run that there was a drug company who had two very similar molecules, loxapine and amoxapine, who thought it might be a good idea to target each of them at a different clinical population.

The issue of whether drugs like flupenthixol or amoxapine are antidepressant in the same sense as the canonical antidepressants, imipramine, amitriptyline and phenelzine, is one that is of importance to more than general practitioners who might be concerned to avoid causing tardive dyskinesia. It is also critical for basic researchers, who try to develop animal models of depression and who are trying to elucidate the mechanisms of action of antidepressants. Reference to widely cited and apparently valid clinical trials will give them the impression that they need to produce behavioural tests and responses or neurobiological changes, sensitive to both the influence of imipramine and phenelzine as well as flupenthixol and amoxapine, but not to haloperidol or chlorpromazine. Ambiguity on the issue of which drugs are and which are not antidepressants, therefore, could potentially set back progress.

5-HT *Uptake inhibition and obsessive-compulsive disorder*

A further marketing strategy has seen the targeting of 5-HT uptake inhibitors for obsessive compulsive disorders (OCD). In the early 1960s, in an attempt to get a stronger antidepressant effect from imipramine, the basic molecule was chlorinated. The resulting compound appeared to have antidepressant activity (Brandner, 1964; Symes, 1967) but to be no more potent than imipramine (Symes, 1967). This left Ciba-Geigy with three tricyclic antidepressants on their books – imipramine, amitriptyline and chlorimipramine. On the basis that all three were much the same and in view of clomipramine's less

favourable side-effect profile, the FDA resisted licensing it in the United States.

Shortly afterwards a number of reports appeared in which a possible beneficial effect of clomipramine in obsessional states was suggested (Cordoba and Lopez-Ibor, 1967; Guyotat, Favre-Tissot and Marie-Gardine, 1968). These led to several open studies of clomipramine in anxiety states (Capstick, 1971, 1973; Rack; 1973; Marshall and Micev, 1973; Walter, 1973; Waxman, 1973). The results of these studies in several different centres appeared to support the notion that clomipramine is useful in obsessional states. They further suggested that it was useful in obsessional states that did not appear to be secondary to depression – in other words that the drug seemed to have a primary anti-obsessional effect. It should be noted, however, that several of these studies also indicated that clomipramine appeared even more useful for phobic than obsessional states (Marshall and Micev, 1973). Furthermore, none of these studies were controlled by reference to another medication or to placebo and all involved small numbers of patients. Nevertheless by 1975, Ciba-Geigy was actively promoting clomipramine for obsessive-compulsive disorder.

However, in a later placebo-controlled study of clomipramine and exposure therapy for obsessive-compulsive disorder, Marks *et al.* (1980) concluded that clomipramine appeared to act more as an antidepressant than as an anticompulsive agent. When depression was minimal, they found clomipramine to be of no appreciable value, whereas exposure therapy specifically affected rituals without appreciable effects on mood. In 1988, Marks *et al.* replicated their 1980 study and concluded that clomipramine had a limited adjuvant role to play in the treatment of OCD. Reviewing the literature, they concluded that there is no evidence that clomipramine is better than other tricyclic drugs in OCD. The impression that there is some specificity of clomipramine to OCD they attributed to its being the drug that has been studied most widely for these conditions, with a dearth of comparisons between it and other antidepressants.

These conclusions provoked a reply from Katz *et al.* of Ciba-Geigy (1988), who argued that significant effects could be demonstrated in OCD patients on clomipramine, even in the Marks *et al.* (1988) study. To this Marks and Basoglu (1989) replied that the demonstration of an effect that reaches statistical significance may yield very little information, and may in actual fact not be of significant clinical benefit to patients. They argued that a more discriminating approach and studies to examine the long-term effects of psychotropic medications were needed.

Has the OCD story then been a matter of serendipitous marketing rather than the discovery of something different about the pathophysiology of this disorder? In favour of the former explanation is the fact that Ciba-Geigy had two other tricyclic antidepressants on the market prior to clomipramine and would have found it difficult to market another 'straight-down-the-middle' agent. So also is the fact that clomipramine appears to be broadly anxiolytic rather than specifically anticompulsive (Marshall and Micev, 1973; Marks and O'Sullivan, 1988) and the continuing paucity of conclusive evidence in favour of any specificity of 5-HT uptake inhibitors to OCD. Nevertheless clomipramine is sold with a specific indication for OCD, as is the recently introduced specific 5-HT uptake inhibitor fluvoxamine. The case of fluvoxamine is particularly interesting as, at the time of marketing, there was no evidence in favour of any specific efficacy it might have for OCD. It appears, therefore, to be benefiting from the *apparent* establishment of the notion that 5-HT uptake inhibitors do something that no other drugs do for OCD.

