Psychiatric Developments (1987), **4**, 349–376

The Structure of Psychopharmacological Revolutions

David Healy

From Department of Psychiatry, University of Cambridge Clinical School, Cambridge CB2 2QQ

(Received 24 February 1987 and in revised form 30 July 1987)

Summary

Thomas Kuhn's model of the structure of scientific procedure is outlined and applied to salient aspects of recent psychopharmacological research into the bioneural substrates of the affective disorders. It is argued that the amine hypotheses of these disorders are irrefutable in practice although not in principle and that their survival despite a lack of convincing supporting evidence and disproof of their initial premises suggests that they serve a paradigmatic function and that the core of this paradigm is psychological in nature rather than neurobiological. An attempt is made to show how an awareness of such functions may help explain otherwise puzzling features of the literature on the psychopharmacology of the affective disorders. Such an awareness may also help to indicate the steps necessary to replace the amine hypotheses or the likely future prospects for these hypotheses.

Introduction

In 1962 Thomas Kuhn[1] in an influential book entitled 'The Structure of Scientific Revolutions' argued that normally science does not proceed by a uniform process of conjecture and refutation on the part of all scientists, but involves visions and re-visions with often lengthy less dramatic periods in between. The initial vision establishes a *paradigm* for a particular field, which accounts for a considerable range of the data in that field and provides a heuristic framework which will lead to future discoveries. While a paradigmatic view holds sway most researchers in a field will assume that certain key questions have been answered and will concentrate on *normal science*. Normal science involves the application of ingenuity to the puzzle of matching the paradigmatic view to the hard details of reality rather than just accepting a fit in broad outline. In times of crisis, when the foundational view is

threatened, such ingenuity may seem increasingly forced or implausible. Nevertheless researchers will ignore a large amount of inconvenient data on the assumption that with time it will become consistent or negatively because rejection of a paradigmatic view without a replacement involves retreat from a comprehensive viewpoint to one less comprehensive. In other words, supporters of paradigmatic conjectures support them rather than attempt to refute them. Following the invasion of new territory, the normal task of supporters of the new regime is one of mopping up old resistances, mapping out the new territory and strengthening its defences rather than plotting its subversion, in turn.

If anomalies do not commonly lead to refutation, how then are paradigmatic views replaced? Usually not by critical experiment, Kuhn argues, but by desertion of their adherents to new faiths. Indeed critical experiments are discouraged as by definition areas not of interest to the paradigmatic view are ignored and their relevance may only become apparent during periods of crisis. The old view then is not refuted so much as perceived, particularly by those engaged in the research enterprise, as offering fewer opportunities. The new view initially may explain no more than the old and indeed some of the old guard may never see the need for change. In turn the revolutionaries become the new orthodoxy and their view is transmitted with the weight of authority. Commonly textbooks, reviews and the introductions to articles do not transmit a balanced view of the problems in a field but rather the stable outcome of past revolutions which yields a structure of science that requires a large measure of belief and argument from authority. However, in times of crisis no amount of authoritative reviews will settle crises. Change is likely to come from those new to a field, who by virtue of youth, or transfer from another discipline or by some other method have escaped the usual moulding pressure and who are more struck by what is not explained by the dominant view than by its improvements on previous views. 'To study the fate of amphetamine it was necessary for me to become an enzymologist. Because of my naivete as an enzymologist . . . I succeeded . . . if I had known more I wouldn't have done the right experiments'[2].

In contrast to Kuhn, Sir Karl Popper has conceived of the advance of science as being a process of conjecture and refutation[3]. He has been concerned with the logic of scientific discovery and has stressed that above all science is a rational process, that develops by adhering to testable hypotheses, which are (or ought to be) subjected to regular and rigorous critical scrutiny. His interest has been in the rational grounds for preferring general relativity to Newton's laws of motion and the process that ensures that scientific formulations are modified progressively rather than with the social formation of or psychology of insights that results from apples falling on heads.

Both Popper & Kuhn have questioned the scientific status of psychoanalysis in psychiatry[4]. Arguably, in the case of psychoanalysis, the scientific process as

advocated by Kuhn has happened particularly clearly in American psychiatry both in the rise and in the fall of psychoanalytic influence. However, as there are doubts about the scientific status of psychoanalysis, Kuhn's model as applied to this case may not prove its general applicability, indeed may argue against its validity. With this in mind the current article attempts to apply Kuhn's model to the modern history of psychopharmacology of the affective disorders and to contrast it with Popperian views.

The Amine Paradigm

In 1957 R. Kuhn[5] first reported on the antidepressant properties of the tricyclic iminodibenzyl, imipramine, to an audience of 12 at the 2nd World Congress of Psychiatry in Zurich. In the same year, iproniazid, a monoamine oxidase inhibitor, used as an antitubercular agent, was found to have antidepressant properties[6]. Subsequent basic research suggested that the MAO inhibitors increased synaptic noradrenaline concentrations[7] and brain catecholamine levels[8]. The tricyclics were found to inhibit amine reuptake[9, 10], to potentiate the effect of amines post synaptically[11] and to protect against the depleting effects of reserpine[12, 13]. These findings were complemented by reports that reserpine, a Rauwolfia alkaloid used as a major tranquillizer in India and as an antihypertensive in the West, could precipitate depression in up to 15 per cent of those taking it[14, 15]. The demonstration by Carlsson and coworkers that reserpine depleted catecholamines from brain[16] and indoleamines from platelets[17] set the scene for the monoamine hypotheses of affective disorders.

These and other findings led to the claim that 'a fairly consistent relationship between drug effects on catecholamines, especially noradrenaline, and affective and behavioural states' had been shown, 'those which cause depletion and inactivation of noradrenaline centrally produced sedation and depression while drugs which increase or potentiate brain noradrenaline are associated with behavioural stimulation or excitement and generally exert an antidepressant effect in man'[18]. A similar claim was put forward by Bunney and Davis[19]. With this 'at best a reductionist oversimplification'[18], the monoamine hypotheses (of which the catecholamine hypothesis was the first) were set on their singular way. It was hoped that the hypothesis would be of 'considerable heuristic value'[18]. The hypotheses remain entrenched despite voluminous evidence that antidepressants have no single action on biogenic amines[20–23]. The original authors (and possibly the majority of the psychopharmacological community) retain a belief that there is some involvement of monoamines in the affective disorders[24, 25] despite initial protestations that the proposed mechanisms of action 'may soon require revision due to rapid progress in

the basic sciences'[19]. This suggests that the hypotheses have been more than heuristic and deserve the label paradigmatic.

The monoamine hypotheses therefore were based on the following pieces of evidence; firstly that reserpine caused depression, secondly that reserpine depletes catecholamines (and indoleamines), thirdly that reserpine induces a behavioural syndrome in animals characterized by sedation which is reversed by antidepressants, and fourthly that antidepressants increase amine levels by blocking uptake or preventing deamination. Retrospectively one can argue that each of the steps in the argument in favour of the hypothesis was flawed.

Firstly, a more careful review of the literature on depression following reserpine and analysis of the only prospective trial done on this issue led Mendels and Fraser[26] to conclude that one could not say with confidence that reserpine causes depression. Even if it does, one can question whether it does so by virtue of its sympatholytic effects as Paykel *et al.*[27] in a particularly comprehensive review of the psychiatric sequelae of antihypertensive agents found no correlation suggestive of an effect of sympatholysis in the precipitation of depression. Secondly, while reserpine does indeed deplete amines, these amines are largely vesicular amines and probably not required for immediate functional use. This can be inferred from experiments with amphetamine which releases cytoplasmic amines, and can elicit effects consistent with catecholaminergic stimulation despite reserpine preadministration[28] and similarly para-chloro-amphetamine, a 5HT releaser will still elicit the 5HT behavioural syndrome despite reserpine preadministration[29]. Given that it is still not certain whether vesicular or cytoplasmic amines are primarily responsible for neurotransmission[30–33], one realizes that Schildkraut's claim involved a bold strike into uncharted territory rather than a careful balance of what was reliably known. Thirdly, while reserpine causes a behavioural syndrome involving sedation in mice and this can be reversed by antidepressants, it can also be reversed by agents not effective in human affective disorders[21]. Furthermore, its reversal by antidepressants is of acute onset whereas the effects of antidepressants on depression in humans have a long clinical latency. In addition, closer inspection of the action of antidepressants to antagonize the behavioural syndrome induced by reserpine leads to the conclusion that they do not do so by increasing amine levels[34].

There is in addition good evidence that antidepressants far from increasing brain amines may do nothing to overall amine levels or may indeed decrease them[20, 35, 36]. Furthermore, logical consequences of the amine hypothesis were that amine precursors would be effective in the treatment of depression and amine depleting agents or synthesis inhibitors would be of use in the treatment of mania[18, 26]. These requirements have not been met[26, 37, 38]. Despite sales of L-tryptophan as an antidepressant, convincing evidence as to its efficacy is lacking and arguably the monoamine hypotheses of depression have done more to support its sales than its

sales do to support the amine hypotheses[22, 39]. Similarly use of l-dopa indicates that it may reverse a motor retardation but that it does not appear to have true antidepressant effects[37, 40].

As reserpine has pronounced effects on both catecholamine and indoleamine systems, the development and investigation in man of drugs able to specifically interrupt noradrenergic neurotransmission 'made it of considerable interest to the catecholamine hypothesis to observe whether these patients also become depressed'[18] or indeed whether such agents are effective in mania[40]. The earliest synthesis inhibitor to be tested clinically was alpha-methyl-para-tyrosine (AMPT) which inhibits tyrosine hydroxylase and thereby the synthesis of noradrenaline and dopamine. This was followed by a number of dopamine-beta-hydroxylase (DBH) inhibitors such as fusaric acid and disulfiram, which leave dopamine synthesis unchanged but prevent the accumulation of noradrenaline. Available clinical data on AMPT do not suggest that it causes depression or that it worsens depression but do indicate a certain usefulness in mania[40]. There are problems with interpreting the latter findings in that AMPT is sedative[26] and it effectively blocks dopaminergic neurotransmission as well as noradrenergic transmission. DBH inhibitors have not been used widely in man. Early trials found that fusaric acid appears to aggravate rather than alleviate mania[40]. Studies in animals, however, do suggest that it blocks intracranial self-stimulation. This has been interpreted as indicating an interruption of 'reward' pathways and offered as evidence in favour of the catecholamine hypotheses. However, subsequent studies of this effect of DBH inhibitors indicate that they produce their effects by virtue of the sedation they cause and not because they demotivate or depress experimental animals[41]. Such findings make it likely that any clinical effectiveness synthesis inhibitors have is by virtue of the sedation they cause rather than by any specific antimanic effect[37, 38]. Their effects bear similarities neurochemically and behaviourally to the sympatholysis following clonidine administration. An antimanic action has been claimed for clonidine but so also has an antidepressant effect[42]. In addition, while lithium also acutely attenuates central catecholaminergic neurotransmission[40] it is effective in the treatment of both mania and depression.

The significance of this failure of agents more specific to the noradrenergic system to have comparably more specific effects in the precipitation or treatment of the affective disorders lies in the effects such findings have had on the catecholamine hypothesis. Where one might have expected the faithful to dwindle in number, there has instead been increasing reference to the monoamine hypotheses of depression rather than the catecholamine hypotheses. The term monoamine when put to this use appears to imply some functional balance between catecholamine and indoleamine systems. The evidence from a study of actions of antidepressants and reserpine implicates both these amines but it has not been possible to build a

convincing case in favour of either. However, the supposed balance between these 2 amines is never operationally defined. This yields therefore an effectively irrefutable yin-yang hypothesis.

Normal Science I

Despite early inconvenient observations such as those outlined above, the amine hypotheses survived just as the psychoanalytic paradigm survived the doubts about actual sexual trauma in the origin of the neuroses. One of the basic strategies pursued to further investigate the mechanism of action of antidepressants has been to administer these drugs to animals and determine what changes in their neurobiology, if any, are brought about. The results found have not been consistent with amine hypotheses[20–23]. The lack of agreement between animal researchers on specific detail is comprehensive and rather than leading researchers to standardize methods seems rather to serve as a repository of information from which to draw convenient supporting evidence for disparate claims. Biological psychiatrists are likely to be impressed by claims stemming from animal pharmacology studies without realizing that frequently basic researchers in the field regard all neurones carrying specific neurotransmitters as homogenous despite evidence that they are not[43], that standard schedules of drug administrations are not commonly adhered to and this may be important as pharmacokinetic factors may significantly influence the final measurements[44], that commonly the results obtained cannot be demonstrated to be more than species specific[45], indeed frequently no more than strain specific[46] and that biochemical and electrophysiological data from one species are often inconsistent[21].

One of the most readily apparent ambiguities in the original hypotheses was the contrast between the delay in the onset of therapeutic action compared with the rapid reversal of the reserpine syndrome or the immediate onset of the pharmacological effects invoked in support of the original hypotheses. This anomaly, along with the lack of a standard profile of presynaptic actions led Ashcroft *et al.* in 1972[47] to suggest that the pathology of depression might lie post synaptically in aminergic receptors rather than simply in amine levels. With the advent of ligand binding techniques this proposal has been eagerly taken up. Indeed so eagerly and so voluminous is the current literature that it is not proposed to review it in detail and the reader is referred to the following[20–23, 48, 49].

This alternative emphasis has led to a beta adrenoceptor down regulation proposal[50] and an alpha$_2$ autoreceptor desensitization hypothesis[51]. These hypotheses have been put forward supported by claims that antidepressants produced the requisite receptor adaptations following chronic but not acute exposure. They are logically consistent with the earlier hypotheses in that hypersensitive alpha$_2$

receptors might bring about a functional depletion of noradrenaline and beta adrenoceptors are its post synaptic target. To date neither of these proposals is convincingly supported by animal or human evidence[22, 23]. Indeed, antidepressant potency seems inversely correlated with intrinsic activity on beta adrenoceptors[52] and alpha$_2$ receptors may not even be autoreceptors[53]. However, even were they supported, a question would remain that was conveniently ignored when the revised hypotheses were first proposed. It is not immediately apparent why anyone should have thought that receptors would adapt slowly (except by virtue of their mysteriousness, that convenient property which by the 1970s, amines themselves had lost). There is no pharmacological basis for such delayed receptor adaptations; the usual process of receptor desensitization takes 12 to 24 hours and certainly should be well completed by 48 hours[49, 54, 55]. Furthermore, it is not clear how such changes might come about as antidepressants do not have common agonist properties[49, 56]. One possibility not commonly adverted to is that such effects demonstrated following prolonged administration of these drugs may be no more than withdrawal phenomena[57]. Another is that changes of delayed onset are secondary to a change in circadian rhythm dynamics[58], as antidepressants do have intrinsic activity on rhythmicity; this would yield delayed receptor changes, although whether these relate to therapeutic activity or are merely side effects is uncertain[49].

Normal Science II

Despite the inability to account for antidepressant actions satisfactorily in terms of an action on amine systems and despite the obvious fact that any drug effects may compensate for rather than reverse a primary defect, researchers have not been deterred from pursuing evidence of pathological deficiencies of monoamines in depression. It is proposed that a review of 2 aspects of such research on amines will strongly indicate paradigmatic influences.

Urinary MHPG

As it has not been possible to get direct evidence of cerebral monoamine concentrations in living subjects an alternative approach has been to look at the metabolites of catecholamines such as urinary MHPG. The first significant result of such studies came in 1972, when Maas *et al.*[59] reported that urinary MHPG was reduced in persons who were depressed. This group claimed the following year that urinary MHPG was unaffected by exercise[60] and that low levels were associated with a predisposition to euphoriant responses to amphetamine[61] and a good response to imipramine but not amitriptyline[62]. Two other studies have claimed a link between urinary MHPG and tricyclic response specificity[63, 64] but both of these studies have had poor designs with a lack of crossover controls.

At the same time, and throughout the 1970s, Schildkraut and coworkers reported similar reductions in urinary MHPG, culminating in a complex paper in 1978[24]. However, there are difficulties in interpreting their findings. Arguably the only clear finding is that for their endogenously depressed group whom they report as having normal urinary MHPG levels. Despite the fact that this is characteristically the group that most convincingly responds to antidepressant medication, they were not led to question the validity of the amine hypotheses as one might expect a Popperian scientist to do. Values were also reported for unclassifiable depressions, unipolar non-endogenous depressions, schizophrenia-related depressions and schizo-affective depressions. One might question exactly what the consequences for the amine hypotheses would be of a lowering of amine metabolites discovered in any of these groups as, compared to endogenous depressives, fewer are likely to respond to antidepressants. One might wonder at the validity of including unclassifiable depressions or schizophrenia-related depressions 'characterised by chronic asocial behaviour with bizarre and eccentric behaviour of several years duration'. It should be noted that the latter 4 groups account for 55 per cent of the total sample and thus their precise constitution is a matter of some concern. Particularly as the escape clause for the amine hypothesis comes later in the paper with the claim that 'the clinical and biochemical heterogeneity of the depressive disorders has been widely recognised for years'. This is a common statement made in research papers in this area confronted with inconvenient data, whereby variability in the data is transformed from indicators of assay unreliability or contamination of the subject pool to evidence for 'biochemical heterogeneity'.

At the same time, as these studies were proceeding more basic studies not bound by the amine paradigm have shown a wide range of normal values for urinary MHPG[65], an effect of diet on this metabolite[66] and an effect of physical activity on this parameter[67]. In all there are now reports that urinary MHPG may be affected by motor activity, diet, diurnal variation, weight, age, sex, the pH of the urine or the consumption of alcohol or nicotine[38]. There is evidence to suggest that no more than 20 per cent of urinary MHPG is derived from central sources[68]. All these factors led Ridges in 1980[69] to conclude that urinary MHPG was too influenced by external factors to reliably indicate central noradrenergic function.