Against this is some recent evidence that the newly developed specific 5-HT uptake inhibitors do appear to have some – as yet incompletely characterized – beneficial effect in OCD (Goodman *et al.*, 1989). There is also some evidence from Zohar *et al.* (1989) that serotonergic agonists such as trazodone and its derivative MCPP in some way worsen symptoms of OCD.

There is also the further intuition of Arvid Carlsson and others (Carlsson, 1982) that tricyclics with a tertiary amine structure, such as imipramine, amitriptyline and clomipramine, differ phenomenologically in some important way from their deaminated derivatives desipramine and nortriptyline. Far from the obvious conclusion that these derivatives must be the real antidepressants, Carlsson and others had the hunch that the parent compounds were doing something else that was important. Biochemically this difference appears to centre on the ability of the original tricyclics to inhibit 5-HT

uptake, which their deaminated metabolites do not do to any significant extent (Carlsson, 1982). On the basis of this phenomenologically based intuition, efforts were begun to synthesize specific 5-HT uptake inhibitors, with some success it would appear. This phenomenological difference may be pertinent to OCD as there appears to be some evidence that imipramine may be useful in OCD (Cottraux, 1988), whereas there appears to be little evidence in favour of desipramine (Marks and O'Sullivan, 1988).

There is a further piece of phenomenological evidence that would appear worth pursuing. In the midst of recent investigations, the initial impetus to the use of clomipramine in OCD appears to have been forgotten. This came from reports from patients of a beneficial effect – a sense that rituals and obsessions became less compelling (Cordoba and Lopez-Ibor, 1967). This lead has not been pursued since, despite an increasing awareness that it is probably not possible to run a 'blind' clinical trial of 5-HT uptake inhibitors in OCD as their effects on the patient are quite distinctive (Marks *et al.*, 1988). Do clomipramine, the older antidepressants or the newer 5-HT uptake inhibitors have comparable phenomenological effects? Is there any affinity between the effects induced by clomipramine in OCD and the ataractic effect (induction of psychic indifference – see Healy, 1989) brought about by neuroleptics?

Perhaps of note here is the fact that both neuroleptics and clomipramine bring about increases in plasma prolactin, whereas 5-HT uptake inhibitors in general do not (Tuomisto and Mannisto, 1985). Of related interest is the fact that there have been no controlled studies of the use of neuroleptics in OCD (Marks and O'Sullivan, 1988) despite clinical impressions going back to 1954 that neuroleptics helped in obsessive states (Kline, 1954). These phenomenological issues appear to have got buried beneath an avalanche of rating scales and subscales, from which it is difficult for an outsider to get any feel for whether the treatments in question make any real difference to patients. Reasons for the neglect of phenomenological issues in psychopharmacology will be explored further in the final section of this article.

MAOIs and atypical depression

With the introduction of amitriptyline in 1961 and the discovery of the cheese effect associated with MAOIs (Blackwell, 1970), drug companies with MAOI antidepressants were faced with a marketing problem. This became particularly acute after the MRC trial of 1965 in which ECT, imipramine, phenelzine and placebo were compared and phenelzine turned out to be no more effective than placebo.

There were two possible responses to this situation for both clinicians and drug companies. One was a rejection of the MRC findings; subsequent research suggests that this would have been the best option (Pare, 1985). The other possibility was to accept the findings but with the caveat that as these drugs were known to be clinically useful, they must therefore be effective for something else other than straightforward depression. There was a ready something else to hand in the concept of atypical depressive disorders, first outlined by West and Dally (1959).

Over the next 15 Years MAOIs were marketed for atypical depressions of all sorts, whether Pollitt and Young's (1971) reversed functional shift depressions or the broader concept of non-endogenous depressions, or for anxiety and phobic disorders uncomplicated by personality difficulties (Kelly *et al.*, 1970; see also Paykel *et al.*, 1983) or alternatively for hysteroid dysphoric patients (Liebowitz and Klein, 1979). Interestingly it would appear that there has been a drift over the past two decades from seeing the MAOIs as useful for phobic patients with good premorbid personalities to the opposite end of the spectrum with the recent claim of a usefulness for borderline personality disorder (Cowdry and Gardner, 1988).