Nevertheless, at the start of one of the most comprehensive psycho-biological research programmes ever conducted, the investigators of the NIMH collaborative study hypothesized in 1980 that urinary MHPG would be lower in bipolar depression, lower in depression than controls, that baseline MHPG would be the only noradrenergic metabolite to correlate with treatment response and that it would be associated with differing responses to imipramine and amitriptyline[70]. Therefore, it is of interest to note the reports now emerging from this study[71]. While making clear that urinary MHPG levels did not predict drug responders, the authors of the report

argument is the need to specify which clinical features antidepressants work on. Particularly as the same authors appear when convenient to both assume that diverse clinical syndromes might have common neurochemical substrates and argue that 'depressive syndromes similar in psychopathological symptoms may nevertheless be based on disparate metabolic substrates'[75]. Claims have also been made that persons with lowered 5HIAA respond preferentially to clomipramine[83], an antidepressant claimed to act primarily on the serotonergic system, despite a lack of clinical features in those with lowered 5HIAA or in those unresponsive to clomipramine that would differentiate them from other depressives. Furthermore, as with urinary MHPG, large variations in 5HIAA results are not interpreted as damaging to the cause but rather as evidence of 'bimodality'[74].

Annitto and Shopsin[38] in a review of CSF 5HIAA studies note that by 1979, there had been 14 studies of this variable, the majority of which had not found it lowered in depression. Nevertheless the NIMH study hypothesized in 1980 that CSF 5HIAA would be lower in depressives than in controls, would be reciprocally related to urinary MHPG and that low values would be associated with response to amitriptyline rather than to imipramine[70]. As they present their data it is not possible to determine how the hypotheses fared apart from the concession that specific drug responses were not found[71]. Indeed it is more likely from the figures offered that CSF 5HIAA is raised in depression compared to controls, especially for female depressives which has been reported also by Gerner *et al.*[84]. Nevertheless they go on to hypothesize that unipolar patients with low values have a serotonergic defect, although these values do not fall outside the control range and despite similar values for bipolar patients. It is not clear why the bipolar values are ignored except perhaps because they have already been categorized on the basis of their urinary MHPG values into hyper- and hyponoradrenergic and presumably as a consequence their serotonergic systems do not count.

The Ingenuity of Normal Science

This review of the above issues in animal pharmacology and human studies in depression is not intended to be either a comprehensive review or even a critique of the amine hypothesis as if Kuhn is right reviews do not tackle the real problems in the field and critiques are ignored, until the time is right. Rather this is an examination of attempts to validate or refute a hypothesis and the studies selected for this purpose have been conducted by some of the best known researchers in the field, whose scientific credentials seem unquestionable. Their biochemical techniques are exemplary, their research programmes are commendable and the attempt to investigate rationally the basis for psychopharmacological treatments is an absolute precondition for any scientific advance in this field. The standing of these

do not admit their failure to demonstrate any evidence in favour of their other hypotheses (and indeed do not list them in 1984[71]). They do not report urinary MHPG to be lower in depressives than controls but do note that the mean of those depressives whose values fall below the mean of the depressed group also fall significantly below the control mean. This is hardly surprising! Those patients whose values exceeded the depressed mean had as a group a mean value greater than the control mean. Categorizing such patients as 'high' and 'low' and juggling, they claim that bipolar patients with low values responded to treatment more frequently than bipolar patients with high values or than unipolars. This led the authors to subdivide the bipolar group into hypernoradrenergic and hyponoradrenergic groups, although their own evidence does not even support a distinction between bipolars and unipolars and their values for urinary metanephrine suggest unipolar depressives to be hyponoradrenergic; unfortunately a finding that is 'empirically robust but from a theoretical standpoint difficult to explain'. This latter quote highlights the clash between a paradigm and actual data.

Cerebrospinal Fluid 5HIAA

A similar sequence of claims is found when one looks critically at the reports of CSF, 5HIAA abnormalities in depression. There have been a number of reports that it is lowered[72–74]. Its accumulation in the CSF, as assessed using the drug probenecid which blocks the egress of acidic metabolites from the CSF, has also been reported to be reduced[75, 76], although the latter studies have not suggested that baseline 5HIAA was abnormal. There are many reasons for caution in the interpretation of these claims as amine metabolites may reflect metabolism divorced from function[77]. Furthermore, 5HIAA passes directly into the blood stream and therefore CSF levels may reflect altered haemodynamics rather than altered cerebral function[78]. Activity has also been shown to affect results[79]. In addition some would argue that a lumbar tap may reveal no more than the metabolism of the lumbar cord[80].

There are further ambiguities in the reports themselves. Thus Van Praag *et al.*[75] found that 5HIAA accumulation was reduced in both endogenous and neurotic depressions. The data of Asberg *et al.*[81] show a greater proportion of neurotic than endogenous depressives had lowered 5HIAA. As with Schildkraut's urinary MHPG studies the issue arises of why 2 clinical populations, distinguishable in part by their response to biological treatments should show a common biological abnormality. There are further problems in that the word neurosis as applied to depression has multiple meanings and it seems unlikely that it defines a homogenous group[82]. One might argue that these several groups of depressives have in common a state of unhappiness but antidepressants are clearly not euphoriants and in general they appear much less likely to have any effect on affect in the absence of demonstrable vegetative disturbances. Central to what could easily become simply a semantic

authors confers the considerable influence of authority on the reports selected; a factor that should have significant influence if Kuhnian dynamics are correct but arguably not if science is simply a cool assessment of evidence and refutation of inadequate conjectures.

A common feature to the reports appears to be the assumption that amines *will* be found to be deranged in the affective disorders despite the evidence presented above that the original pharmacological basis for this expectation no longer warrants an exclusive focus on amines. Given the expectation, and faced with inconvenient data, it is the contention of the present article that the authors of the above reports have handled these problems in a manner consistent with their being under the influence of a paradigmatic view as suggested by Kuhn[1]; that is they will develop accessory explanations or methods of evading inconvenient data rather than countenance refutation of the paradigm. Such influences can be found in any area of research on amines and affective disorders from post mortem investigations to receptor binding studies and from animal pharmacology to neuroendocrine challenge tests in depressed patients[22, 49]. Kuhn's model specifically predicts difficulties in reconciling paradigmatic views with hard facts but reluctance to forsake the view simply because of inconvenient data. While Sir Karl Popper also concedes that scientific hypotheses should not be given up too readily, one wonders what he would make of current research on amines!

Accessory explanations appear to follow a pattern. Thus antidepressants not found to act on noradrenergic systems were conveniently discovered to have metabolites which did and their therapeutic action could be ascribed to such metabolites discovered or potential. Failure to find evidence of a noradrenergic lesion led to notions of noradrenergic and serotonergic depressions with the inference that all would be well if only the right patients were selected. Alternatively one can invoke the spectre of clinical heterogeneity—'clinical and biochemical heterogeneity has been recognised for years'[24]—despite the assertion by Kraepelin[85], who delineated manic depressive illness, and who had 'become convinced that all the above mentioned states are only manifestations of a single morbid process'. Indeed, when one considers that little heed is paid to the one clinical distinction that might count as a matter of definition, that between psychotic and neurotic (endogenous/reactive), one might question whether clinical detail is often merely a cloak of convenience. Another such garment is statistics. Where wide variability in the data might otherwise be a cause for concern, for the committed it provides evidence of 'bimodality'.

A more central ploy around which other defences can be deployed, is to relocate the supposed defect. Thus as levels of amine metabolites and studies of amine precursors in turn failed to support the original contention, amine receptor defects were invoked, entities whose mysteriousness offered a few more years grace. If as

receptors become better known results continue to confound expectations, as they have done to date[22, 49], the burden can be shifted again to endogenous modulators (endocoids)[86–88] or to neuromodulation of amine systems by neuropeptides[89]. With such a renewed focus of interest, research on the amine substrates of depression may proceed happily for some more years without the need to question whether the basic strategy of investigating amines at all is warranted. One can suggest that this process of hypothesis revision, or updating, is good evidence of a process of conjecture and refutation moving ever closer to the truth. But there are no grounds for believing that amine receptors are any closer to the truth than the neurotransmitters themselves. Indeed one could argue the opposite in that at least most antidepressants acutely affect amine levels but generically and specifically these drugs are nonspecific receptor ligands[90].