Allied to this, the impression developed in the late 1960S and early 1970's that tricyclic antidepressants were only effective for the endogenomorphic form of the illness and that MAOIs were only effective for the non-endogenomorphic forms of depression. However, there are now nine controlled trials of MAOIs in which the dose used was 60–90 mg/day phenelzine, or the equivalent of other MAOIs, and the results suggest that MAOIs are as effective as tricyclics for endogenomorphic forms of the disorder (Pare, 1985). Conversely while it is unquestionably the case as Roland Kuhn has argued, that tricyclic antidepressants are most clearly efficacious in the classical endogenomorphic form of depression (Kuhn, 1970), they have increasingly been shown to be effective in a wide

variety of depressive states characterized by prominent anxiety (Paykel, 1989). Furthermore, there is the fact that both the tricyclics and MAOIs bind at least weakly to a multiplicity of aminergic receptors (Healy, 1987b). Given this it would be surprising if a number of antidepressants did not have some independent anxiolytic action.

Thus, while MAOIs and tricyclics differ somewhat in that some patients respond to one rather than the other (Pare, 1985) and the MAOIs appear more likely to have a transient psychostimulant effect, there nevertheless appears to be little of substance in the difference between them, other than their pasts and the impressions that have been created about what they do. As none of the various atypical affective disorders have ever been rigorously established as clearcut psychopathological entities in their own right responsive to specific treatments (Paykel *et al.*, 1983) and as biochemically there is little of substance in the difference between MAOIs and tricyclic antidepressants, how have these impressions been created?

In the absence of a solid basis in empirical observation it can be suggested that these impressions have come about in part by virtue of a Matthew effect (Merton, 1968, 1969). This effect refers to the increased likelihood of factors such as the prior fame of one of the authors affecting the reception of the ideas in question, or the likelihood of influential journals accepting the piece of work. In other words, as the Matthew Gospel put it in the parable of the talents, to him who has more shall be given. Many eminent names have been associated with various forms of atypical depression. This perhaps has unduly influenced the reception of these ideas.

But as Paykel *et al.* (1983) have noted, the various concepts have also been defined in large part around a supposed responsiveness to MAOIs. This focusing of issues on a response to a particular group of drugs was tailormade for the promotional purposes of those drug companies who had MAOIs on their hands and were facing a shrinking market. This in part has probably helped produce what may be termed a Luke effect. Ideally the spread of ideas in science is supposedly one that is determined by the intrinsic quality of the ideas. But today in all branches of the biomedical enterprise, drug companies disseminate large amounts of scientific literature. It is probable that literature from such sources makes up a significant proportion of what is read by many clinicians. (It made up a significant proportion of the reference list of this article.) Not unreasonably the material that is passed on relates favourably to company market concerns. In this manner many concepts that might otherwise be retired early to inhabit the backshelves of libraries may these days be given an extended lease of life. Put another way, drug companies obviously make drugs but less obviously they make views of illnesses by selectively reinforcing certain possible views.

The notion of a Luke effect is taken from the parable of Luke the physician about the sower sowing the seed, some of which fell on stony ground, some of which fell on fertile ground but growing up was choked by weeds. This parable ends with an exhortation to those who have ears to listen. Listening is arguably what drug companies have been doing very successfully where the MAOIs, flupenthixol and clomipramine are concerned, as well as for alprazolam and calcium entry blockers as outlined below.

In marked contrast a radically different agent, lithium, has not been promoted in anything like the same way. It has been argued that this is because there has been little money to be made from it (Amdisen, 1984; Johnson, 1984). As a consequence lithium therapy has taken a long time to get established and even now is a poor cousin to the other psychotropics.

Alprazolam and panic-disorder

The recent study of alprazolam in panic disorder provides perhaps one of the best possible examples of a Luke effect. When Upjohn produced a new triazolo-benzodiazepine in the early 1980s, they had a marketing problem as benzodiazepines were becoming increasingly unpopular. One response was to market the new compound as an antidepressant. As the case of flupenthixol shows it is relatively easy to produce antidepressant credentials in the shape of reduction of Hamilton rating scale scores – and this has been done for alprazolam (Rickels, Feighner and Smith, 1985) – but also for other benzodiazepines (Tiller *et al.*, 1989). This option, however, has been neglected almost certainly because of the sudden opportunity provided by the creation of panic-disorder in 1980.

Panic-disorder only came into existence formally in 1980 with the publication of DSM 111,

in which it was controversially separated from agoraphobia as a diagnostic entity (Klerman *et al.*, 1989). This led, to the mutual benefit of the proponents of panic-disorder and the makers of alprazolam, to a large multicentre placebo-controlled study of alprazolam in the treatment of agoraphobia and panic-disorder starting in 1983 (Klerman *et al.*, 1989). In 1988 the results of this study were published, claiming that alprazolam was effective for both agoraphobia and panic-disorder. However, it has been argued by Marks *et al.* (1989) that this claim is misleading; that one can legitimately read the results as indicating that there was no significant effect of alprazolam. Alternatively, even if one reads the results in the manner favoured by the principal investigators, the effects were minimal, of brief duration and liable to lead to a worsening of the clinical state of the patient on discontinuation of treatment. As the results were presented however, these latter issues are glossed over and the casual reader is liable to be left with the impression that alprazolam is a specific therapy for both panic-disorders and agoraphobia, and that panic-disorder is an autonomous biological entity. Quite apart from any effectiveness of alprazolam for panic-disorder or any autonomy of panic disorder as an entity, the focus of this article is on Upjohn's investment in panic-disorder. So great has this been that panic-disorder was commonly referred to in the mid-1980s as Upjohn illness.