A very similar pattern of relocation of supposed defect can be found in psychoanalysis. When it became impossible to sustain the hypothesis that actual abuse had occurred in childhood or of an actual progression of childhood stages with specific developmental tasks associated with each, the strategy adopted was to relocate the problem from the sphere of the actual to that of phantasy. Many scientists have been concerned that this strategy has made psychoanalysis irrefutable in principle and one has to agree that at the very least this was an inspired relocation. However, it can be argued on Kuhn's view that as a paradigm psychoanalysis would never have failed through precise refutation but would only have been superseded by a wholly different point of view that was more satisfactorily able to account for novel rather than current data. As such, in retrospect one could have predicted that it would have been unlikely to survive the introduction of effective psychopharmacological agents. In like manner this consistent relocation of supposed defects in amine systems may seem to make the amine hypotheses irrefutable in practice, although testable in principle. Many reviewers have wondered at the survival of the amine edifice suggesting that it has been erected on a quick-sand of mistaken assumptions and that it apparently lacks the mortar of supporting evidence[37, 38, 91]. From the present perspective, it can be suggested that such survival stems from the hypotheses possessing advantages other than their ability to account for neuropharmacological data.

Neuropharmacology and Psychobiology

Much of the initial weight behind the monoamine hypotheses derived from the observation that reserpine carried a 15 per cent risk of depression. Yet thyroid disorders have been known for some time to be associated with affective disorders in up to 20 per cent of cases[92, 93] and Cushing's disease carries a 50 per cent risk of

depression[94, 95] but neither of these clinical observations have had the same influence as those concerning reserpine. It also seems that while workers countenanced a 'strategic reductionism' as advocated by Schildkraut they refused a more radical reductionism in the face of good evidence. As early as 1945 Klein and Nunn[96] observed altered body water distribution in depressives, while Coppen and Shaw showed that this fact is associated with a retention of sodium and that a similar effect could be found in manics[97]. Allied to this was the demonstrable action of lithium on electrolyte distribution[98] and the influence of electrolytes on overall metabolism through amino acid transport mechanisms[99].

Confronted with these other possibilities, one might wonder at the favoured place of biogenic amines in the study of affective disorders. Perhaps the following factors may help account for it. For the psychopharmacologist, amines had, in the 1950s and 1960s, the properties of being discrete and imaginable, unlike the complex proteins involved in neuroendocrine regulation. And yet they retained some mystery, in contrast to sodium and other ions, which might be employed to account for affects. Secondly, there was the availability of techniques to measure amines and their metabolites developed from earlier studies of peripheral amines, whereas measurement of proteins and the determination of their sequences has only become possible recently. Thirdly, and perhaps more importantly, the techniques developed to study amines had been developed to investigate fight and flight reactions, the physical manifestations of emotions as mediated by catecholamines[100]. The success of such research undoubtedly predisposed many to assume that amines also play some part in the regulation of mood. However, although mood and emotion can be subsumed under the term 'affect' they are not necessarily themselves synonymous and may not even be related[101]. Most of us if forced to distinguish between these terms might fall back on some sort of criterion such as duration, moods being simply extended emotions, but this only holds good in common usage and does not survive analytical scrutiny[101, 102].

In particular, however, amines may also have offered an answer to another complex issue, hinted at by Schildkraut in his initial formulation: 'catecholamine neuronal systems may be of importance in the physiology of reinforcement and reward, as well as in arousal and motor activation'[18]. Perhaps the most potent reinforcement of the amine hypotheses has been their consonance with behaviourist notions of depression. It is a short step from the notion that depression results from the lack of reward or reinforcement to one which associates it with a depletion of the reward neurochemical or a defect in reward pathways; a step that has frequently been taken[103–108]. Where the clinical or pharmacological evidence of noradrenergic involvement looks unconvincing, or that implicating the serotonergic system looks disturbing, a balance between noradrenergic reward mechanisms and serotonergic punishment mechanisms is often invoked[107–109] but as operational criteria for

'balance' are never specified this position although testable in principle in practice approaches irrefutability.

In contrast to the many studies which derive their justification (and funding) from their testing of pharmacological aspects of the amine hypotheses, critical testing of the *psychological* heart of these hypotheses is rarely undertaken despite observations that would suggest such testing might be profitable. Strictly speaking there is no aversive pathway in the brain or reward neurotransmitter[110, 111]. Pleasure and displeasure is associated rather with the patterning of incoming material and is closely related to the familiarity of such material[111–113]. One and the same pathway may mediate both reward and punishment[112, 113]. There are, however, centres whose activation by implanted electrodes may lead to sustained intra-cranial self-stimulation (ICSS) and it has been inferred that this is because of the 'rewarding' quality of the stimulation; an inference not immune to dispute. Claims regarding the nature of the chemical neurotransmitter of this pathway, which have been important to amine hypotheses, have to date been based on inferences, rather than actual dissection and chemical analysis. Assertions that the neurotransmitter involved is either noradrenaline or serotonin have been unwarranted, given the experimental paradigms used[41, 114]. The primary substrates of the best characterized of such centres, that lying in the median forebrain bundle are at present unknown although dopaminergic systems may have a modulatory influence on the final expression of activity in this pathway[41, 114, 115]. And indeed effects on this pathway through dopaminergic manipulations may well be the principal locus of action of neuroleptics, which interrupt ICSS and conditioned reflex activity in general. In contrast sympatholytic agents, such as clonidine may also interrupt such activity but apparently do so, only indirectly, by virtue of the sedation they induce[115].

There are further critical problems in the proposed marriage of learning theory and neurobiology that proponents of amine hypotheses rarely address. Firstly, while learning theories make useful predictions in the case of anxiety[116, 117] and while a consideration of underlying biological mechanisms fleshes out the operations of psychological factors in anxiety states, attempts to extend learning theory to cover the behavioural manifestations of depression seem much less satisfactory[118]. Secondly, the introduction of biological abnormality is radically inconsistent with the operation of learning theories, introducing as it does the notion of behaviours that do not adhere to the laws of learning theory[119]. Thirdly, it is far from clear that depression is simply the result of loss of reward or the consequence of aversive experiences, such as a learning theory would appear to require[102, 118].

Despite such potential difficulties, an 'affective dimension' to catecholamines and indoleamines seems to be taken for granted. In contrast, there have also been dopaminergic[120, 121], cholinergic[122, 123], opiate[124], GABAergic[125] and a variety of circadian rhythm hypotheses[49]. But although these hypotheses can claim a compar-

able amount of neurobiological support[48] as the catecholamine/indoleamine hypotheses, they have lacked their psychological congruence and hence a comparable degree of overall coherence. This advantage on the part of the amine hypotheses is not minimal as their terms of reference (loss, reward and reinforcement) may have been so persuasive by virtue of obvious clinical utility rather than because of compelling neurobiological coherence. Arguably the survival of the amine hypotheses has depended on this conjunction of interests: a uniting of clinical views of the illness with areas for research. Their novelty or paradigmatic core consisted in a dressing of psychological ideas in neurobiological language rather than a radical neurobiological departure. Indeed one might suggest that if behaviourism had not existed psychopharmacologists might have had to invent it, given that the state of the art in the 1960s and 1970s did not permit much more than simple testing for excesses or deficiencies. It is this core which survives refutation of particular neurobiological formulations.

If this analysis is correct, one can predict that the influence of the amine paradigm will only wane when another view emerges that offers to explain both clinical and biological aspects of the illness. Indeed any new view is likely to succeed by virtue of greater clinical plausibility than by neurobiological sophistication and ironically the amine paradigm has led to the unrecognized survival of what, applied to the affective disorders, are outmoded psychological ideas. An attempt has been made to provide such a model involving circadian rhythm disruption rather than biogenic amine disturbances[102]. It should be noted, however, that circadian rhythm hypotheses offer even greater scope for practical irrefutability, ingenious statistical manipulations and the development of accessory explanations for inconvenient data than do the amine hypotheses. A Kuhnian analysis would suggest, however, that adoption of one or other view will depend not so much on refutability, although both should be potentially testable, or on the weight of supporting evidence for either one but will be influenced by theoretical coherence and research possibilities[1].

Visions and Re-visions

It has been argued that the success of the amine paradigm in affective disorders has lain in its marriage of neurobiology and clinical psychiatry and that the above process of normal science would take place, whether or not the amine hypotheses ultimately prove correct. Present lack of supporting evidence may be only temporary and many paradigmatic views (Newton's and Einstein's) have had to wait much longer for evidence to support them. The example of Prout's hypothesis of the integral nature of atomic weights may be cited, where theoretical coherence won the day despite repeated experimental failure to provide the necessary proof[126].

As outlined by Kuhn, one consequence of a paradigm is a neglect of issues which may later seem relevant. Revisions of paradigms frequently come from these areas of neglect rather than from the results of experiments being conducted in areas of interest to the paradigm. In this respect the renaissance of interest in psychopathology in recent years may prove fruitful. Of interest would be a modern reworking of the psychopathological distinctions between psychoses and psychic reactions that can be found for instance in Schneider[127, 128] or between psychoses and neuroses[129]. Currently these distinctions are not made clearly, in terms that capture the attention of modern psychopharmacologists. Clinically one wonders whether a defect of one neurotransmitter system could possibly mediate sleeplessness, anorexia, anergia, dysphoria, hopelessness, guilt and all the other manifestations of a depressive psychosis. If not and if amines are deranged in depression, to which clinical aspect do they give rise? While a particular aminergic defect might underlie depression and its opposite be responsible for mania, how do amine theories propose to account for mixed affective states? Without such specifications, the amine hypotheses are *psychopathologically* untestable or can accommodate as many anomalies as the Freudian hypotheses before them, which are currently dismissed as unscientific because of their capacity to swallow anomalies. Not only do the amine theories lack psychopathological specification but they also lack a pathophysiological dimension, despite the fact that the only abnormal findings in depression to date—hormonal and rhythmic abnormalities—reflect pathophysiological rather than neurochemical disturbances[49].

Also ignored have been phenomenological aspects of the illness. What is distinctive about the quality of the dysphoria experienced in depression? This is a particularly poorly defined aspect of the illness being only negatively defined, as something different to that normally found in adversity[130, 131]. To some extent then it is an inconvenient quality for the amine hypotheses, which necessarily assume a continuity between reactions to adversity and depression[116, 118]. Also neglected and inconvenient for the amine hypotheses yet a hallmark of endogenous depression has been the diurnal variation of mood found in the illness which is confusingly both a pathognomonic and an inconstant feature of the illness[132]. Such findings do not readily fit a picture of neurotransmitter deficiencies.

Apart from these areas of neglect, there are areas of research that seem to have been avoided. And it would seem particularly difficult to explain this avoidance if one also believes that researchers are attempting to refute rather than to support a particular paradigm. It can be suggested that any adequate theory of the affective disorders should account also for mania and that neither psychoanalytic nor aminergic hypotheses have happily done so. Current research increasingly suggests that drugs effective in depression are also effective for mania. Thus lithium is both antidepressant and antimanic[133], as is carbamazepine[134]. Similar claims have been

made for newer agents such as sodium valproate and verapamil which have recently been introduced into the treatment of affective disorders[134, 135]. There is furthermore, a long tradition that ECT is an effective antimanic agent as well as being antidepressant[136, 137]. Perhaps part of the reason why this research has been neglected has lain with its inconsistency with the original amine formulations which suggested that depression resulted from a deficiency of amines and elation correlated with an excess of amines and that an effective antidepressant treatment acted to increase amines and therefore would be unlikely to be therapeutic in mania. Such considerations seem to have precluded the use of tricyclics in manic states. When R. Kuhn[138] introduced imipramine he was aware that it had both antimanic and antidepressant efficacies but withheld reports of antimanic actions in the interests of avoiding ambiguity. He is not alone in claiming an antimanic action for imipramine. Akimoto in Japan has also found such an action[139]. Indeed early reports of such actions led Mogen Schou[139] to predict that all antidepressants would show antimanic profiles as well. Such a view might seem startling to most psychiatrists at present. It is significant that it was articulated before the catecholamine hypothesis was introduced by Schildkraut.

So much has the notion that tricyclics exert their antidepressant actions through correcting a deficiency of amines taken hold of general opinion that to attempt to treat mania with tricyclics would be most unlikely to get ethical approval. Indeed one current support offered for the amine hypotheses are recent reports of tricyclic induced mania. However, these reports are anecdotal. In contrast, in an elegant record linkage study, Jules Angst[140] has demonstrated that there has always been a considerable incidence of mania following depression, and conversely of depression following mania, and that the incidence of mania following depression is no higher now than it was before the introduction of tricyclic antidepressants. At a recent meeting of the British Association for Psychopharmacology[141] he suggested that we are over hasty to attribute both cures and side effects (in this case, mania) to the agents we use. Such attributions are more understandable given the expectation that tricyclics should induce mania. But if one is not convinced by such record linkage studies what is one to say to cognitive therapists who claim that cognitive therapy can induce mania[142]?

One further area of neglect has been research on the history of psychiatry. If this history were simply a story of linear progress resulting from successive conjectures and refutation supplemented by technical advances then it would prove boring and uninstructive. But if the history of psychopharmacology as that of other branches of science is characterized by the rise and fall of paradigmatic views then such a history should prove far more instructive and perhaps a more useful guide to what is currently happening and why, than reviews by experts within the discipline. A recent historical reconstruction of the significance of morbid heredity (degeneration theory)

in French psychiatry in the 19th century[143] suggests that this paradigm bore striking similarities to the amine paradigm in its practical irrefutability, its scientific capaciousness which united holders of quite disparate orientations and in its consonance with the spirit of the times. In hindsight it can be seen that apart from meeting scientific needs it also answered to a number of legal, professional and ideological pressures many of which have been pressing once again recently.

Meta-Psychopharmacology

One lesson from such a history might be that good news introduced to audiences of 12, whether in Zurich or Jerusalem, is liable to explosive propagation, particularly when conversion is accompanied by the creation of titular offices. Whether the new faith represents progress or not is a much more ambiguous question that takes us beyond the history of views to questions of epistemology[144]. While a wholly new faith may grow explosively, revisions within a field are not characterized by rapid conversion as paradigmatic views do not simply concede the field when more plausible revisions are presented and even were a broad consensus to develop around some new view, there may long be a significant number who remain convinced that amines have something to do with affective disorders although their convictions may command ever less general assent. However, Karl Popper also advocates caution in discarding established views[145]. Are distinctions between these 2 philosophical positions merely a matter of degree?

In contrast to the difficulties in delineating a common mechanism of action of the antidepressants, research on the mode of action of neuroleptics has progressed smoothly. In 1963, Carlsson and Lindquist[146], based on neurotransmitter turnover studies, hypothesized that these agents acted to block catecholaminergic neurotransmission, whether noradrenergic or dopaminergic. Further studies confirmed that it was dopamine and not noradrenaline that was the pertinent neurotransmitter[147]. Given that the role of dopamine as a neurotransmitter was unknown before 1959[148], this progress toward isolating dopaminergic systems as the locus of action of neuroleptics was remarkably rapid. Anomalies in the data were accounted for satisfactorily by the discovery of several dopaminergic pathways[149, 150], with the action of neuroleptics on the mesolimbic pathway being more specifically correlated with clinical effect. Support was enhanced when close correlations were discovered between clinical efficacy and dopamine receptor blocking potency[151], particularly mesolimbic D2 receptor blocking effects[152]. It is notable in this case that biochemical and behavioural effects can be closely correlated[153]. All this permits one to say, however, is that neuroleptics, through an action on dopaminergic neurotransmission modify behaviour. Whether dopamine systems are disordered in schizophrenia is not

implied by such findings and indeed a dopamine hypothesis of schizophrenia only clearly appeared in 1976[151].

A classical Popperian pattern of conjecture and refutation might have followed had the hypotheses simply been a catecholaminergic hypothesis of antidepressant action and a dopaminergic hypothesis of neuroleptic action. These are testable and refutable conjectures. In particular, the development of a neuroleptic without dopamine blocking effects would most likely have finished off this particular dopaminergic hypothesis. In actual fact, since its proposal, the dopamine hypothesis has progressively accounted for the anomalies present at the start. In contrast, a catecholamine hypothesis of antidepressant action has coped less well with the anomalies apparent from the onset and indeed with the development of novel antidepressants and the advance of neurobiological knowledge, these anomalies have multiplied. Whether this would have led to the abandonment of such a hypothesis of antidepressant action is impossible to determine.

In contrast the catecholaminergic hypotheses of depression and dopaminergic hypotheses of schizophrenia appear irrefutable. While apparently testable, negative evidence to date has had little effect and there is almost infinite scope to resist refutation by citing biochemical heterogeneity, neurotransmitter balances or otherwise. Perhaps significantly a catecholaminergic hypothesis of antidepressant action or dopaminergic hypothesis of neuroleptic action could have arisen from evidence to hand. The corresponding psychopathological hypotheses started from indirect evidence and have ever since been hypotheses in search of evidence. This suggests a need for caution regarding 'heuristic' hypotheses in general and a need to refine criteria of what makes a scientific hypothesis. Refutability or testability, while required, seem less important than a refusal to conjecture, unless there are sufficient grounds to do so. A very similar situation occurred in psychoanalysis, where a more parsimonious hypothesis might have been 'certain mental discomforts can be alleviated by invoking "Oedipal" conflicts'. However, as is well known such successes were taken as evidence for the existence of something else.

Conceding that 'revolutionary' developments do happen in science, Sir Karl Popper has distinguished between scientific and ideological revolutions[154]. The former are strictly scientific in character and relate closely to their empirical content. They may be revolutionary in their scientific implications but have little effect outside of the scientific community to which they are addressed. As examples of such pure scientific revolutions, he cites J. J. Thompson's discovery of the electron, Mendel's discovery of the laws of genetics, the discovery of X-rays, radioactivity, isotopes and the unravelling of the double helix by Crick and Watson. In the category of scientific revolution admixed with ideological revolutions he puts the Copernican and Darwinian and Einsteinian revolutions. These latter have had an impact beyond their respective scientific communities and the debates they stimulated often bore little

close relation with the empirical basis of the scientific hypothesis. Common to these latter revolutions is a shift in our understanding of ourselves and our place in the universe. To these can be added the Freudian revolution, which appeared to displace us even from the centre of our own psyches.