Making visible the invisible – paradoxical serendipity

The history of varying associations between the MAOIs and a range of exotic clinical syndromes, as well as the targeting of neuroleptics for depression and 5-HT uptake inhibitors for OCD, points to the existence of a gap between the pathogenetic bases of affective disorders and the pathoplastic effects that they may give rise to, and gap between depression and the anxiety it may give rise to. There is a comparable gap between the pathogenetic basis of schizophrenia and the delusional and neurotic behaviours it may stimulate (Healy, 1990b). Through these gaps, propelled by their respective market forces, academic investigators and drug companies have all too quickly attempted to march. The tramp of their passing feet has for the most part, it would seem, only served to deepen psychopathology's classificatory quagmire and to blurr the outlines of what Nathan Kline (Sandler, 1990), Roland Kuhn (1990) and Henri Laborit had first made visible.

But, just as Columbus sailed in search of the Indies and profits but found instead something unsuspected, so also it can be argued that the siren call of the market has also led, or is leading to a revolution in the perception of mental illness. Early work on the epidemiology of mental illness revealed that affective disorders are very widespread in the community (Shepherd *et al.*, 1966). This can be taken to support either the view that the greater part of the affective disorders are mild and self-limiting or that there are two forms of the illness: one a mild 'psychological' problem, and the other a severe medical illness only correctable by physical treatments. While the latter view was possibly the conclusion most commonly drawn from early community surveys, a significant new element in the current debate on mental disorders in the community has come from the use of antidepressants by general practitioners (Fahy, 1989).

Where earlier surveys looked at the degree of misery and anxiety in community samples, more recent work has had to address itself to the question of who is getting antidepressants from their general practitioners and what effects these drugs are having. The reply would appear to be that many relatively mild disorders, that might otherwise have been taken to be psychological problems (distress rather than disease), respond to antidepressants (Sireling, *et al.*, 1985; Blacker and Clare, 1987). One possible interpretation of this is that 'biological' depression is a mild illness for the most part and that those who end up being hospitalized for the disorder are an unrepresentative minority.

Furthermore, there would seem to be a good deal of evidence that many subjects with very similar clinical conditions get well spontaneously without antidepressants and in relatively short periods of time – within a matter of weeks (Blacker and Clare, 1987). If this is the case, the therapeutic agenda at least for the affective disorders would shift from one dominated by the question of how do we get depressives well to one of why do a few patients not get well spontaneously. This is a far more optimistic therapeutic agenda than the one that faced psychiatrists in the early 1950s.

Similarly, notwithstanding the evidence that can be marshalled in favour of the argument that the emptying of the asylums did not depend on the introduction of these agents (Shepherd, 1990) or the evidence in favour of the argument that neuroleptics are not directly antischizophrenic (Healy, 1990a), the advent of the neuroleptics has altered the perception of schizophrenia. Thus while the promotional activities of drug companies may sometimes obscure the barely visible outlines of a rational psychopathology, so also the aggressive marketing of psychotropics is leading just as much as the insights of any detached scientists to unexpected discoveries – and just as serendipitously.

Science, business and history

It was noted in the introduction that histories of the psychopharmacological era focus on the achievements of eminent discoverers and in general neglect other factors. Such a focus is typical of the earliest approaches to the history of a branch of medicine. In general such approaches give way to increasing interest in medical politics and in the politics surrounding medicine (Porter and Porter, 1989). But even in the more developed branches of medical history, there appears to be a blind spot for the economics or business of medicine (Liebenau, 1987; Porter and Porter, 1989). Such a focus would seem indicated as modern medicine unlike medieval medicine has from about 1600 onwards involved the sale of a rapidly increasing number of drugs alongside the traditional sale of skills. This latter development gave rise to the pharmaceutical industry, to concern about the monstrous profits of druggists and to an increasing consumption of medicaments (Liebenau, 1987; Porter and Porter, 1989), all of which remain themes that characterize the psychopharmacological era.