Based on such considerations Popperians sometimes suggest that Kuhn's model applies to matters of social psychology and ideology rather than to the logic of science[145]. The discovery of effective and specific psychopharmacological agents was a technical development, with the profoundest ideological implications as it permitted the manipulation of the psyche by physical methods. Perhaps not surprisingly then, the catecholamine hypotheses of depression and the dopaminergic hypothesis of schizophrenia are associated with the intrusion of ideological factors and Kuhnian dynamics into a scientific revolution. Prior to their emergence Freudian psychoanalysis held sway as the dominant school of thought in American psychiatry. It has since been almost completely replaced by a biological psychiatry, largely because of the effectiveness of specific neurobiological agents. Following the revolution, there has been a period of what Kuhn would call normal science characterized by attempts to match the paradigm with the knobbly face of reality. During this period workers have been prepared to countenance glaring anomalies without rejecting the paradigmatic view in a way that is quite comparable to the supposed irrefutability of the Freudian hypotheses before them. In contrast to an evolutionary relationship between scientific positions as might be expected on the basis of Popperian dynamics, Kuhn's model predicts incommensurability between paradigmatic views. Interestingly, there is almost a full-blown incommensurability between the current hypotheses of biological psychiatry and prior psychoanalytic hypotheses, which is most strikingly demonstrated in the declaration that key psychoanalytic terms, such as the word neurosis, are now non-words[155]. A de facto incommensurability is also demonstrated in the fact that each theoretical orientation has its own journals, seminars and conferences.

There is an irony in characterizations of Kuhnian dynamics in terms of social psychology as recent research in experimental social psychology has shown how beliefs may persevere in the face of potent logical and empirical challenges, may even be bolstered by contrary evidence or survive the total destruction of their original evidential bases[156, 157]. Such considerations suggest that heuristic hypotheses do not readily fit a logical model of science. But an equally notable aspect of science is its progressive character. Logic of itself is not a progressive operation. One wonders where we would be without heuristic hypotheses. Would there have been comparable progress to that that has undoubtedly been made in the field of psychobiology without the guidance of a heuristic framework? That such visions in psychopharmacology have been accompanied by marked scotomata suggests a factor to be reckoned with in scientific endeavour and a potential

usefulness in considering such developments from a Kuhnian perspective rather than dismissal as peripheral to the central dynamic of scientific advance (especially as relevance to paradigmatic concerns is pertinent to obtaining research funds—at least in psychobiological research). In particular, this analysis of the psychopharmacology of the affective disorders from that perspective points to the possibility that the amine hypotheses have been principally a psychological hypothesis, rather than a neurobiological one, and that they succeeded the Freudian hypotheses before them by virtue of a more adequate handling of the relation of the mind to its cerebral substrates, in certain strategic respects. However, considerably greater sophistication seems necessary to adequately characterize this complex nexus and accordingly the amine hypotheses are liable in turn to be replaced.

References

1. Kuhn T. The Structure of Scientific Revolutions. Chicago: University of Chicago Press, 1962.
2. Axelrod J. Biogenic amines and their impact on psychiatry. Seminars in Psychiatry 1972; 4: 199–210.
3. Popper K. The Logic of Scientific Discovery. London: Routledge & Kegan Paul, 1959.
4. Slater E. The psychiatrist in search of a science II: Developments in the logic and sociology of science. Br J Psychiatry 1973; 122: 625–636.
5. Kuhn R. The imipramine story. In: Ayd FJ and Blackwell B (Eds), Discoveries in Biological Psychiatry. U.S.A.: Lippincott, 1970; 205–217.
6. Loomer HP, Saunders JC and Kline NS. A clinical and pharmacodynamic evaluation of iproniazid as a psychic energiser. In: Cleghorn RA (Ed), Research in Affect. Psychiatric Research Reports 1957; 8.
7. Spector S, Shore PA and Brodie BB. Biochemical and pharmacological effects of the maoi's, iproniazid, i-phenyl-2-hydrazinopropane (JB 516) and 1-phenyl-3-hydrazinobutane (JB 835). J Pharmacol Exp Ther 1960; 128: 15–21.
8. Spector S, Hirsch AO and Brodie BB. Association of behavioural effects of pargyline, a non-hydrazide monoamine oxidase inhibitor with increase in brain norepinephrine. Int J Neuropharmacol 1963; 2: 81–93.
9. Axelrod J, Whitby L and Hertting G. Effect of psychotropic drugs on the uptake of 3H.noradrenaline by tissues. Science 1961; 133: 383–384.
10. Axelrod J and Inscoe JK. The uptake and binding of circulating serotonin and the effect of drugs. J Pharmacol Exp Ther 1963; 141: 161–165.
11. Sigg E, Soffer L and Gyermek L. Influence of imipramine and related psychoactive agents on the effect of 5HT and catecholamines on the rat's nictitating membrane. J Pharmacol Exp Ther 1963; 142: 13–20.
12. Sulser F and Bickel MH. On the role of catecholamines in the anti-reserpinic action of desmethylimipramine. Pharmacologist 1962; 4: 178.
13. Sulser F, Bickel MH and Brodie BB. The action of desmethylimipramine in counteracting sedation and cholinergic effects of reserpine like drugs. J Pharmacol Exp Ther 1964; 144: 321.
14. Frize ED. Mental depression in hypertensive patients treated for long periods with high doses of reserpine. N Eng J Med 1954; 251: 1006–1008.

15. Harris TH. Depression induced by rauwolfia compounds. Am J Psychiatry 1957; 113: 950.
16. Carlsson A, Rosengren E, Bertler A and Nilsson J. Effect of reserpine on metabolism of catecholamines. In: Garattini S and Ghetti V (Eds), Psychotropic Drugs. Amsterdam: Elsevier Press, 1957a.
17. Carlsson A, Shore PA and Brodie BB. Release of serotonin from blood platelets by reserpine in vitro. J Pharmacol Exp Ther 1957b; 120: 334–339.
18. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965; 122: 509–522.
19. Bunney WE and Davis JM. Norepinephrine in depressive reactions. Arch Gen Psychiatry 1965; 13: 483–494.
20. Charney DS, Menkes DB and Heninger GR. Receptor sensitivity and the mechanisms of action of antidepressant treatment. Arch Gen Psychiatry 1981; 37: 1160–1180.
21. Maj J, Przegalinski E and Mogilnicka E. Hypotheses concerning the mode of action of antidepressant drugs. Rev Physiol and Biochem Pharmacol 1984; 100: 1–74.
22. Healy D. Biochemical correlates of depression. MD Thesis, National University of Ireland, 1985.
23. Leonard BE. Neurotransmitter receptors, endocrine responses and the biological substrate of depression: a review. Hum Psychopharmacol 1986; 1: 3–22.
24. Schildkraut JJ, Orsulak P, Schatzberg A, *et al.* Towards a biochemical classification of depressive disorders. Arch Gen Psychiatry 1978; 35: 1427–1439.
25. Garver DL and Davis JM. Biogenic amine hypotheses of affective disorders. Life Sciences 1979; 24: 383–394.
26. Mendels J and Frazer A. Brain, biogenic amine depletion and mood. Arch Gen Psychiatry 1974; 30: 447–451.
27. Paykel ES, Fleminger R and Watson JP. Psychiatric side-effects of antihypertensive drugs other than reserpine. J Clin Psychopharmacol 1982; 2: 14–39.
28. Farnebo LO. Effect of d-amphetamine on spontaneous and stimulation induced release of catecholamines. Acta Physiologica Scand 1971; (Suppl.) 371: 45–52.
29. Kuhn DM, Wolf W and Youdim M. 5-hydroxytryptamine release in vivo from a cytoplasmic pool; studies on the 5-HT behavioural syndrome in reserpinised rats. Br J Pharmacol 1985; 84: 121–129.
30. Katz B. The transmission of impulses from nerve to muscle and the subcellular unit of synaptic action. Proc Roy Soc (Biol) 1962; 155: 455–479.
31. Folkow B, Haggendal J and Lisander B. Extent of release and elimination of noradrenaline at peripheral adrenergic nerve terminals. Acta Physiol Scand 1967; (Suppl.) 72: 307.
32. Zimmerman H. Vesicle recycling and transmitter release. Neurosci 1979; 4: 1773–1804.
33. Tauc L. Nonvesicular release of neurotransmitters. Physiol Rev 1982; 62: 857–893.
34. Pettibone DJ, Pflueger AB and Totaro JA. Tetrabenazine–induced depletion of brain monoamines; mechanism by which desmethylimipramine protects cortical norepinephrine. Eur J Pharmacol 1984; 102: 431–436.
35. Bruinvels J. Inhibition of the biosynthesis of 5-hydroxytryptamine in rat brain by imipramine. Eur J Pharmacol 1972; 20: 231–237.
36. Carlsson A, Fuxe K and Ungerstedt U. The effect of imipramine on central 5-hydroxytryptamine neurones. J Pharm Pharmacol 1968; 20: 150–151.
37. Luchins D. Biogenic amines and affective disorders. A critical analysis. Int Pharmacopsychiatry 1976; 3: 135–149.
38. Annitto W and Shopsin B. Neuropharmacology of mania. In: Shopsin B (Ed), Manic Illness. New York: Academic Press, 1979; 105–164.

60. Goode DJ, Dekirmenjian H, Meltzer HY and Maas JW. Relation of exercise to MHPG excretion in normal subjects. Arch Gen Psychiatry 1973; 39: 391–396.
61. Fawcett J, Maas J and Dekirmenjian H. Depression and MHPG excretion response to dextroamphetamine and tricyclic antidepressants. Arch Gen Psychiatry 1972; 26: 246–251.
62. Maas JW. Biogenic amines and depression. Arch Gen Psychiatry 1975; 32: 1357–1361.
63. Cobbin DM, Requin-Blow B, Williams LR and Williams WO. Urinary MHPG levels and tricyclic antidepressant drug selection. Arch Gen Psychiatry 1979; 36: 1111–1115.
64. Sachetti E, Allaria E, Negri F, Biordi P, Smeraldi E and Cazzullo C. 3-methoxy-4-hydroxy-phenylglycol and primary depression: clinical and pharmacological considerations. Biol Psychiatry 1979; 14: 473–483.
65. Hollister LE, Davis KL, Overall JE and Anderson JE. Excretion of MHPG in normal subjects. Arch Gen Psychiatry 1978; 35: 1410–1415.
66. Muscettola G, Wehr P and Goodwin FK. Effect of diet on urinary MHPG. Am J Psychiatry 1977; 134: 914–917.
67. Ebert MH, Post RM and Goodwin FK. Effect of physical activity on urinary MHPG excretion in depressed patients. Lancet 1972; ii: 766.
68. Blumberg P, Kopin I, Gordon E, Markey S and Ebert M. Conversion of MHPG to VMA: implications for the importance of urinary MHPG. Arch Gen Psychiatry 1980; 37: 1095–1098.
69. Ridges AP. The amine hypothesis in relation to the present understanding of depressive illness. Br J Clin Practice 1980; (Symp Suppl.) 7: 12–21.
70. Maas J, Koslow S, Davis J, *et al.* Biological component of the NIMH clinical research branch collaborative programme on the psychobiology of depression. Psychol Med 1980; 10: 759–777.
71. Maas J, Koslow S, Katz M, *et al.* Pretreatment neurotransmitter levels and response to tricyclic antidepressant drugs. Am J Psychiatry 1984; 141: 1159–1171.
72. Ashcroft G, Crawford T and Eccleston E. 5-hydroxyindole compounds in the csf of patients with psychiatric or neurological diseases. Lancet, 1966; ii: 1049–1052.
73. Asberg M, Bertilsson L, Tuck D, Cronholm B and Sjoqvist F. Indoleamine metabolism in the csf of depressed patients before and during treatment with nortriptyline. Clin Pharmacol Ther 1973; 14: 277–283.
74. Traskman-Bendz L, Asberg M, Bertilsson L and Thoren P. CSF monoamine metabolites of depressed patients during illness and after recovery. Acta Psychiatr Scand 1984; 69: 333–342.
75. Van Praag HM, Korf J and Schut D. Cerebral monoamines and depression; an investigation with the probenecid technique. Arch Gen Psychiatry 1973; 28: 827–831.
76. Goodwin FK and Post RM. CSF amine metabolites in affective illness. J Psychiatric Res 1974; 10: 320.
77. Green AR and Grahame-Smith DG. 5-hydroxy and other indoles in the C.N.S. In: Iversen LL, Iversen SD and Snyder SH (Eds), Handbook of Psychopharmacology, vol 3. New York: Plenum, 1975; 169.
78. Meek JL and Neff NH. Is csf the major source for the removal of 5-hydroxyindole acetic acid from the brain? Neuropharmacol 1973; 12: 497–503.
79. Post R, Kotin J and Goodwin F. Psychomotor activity and csf. amine metabolites in affective illness. Am J Psychiatry 1973; 130: 67–72.
80. Bulat M. Some criteria for the study of biochemical processes in CNS analysis of cerebrospinal fluid. Clin Neuropharmacol 1984; 7: (Suppl. 1), S153.
81. Asberg M, Thoren P, Traskman L, Bertilsson L and Ruigleergen N. Serotonin depression—a biochemical subgroup within the affective disorders? Science 1976; 191: 478–479.

39. Carroll BJ, Mowbray R and Davis B. Sequential comparison of l-tryptophan with ECT in severe depression. Lancet 1970; i: 967–969.
40. Zis AP and Goodwin FK. The Amine Hypothesis. In: Paykel ES (Ed), Handbook of the Affective Disorders. Edinburgh: Churchill Livingstone, 1982; 175–190.
41. Mason ST. Catecholamines and Behaviour. Cambridge: Cambridge University Press, 1984.
42. Bond WS. Psychiatric indications for clonidine: the neuropharmacological and clinical basis. J Clin Psychopharmacol 1986; 6: 81–87.
43. Fuxe K. Evidence for the existence of monoaminergic neurones in the C.N.S. Acta Physiol Scand 1965; (Suppl. 247) 64: 39–85.
44. Daniel W, Adamus A, Melzacka M, Szymura J and Vetulani J. Cerebral pharmacokinetics of imipramine in rats after single and multiple dosages. NS Arch Pharmacol 1981; 317: 209–213.
45. Hu HY, Davis JM, Heinze WJ and Pandey GN. Effect of chronic treatment with antidepressants on beta adrenergic receptor binding in guinea pig brain. Biochem Pharmacol 1980; 29: 2895–2896.
46. Kopanski C, Turek M and Schultz JE. Effects of longterm treatment of rats with antidepressants on adrenergic receptor sensitivity in cerebral cortex: structure-activity study. Neurochem Int 1983; 5: 649–659.
47. Ashcroft G, Eccleston D and Murray I. Modified amine hypothesis for the aetiology of affective illness. Lancet 1972; 2: 573–577.
48. Healy D and Paykel ES. Neurochemistry of Depression. In: Howells JG, (Ed). Modern Perspectives in Psychiatry. New York: Brunner/Mazel (in press).
49. Healy D. Rhythm and Blues. Neurochemical, neuropharmacological and neuropsychological implications of a hypothesis of circadian rhythm disruption in the affective disorders. Psychopharmacology 1987; 93: 271–285.
50. Vetulani J, Stawarz RJ, Dingell JV and Sulser F. A possible common mechanism of action of antidepressant drugs. NS Arch Pharmacol 1976; 293: 109–114.
51. Crews FJ and Smith CB. Presynaptic alpha receptor subsensitivity after longterm antidepressant treatment. Science 1978; 202: 322–324.
52. Willner P. The ability of antidepressant drugs to desensitise beta-receptors is inversely correlated with their clinical potency. J Affect Disord 1984; 7: 53–58.
53. Laduron PM. Presynaptic heteroceptors in regulation of neurotransmission. Biochem Pharmacol 1985; 34: 467–470.
54. Schwartz JC, Costentin J, Maitres MP, Protais P and Baudry M. Modulation of receptor mechanisms in the CNS: hyper and hyposensitivity to catecholamines. Neuropharmacol 1979; 17: 665–683.
55. Pittman R, Rabin R and Molinowsky P. Desensitisation of Beta adrenergic receptor coupled adenylate cyclase activity. Biochem Pharmacol 1984; 33: 3579–3584.
56. Healy D and Leonard BE. Monoamine transport in depression; kinetics and dynamics. J Affect Disord 1987; 12: 91–103.
57. Stolz JF and Marsden CA. Withdrawal from chronic treatment with metergoline, d-l-propranolol and amitriptyline enhances serotonergic receptor mediated behaviour in the rat. Eur J Pharmacol 1982; 79: 17–22.
58. Kafka M, Wirz-Justice A and Naber D. Circadian and seasonal rhythms in alpha and beta adrenergic receptors in the rat brain. Brain Res 1981; 207: 409–419.
59. Maas JW, Fawcett JA and Dekirmenjian K. Catecholamine metabolism depressive illness and drug response. Arch Gen Psychiatry 1972; 26: 252–262.