Some further examples to add to those above may indicate the need to take the policies of pharmaceutical companies into account when writing any history of this era. As was noted above there has been widespread use in recent years of calcium entry blockers but a seeming blindness to any mental state changes they may have been bringing about. While the current bias against using the observations of individual clinicians or patients as a basis for therapeutic development is undoubtedly one reason for this, other factors can be cited. One such is that drug companies marketing calcium entry blockers successfully for angina have effectively had an interest in denying that their drugs crossed the blood–brain barrier. This at least was the response to a colleague of mine interested to pursue the question of calcium entry blockers for tardive dyskinesia (Dinan, personal communication, Dinan and Capstick, 1989). The underlying thinking appears to be one of not risking a certain market by opening to clinical scrutiny an area that might as quickly lead to curtailments on the marketing of the product as it would to further applications.

Following the observations of Barrow and Childs (1986) that calcium entry blockers seemed to be of benefit in tardive dyskinesia, it would appear that there has been an explosion of interest in possible therapeutic applications. Is this a case of academics striking off shackles put on them by business? Against this possibility, a further factor can be set – the development of laser surgery for coronary artery disease. This development potentially could substantially reduce the market for calcium entry blockers, which at present have angina as their primary indication. Could it be therefore that recent clinical interest reflects business concerns more than any other?

Writing a history also involves accounting for why certain questions do not get properly addressed. For the conventional mythologies of science, the notion that certain questions are being systematically avoided is unbelievable (Healy, 1987a) – for example, the use of antidepressants for mania and the administration of antidepressants every few days rather than a few times every day. Any of the clinical trials done to date of tricyclics in mania have indicated that they may have antimanic properties, which would be in accord with the fact that both lithium and ECT are both antimanic and antidepressant (Healy and Williams, 1989). Yet given the weight of popular expectation that far from curing mania, tricyclic antidepressants are liable to *cause* it, expectations that have possibly survived the demise of the original catecholamine hypothesis in the way that grins survive cheshire cats, drug companies are reluctant to fund a study of the issue (personal observation). The principal reason seems to be a certain nervousness about jeopardizing their markets – something comparable to the thinking, which denied that calcium entry blockers enter the brain.

There are further studies that drug companies are not enthusiastic to fund. For example, there is little evidence that antidepressants act in the same way as other psychotropic agents – that is acutely and for a limited duration, thereby necessitating b.d, t.d.s or q.d.s regimes (Baumann *et al.*, 1988). Increasingly, companies seem to be moving toward single-dose regimes, or clinicians seem to be giving single-dose regimes, whether or not this is advocated by the company. There are furthermore a number of studies in which antidepressants have been given every few days, with seemingly as good results (Pollock *et al.*, 1989; Montgomery *et al.*, 1986). Indeed a further point that can be noted is that owing to the differences between rat and human metabolism the antidepressant regimes that laboratory rats are given to bring about 5-HT receptor sensitization or beta-receptor downregulation or to reverse depressive behaviours in animal models, typically produce large-dose pulsatile profiles rather than the more even steady state regimes supposedly being aimed at in man (Baumann *et al.*, 1988). Thus there is some evidence that points toward the possibility that antidepressants might work optimally, in the same way as ECT – that is once every few days rather than a few times per day.

Such findings, if upheld, would pose serious questions for any theories about the mode of action of antidepressants. But there are problems doing the research involved in that drug companies are not likely to willingly support it, for the very good reason that the volume of their sales might be threatened by the results. This could provide at least two barriers to progress: difficulty in getting placebo tablets; difficulty in getting funding for the research. The outcome of this will inevitably be a lack of research in these areas as it is easier to research issues for which funding is readily available – research that is difficult to fund remains undone by default.

To answer these and other questions, a future historian would need access to company records. Far from some future history being simply a chronicle of the perceptions of scientists of what they were doing and why, it would also need to include a chronicle of marketing and company research decisions. Books such as the recent *Discoveries in Pharmacology* (Parnham and Bruinvels, 1983) urgently need supplementing with volumes on the same period as seen from the perspective of the pharmaceutical industry. There needs to be some assessment of how the various companies stand as regards scientific issues. Are they genuinely concerned to promote developments or do they simply use the language of science for marketing purposes? Historically, the major companies have differed in this regard (Liebenau, 1987).

Science, business and politics

There is a further factor whose influence a historian might wish to assess. At the start of the psychopharmacological era, the interactions between industry and academia were relatively immediate. Drugs could be synthesized and administered to patients within a matter of months. Now that interval is more likely to be of the order of 10–15 years. As a consequence any 'rational' basis there might bave been to the manufacture of the drug in the normal course of events is increasingly likely to be superseded by the time that rationality is put to the test.

This delay has much to do with the operations of governmental agencies, the relation of whose interests to those of the pharmaceutical–academic complex is uncertain. These agencies act both to delay the clinical use of a drug by increasingly detailed premarketing surveillance, and to affect the reception of a drug through post-marketing surveillance. The latter is exerted in part through national schemes instituted in the 1960s for the reporting of adverse drug reactions.

To appreciate how such factors have altered the psychopharmacological landscape, consider the latter schemes. The 1970s saw the introduction of agents such as nomifensine, mianserin, and the 1980s the specific 5-HT uptake inhibitors zimelidine, fluvoxamine and fluoxetine for the treatment of depression. As a consequence of schemes for the reporting of adverse drug reactions, the past 5 years have seen the first removal of psychotropics from the market. This has almost exclusively affected the newer agents, with nomifensine and zimelidine being the prominent casualties, and mianserin being more recently under threat.

The basis for withdrawal has been the occurrence of fatal adverse reactions, as reported to the Committee on Safety of Medicines (CSM). From recently released data it would seem that these were quite considerable in the case of zimelidine, far less marked in the case of nomifensine,

but not unknown for all other antidepressants (nomifensine was comparable to clomipramine, for example; (see Pinder, 1988; Beaumont, 1989). However there are ambiguities in the CSM figures in that the older antidepressants were introduced in an era before the reporting of adverse reactions received the attention it now does (Girard and Biscos-Garreau, 1989). There is now a particular onus on clinicians to report all adverse reactions to a drug during its first 3 years on the market. A further problem with antidepressants is that the newer agents appear to be more likely to be given to populations who may be particularly at risk for adverse reactions, such as resistant depressives, the elderly, the physically ill or those extensively treated previously with other drugs (Pinder, 1988).

The cases of lofepramine and mianserin illustrate the effects of the present operating of the CSM. Lofepramine seems least likely of all the tricyclics to lead to fatalities in overdose. Yet recently the CSM has drawn the attention of prescribers to the propensity of tricyclics to raise liver enzymes, in a manner that appeared to specifically target lofepramine (CSM update, 23 1988). This is despite the fact that liver toxicity was a notable feature of the early use of tricyclics – running to 10% of subjects showing increased SGOT levels on amitriptyline (Holmberg and Janssen, 1962; Klerman and Cole, 1965; Davies, 1981; Dukes, 1988).

A similar story appears to apply to mianserin. From being one of the most widely prescribed antidepressants, this agent is now used much less frequently, in part almost certainly because of concerns about the agranulocytosis it has been reported to produce. But in a recent review of leucopenia after antidepressant use, Moller, Meier and Wernicke (1988) found that amitriptyline was no less likely to produce leucopenia than mianserin. In a survey of published data from clinical trials, Girard and Biscos-Garreau (1989) concluded that the data does not exist to say that mianserin is more haematoxic than the older tricyclics. In the case of both mianserin and lofepramine, these drugs are suffering from an inbuilt bias in the CSM against novel agents. Indeed it can be suggested that neither amitriptyline or imipramine would get product licences if Ciba-Geigy had to apply for them today. Given that the toxicity programmes that the more recent antidepressants have to go through prior to launch, it would be most surprising if they were not at least on balance as safe as the older agents, which were not subject to such thorough assessment.

However, the population of depressed patients who are at by far the greatest risk of drug-induced fatalities are those who are suicidal or who take overdoses. At present 15% of deaths by fatal poisoning involve antidepressants (Office of Population Censuses and Surveys (OPCS), 1977–86). Indeed antidepressant overdose is the commonest life-threatening drug ingestion worldwide (Pinder, 1988). With the current cloud over the prescription of benzodiazepines for anxiety and the targeting of the treatment of anxiety by tricylic antidepressants now being undertaken by some drug companies, this figure seems set to rise.

In this particular at-risk population, the major risk of fatal adverse reactions comes from the older tricyclic antidepressants rather than the newer agents. If one adds the fatal adverse reactions occurring during therapeutic intake of antidepressants to those occurring after overdosage, then agents such as nomifensine, mianserin and lofepramine emerge as clearly safer than the older tricyclics (Pinder, 1988). That is, if all antidepressants were prescribed equally, fewer people would die on nomifensin or mianserin than on imipramine or dothiepin. One might question on this basis which agents should be withdrawn.

In reply it may be said that it is difficult to take suicide into account in this kind of calculation. [Whatever about deaths from overdose, antidepressants should not be agents which are liable to kill subjects during routine use.] It is not clear, however, that this is the thinking of the CSM or the true grounds on which drugs are removed from use. There are three other factors that may be influencing current events. One is the cost of newer drugs, which may be up to 25 times more costly than the older agents. In terms therefore of burden on the exchequer, there is a very good reason why antidepressant prescribing should be restricted to the older agents such as desipramine, amitriptyline and imipramine. A separate reason may be the belief that drug companies are being allowed to make too much money – a belief that has been present for over a century (Liebenau, 1987; Porter and Porter, 1989), although the current evidence in its favour has been called into doubt (Cantopher, Edwards and Olivieri, 1988). Another may be a need to

be seen to be responding to consumer pressure. Similar political forces have in the past led to the outlawing of ECT in some American states and hence the responses to such pressures need careful consideration.

However, it can also be noted that historically it would appear that there has always been an exchange of personnel between regulatory bodies and drug companies and that the introduction of regulations, if not actively sponsored by the major drug companies, have always favoured their interests – although superficially this may not have been apparent at the time (Liebenau, 1987). Is this still the case? Some assessment of these issues will be needed if a history of the psychopharmacological era is to be comprehensive.

An assessment of the impact of regulatory agencies will also be needed. For example, the present approach, which is progressively restricting the agents available to treat mental illnesses to the older psychotropics will in effect 'reserpinize' the database for laboratory, clinical and phenomenological studies of psychotropics and the illnesses they treat. As has been noted, the newer 5-HT reuptake inhibitors were synthesized on the basis that it seemed that they might differ phenomenologically from desipramine and nortriptyline (Carlsson, 1982). While it seems clear that these agents are antidepressants in the sense of reducing Hamilton Rating scale scores, it has not yet become clear just what phenomenological differences there are between them and the tricyclics. If the operations of the CSM continue as before, we may not be given the time to find out.

Science, business and culture

> There is something seriously missing in a field of mental illness that does not attend closely and broadly to patient's subjective experiences . . . And yet much of the contemporary scene in disciplines that focus on mental illness reflects this neglect. Driven by various theoretical models and the quest for being scientific in only a narrow sense, clinicians neglect many aspects of patients' reports, their implications for understanding illness and healing processes and the need to develop improved methods for studying subjective experience . . . (Strauss and Estroff, 1989).

One of the themes that runs through the various examples detailed above is the neglect of the subjective effects of drug ingestion. They are neglected as a means of discovering new psychotropic agents as subjective impressions are not methodically sought. If offered they are all too likely to be dismissed as 'neurotic'. I have argued above that good clinical observation has a better track record in discovering new drugs than current 'rational' drug development programmes.

But does good clinical observation need to be the preserve of men such as Roland Kuhn, Jean Delay or Nathan Kline? Cannot the patients who take these agents also be observers? At present we appear to assume that having a mental illness precludes an ability to observe empirically (Healy, 1990b). There is no evidence in favour of this presupposition. Indeed it is conceded that drug abusers may be very discriminating of the effects of many of the same medications. They appear able to distinguish agents from each other and different phases in the effects of the one agent, such as cocaine, and these different phases can be independently manipulated (Scherer, 1988).

There is, furthermore, some elegant work by Philip May and colleagues to show that tailoring neuroleptic regimes according to the subjective responses of the takers produces the best clinical effects (May, Van Putten and Yale, 1976). One might wonder about our willingness to ignore the often heard statements of patients that their particular neuroleptic regimes have not been helping them (Healy, 1990b).

Paying heed to subjective effects might help to resolve the issue of whether flupenthixol is an antidepressant or a neuroleptic and might clarify the role of clomipramine in obsessive-compulsive disorders. It can also be argued that paying heed to the subjective effects of neuroleptics affords perhaps the most cogent piece of evidence against the dopamine hypothesis of schizophrenia (Healy, 1989, 1990a). Briefly, neuroleptics induce an ataractic effect (an indifference) in everyone who has them, whether control or schizophrenic, within hours of taking them, provided that 60–80% of D_2 receptors are blocked by the dose given. This effect parallels in time course the blockade of D_2 receptors they also bring about. If this effect is mediated through D_2-receptor blockade, its occurrence in both schizophrenics and controls would point toward a normal functioning of the dopaminergic system in schizophrenia.

Similarly if 85% or more of D_2 receptors are blocked, rapid behavioural control in the form of the experience of internal straitjacketing is achieved – and can be achieved in personality disordered patients, manic patients and schizophrenics as well as in volunteers. This drug companies have always known and have accordingly filled many of the advertisements for neuroleptics with images of aggression being rapidly brought under control. This also argues for a normal functioning of dopaminergic systems in psychiatric patients. It has suited drug companies, however, to support the idea of a dopamine hypothesis of schizophrenia, as if patients fail to get well the obvious remedy is more drugs. It also suits almost everybody else as well, as if the dose of chlorpromazine were to be restricted to around 400 mg/day or that of haloperidol to 30 mg/day – the amounts needed to block up to 80% of D_2 receptors – psychiatric hospitals would become ungovernable and mental illness even more of a pressing political issue.

Perhaps symbolic of the present orientation is the shift that has occurred from the term pharmacopsychology, which was coined by Kraepelin, to the modern term, psychopharmacology. The former suggests an exploration of the psyche by means of drugs. The latter conjures up concerns with plasma drug levels and receptor numbers, with the psyche being of secondary concern and then principally by virtue of the quantitative complexity that it presents, when compared to organs such as the heart, rather than because of any qualitatively different problems that emerge in this particular branch of pharmacology.

There are historical reasons for this neglect of subjective impressions (Healy, 1990b). The neglect, however, is not inevitable or necessary. This current period began with the demise of introspection at the end of the nineteenth century and the rise of behaviourism at the start of the twentieth. However, there are indications that with the development of neuropsychology and cognitive psychology that a willingness to work with the subjective experiences consequent on altered neuropsychological functioning is re-emerging (see Strauss and Estroff, 1989).

A further cultural factor that is of significance here relates to cultural conceptions of the role of medicine. At present the public perception of the medical enterprise is one that credits the dramatic improvements in health over the past two centuries to medical intervention and to the increasing complexity of medical biotechnology (McKeown, 1979). The evidence however does not support this view. While medical developments have been important, it would seem that social and economic factors have been much more influential in improving health and are likely to remain so for the forseeable future (McKeown, 1979). This has led to a neglect of social and behavioural inputs to the origin of disease and also to its treatment.

Perhaps this background of overvaluing biotechnical contributions to solution of health problems, leads to relatively minor effects such as that of clomipramine and other drugs in OCD that do, however, reach the 0.05 confidence intervals, being seen as 'significant'. The way such data are presented in academic journals, and indeed the language used, obscures the larger question of whether such effects are indeed significant. Technically the term significant is often misused in current practice and should in many cases be replaced by reference to confidence intervals (Gardner and Altman, 1986). It is all too easy to produce effects, regarding whose replicability one can speak with specifiable amounts of confidence but should such effects dominate clinical practice if they offer patients little of tangible benefit? (Marks *et al.*, 1988, 1989; O'Sullivan and Mark, 1990). The answer in practice at present would appear to be that if these effects are brought about by biotechnical means rather than by efforts to modify individual behaviour, then the weight of current cultural beliefs regarding the role of medicine will lead to their widespread promulgation and to the impression that the effects are 'significant' (Marks, 1989).

Concluding remarks

The thrust of this paper has been that while individual scientists may make discoveries, there are larger cultural and economic forces which also have a bearing on the likelihood of significant discoveries being made in psychiatry and the brain sciences. Regarding these forces, access to the data that reveal their influences is at present restricted. Accordingly one has to ask whether a history (as opposed to a mythology) of the psychopharmacological era can be written. The only work that approaches being a history of this area is Josephine Swazey's 1974 study of

chlorpromazine, in which the contributions of individuals, the academic community, the pharmaceutical industry, state agencies and the *zeitgeist* are all weighed in the balance (Swazey, 1974). Perhaps what is needed is further volumes on individual drugs rather than on individual scientists.

More generally where economic factors are concerned, their operation can be described, at least in part, in terms of a Luke effect; determining which scientific seeds will fall on barren ground, which will be choked by thistles and weeds on growing and which will yield up their bounty. The commercial underpinning of the psychopharmaceutical industry has almost certainly helped to prepare the soil for selected scientific seedlings. Whether it also fosters the development of choking weeds is a question that needs addressing – one on which a certain historical perspective can now be brought.

Aside from such major issues in the sociology of science, can any more modest conclusions be drawn from the data of the psychopharmacological era? At present two would seem to be possible. The first is that nothing of note has happened as regards the development of new (legal) psychotropic drugs since the 1950s. In particular we still await a truly antischizophrenic agent, and we have no idea why the antidepressants we have seem as limited in their effectiveness as they do. One might suggest that the current fashion for operational criteria might be usefully extended to cover antidepressants and neuroleptics, although this might not be easily achieved (Shepherd, 1990). Perhaps partly because criteria of the type that restricted the use of the term antidepressant, for example, to compounds whose effects *closely* resembled those of imipramine, would be bad for business. Whatever the reason, the current profusion of increasingly sophisticated research instruments and methodologies only seems to make it easier for investigators to claim anything they want. It would seem to paraphrase an old dictum, that there is fraud, damned fraud and there is research methodology.

Second, the most substantial development of recent years would appear to be in the realm of attitudes to mental illness – a change that drug companies have helped to bring about – but paradoxically not because of any great effectiveness of current psychopharmacological agents!

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