106. Carroll BJ. Neurobiologic dimensions of depression and mania. In: Angst J (Ed), The Origins of Depression. Berlin: Springer-Verlag, 1983.
107. Deakin JFW and Crow TJ. Monoamines, rewards and punishments; the anatomy and physiology of the affective disorders. In: Deakin JFW (Ed), The Biology of Depression. Oxford: Alden Press, 1986.
108. Crow TJ and Deakin JFW. Neurohumoural transmission, behaviour and mental disorder. In: Shepherd M (Ed), Handbook of Psychiatry, volume 5. Cambridge: Cambridge University Press.
109. Wise C, Berger B and Stein L. Evidence of alpha-noradrenergic mediated reward receptors and serotonergic punishment receptors in the rat brain. Biol Psychiatry 1973; 6: 3–21.
110. Gloor P. Inputs and outputs of the amygdala: what the amygdala is trying to tell the rest of the brain. In: Livingstone KE and Hornykiewicz D (Eds), Limbic Mechanisms. New York: Plenum Press, 1978; 189–209.
111. Melzack R and Wall P. The Challenge of Pain. Harmondsworth, Penguin Books, 1982.
112. Klein DF. Endogenomorphic depression: a conceptual and terminological revision. Arch Gen Psychiatry 1974; 31: 447–454.
113. Cazala P. Self-stimulation behaviour can be elicited from various 'aversive' brain structures. Behav Brain Res 1986; 22: 163–171.
114. Gallistel CR, Shizgal P and Yeomans JS. A portrait of the substrate for self-stimulation. Psychol Rev 1981; 88: 228–273.
115. Gallistel CR. The role of dopaminergic projections in Median Forebrain Bundle self-stimulation. Behav Brain Res 1986; 22: 97–105.
116. Wolpe J. The positive diagnosis of neurotic depression as an etiological category. Compr Psychiatry 1986; 27: 449–460.
117. Gray JA. The Neuropsychology of Anxiety. Oxford: Oxford University Press, 1982.
118. Eastman C. Behavioural formulations of depression. Psychol Rev 1976; 83: 277–291.
119. Healy D. The comparative psychopathology of animal and human affective disorders. J Psychopharmacology (in press).
120. Randrup A and Braestrup C. Uptake inhibition of biogenic amines by newer antidepressant drugs; relevance to the dopamine hypothesis of depression. Psychopharmacol 1977; 53: 309–314.
121. Downs NS, Britton KT, Gibbs DM, Koob GF and Swerdlow NR. Supersensitive endocrine responses to physostigmine in dopamine-depleted rats: a model of depression. Biol Psychiatry 1986; 21: 775–786.
122. Janowsky DS, El-Youssef MK, Avis JM and Serkerke HJ. A cholinergic-adrenergic hypothesis of mania and depression. Lancet 1972; ii: 632–635.
123. Dilsaver SC. Pathophysiology of the "cholinoceptor supersensitivity". Biol Psychiatry 1986; 21: 813–829.
124. Davis GC. Endorphins and pain. Psychiatric Clin N Amer 1983; 6: 473–487.
125. Lloyd KG, Thoret F and Pilc A. GABA and the mechanism of action of antidepressant drugs. In Bartholini G, Lloyd KG and Morselli PL (Eds), L.E.R.S., 4. New York: Raven Press, 1986; 33–42.
126. Lakatos I. Falsification and scientific progress. In: Lakatos I and Musgrave A (Eds), Criticism and the growth of scientific knowledge. Cambridge: Cambridge University Press, 1970.
127. Schneider K. Clinical Psychopathology. New York: Grune & Stratton, 1959.
128. Fish F. Clinical Psychopathology. Bristol: Wright, 1974.

82. Klerman G, Endicott J, Spitzer R and Hirschfeld R. Neurotic depression: a systematic analysis of multiple criteria and meanings. Am J Psychiatry 1979; 136: 57–61.
83. Van Praag HM. New evidence of serotonin deficient depressions. Neuropsychobiol 1977; 3: 56–63.
84. Gerner RH, Fairbanks L and Anderson G, *et al.* CSF neurochemistry in depressed, manic and schizophrenic patients compared with that of normal controls. Am J Psychiatry 1984; 141: 1533–1540.
85. Kraepelin E. Manic Depressive Insanity and Paranoia. Edinburgh: Churchill, 1921.
86. Langer SZ, Arbilla S, Tahraoui L and Lee CR. Association of high affinity 3H.imipramine binding sites with the serotonin transporter: possible role of endogenous modulators. Clin Neuropharmacol 1984; 7: (Suppl. 1), S467.
87. Barbaccia ML, Karoum F and Costa E. Characteristics of the endocoid for imipramine recognition sites. In: Lal H, Labella F and Lane J (Eds), Endocoids. New York: Alan R Liss, 1985; 431–440.
88. Giambalvo CT. Purification of endogenous modulators of monoamine oxidase from plasma. Biochem Pharmacol 1984; 33: 3929–3932.
89. Lundberg JM and Hokfelt T. Coexistence of peptides and classical neurotransmitters. Trends in Neurosci 1983; 325–333.
90. Biegon A and Samuel D. Binding of a labelled antidepressant to rat brain tissue. Biochem Pharmacol 1979; 28: 3361–3366.
91. Shopsin B, Wilk S, Sathanantha G, Gershon S and Davis K. Catecholamines and affective disorders revised; a critical assessment. J Nerv Ment Dis 1974; 158: 369–383.
92. Dunlap HF and Moersch FB. Psychiatric manifestations associated with hyperthyroidism. Am J Psychiatry 1935; 91: 1215.
93. Lidz T and Whitehorn J. Psychiatric problems in a thyroid clinic. JAMA 1949; 139: 698.
94. Trethowan WH and Cobb S. Neuropsychiatric aspects of Cushing's syndrome. Arch Neurol Psychiatry 1952; 67: 283.
95. Cohen SI. Cushing's syndrome; a psychiatric study of 29 patients. Br J Psychiatry 1980; 136: 120–124.
96. Klein R and Nunn RF. Clinical and biochemical analysis of a case of manic-depressive psychosis showing regular weekly cycles. J Ment Sci 1945; 91: 79.
97. Coppen A and Shaw DM. Mineral metabolism in melancholia. BMJ 1963; ii: 1439.
98. Coppen A, Malleson A and Shaw DM. Effect of lithium carbonate on electrolyte distribution in man. Lancet 1965; i: 682–683.
99. Christensen HN, Inui Y, Wheeler KP and Eavenson E. Amino acid transport and the sodium ion. Fed Proc 1966; 25: 592.
100. Cannon WB. Bodily Changes in Pain, Hunger, Fear & Rage. New York: Appleton Century, 1929.
101. Berrios GE. The psychopathology of affectivity. Psychol Med 1985; 15: 745–758.
102. Healy D and Williams JMG. Dysrhythmia, dysphoria and depression: the interaction of learned helplessness and circadian dysrhythmia in the pathogenesis of learned helplessness. Psychol Bull (in press).
103. Poschell BP. Do biological reinforcers act via the self-stimulation areas of the brain? Physiol and Behav 1968; 3: 53–60.
104. Crow TJ. Catecholamine containing neurones and electrical self-stimulation. ii A theoretical interpretation and some psychiatric implications. Psychol Med 1973; 3: 66–73.
105. German DC and Bowden DM. Catecholaminergic systems as the neural substrate for intra-cranial self-stimulation: a hypothesis. Brain Res 1974; 73: 381–419.

129. Roth M. Neurosis, psychosis and the concept of disease in psychiatry. Acta Psychiatr Scand 1963; 39: 128–145.
130. Spitzer RL, Endicott J and Robins E. Research diagnostic criteria (RDC) for a selected group of functional disorders. 3rd Edition, New York State Psychiatric Institute, New York, 1978.
131. Carney MWP, Roth M and Garside RF. The diagnosis of depressive syndromes and the prediction of ECT response. Br J Psychiatry 1965; 111: 659–674.
132. Stallone F, Huba GJ, Lawlor WG and Fieve RR. Longitudinal studies of diurnal variations in depression: a sample of 643 patient days. Br J Psychiatry 1973; 123: 311–318.
133. Fieve R, Dunner D, Kunbarai T and Stallone E. Lithium carbonate in affective disorders iv: a double blind study of prophylaxis in recurrent unipolar depression. Arch Gen Psychiatry 1975; 32: 1541–1544.
134. Emrich HM. Use of Gabamimetics and anticonvulsants in the treatment of affective disorders. In: Bartholini G, Lloyd KG and Morselli PL (Eds), L.E.R.S., 4. New York: Raven Press, 1986; 195–199.
135. Dubovsky SL, Franks RD, Allen S and Murphy J. Calcium antagonists in mania: a double blind study of verapamil. Psychiatric Res 1986; 18: 309–320.
136. McCabe MS and Norris B. ECT versus chlorpromazine in mania. Biol Psychiatry 1977; 12: 245–254.
137. Fink M. Mania and electroseizure therapy. In: Shopsin B (Ed), Manic Illness. New York: Raven Press, 1979; 219–228.
138. Kuhn R. The treatment of masked depression. In: Kielholz P (Ed), Masked Depression. Berne: Hans Huber Publ., 1973; 188–197.
139. Schou M. Normothymotics, "mood normalisers": are lithium and the imipramine drugs specific for affective disorders? Br J Psychiatry 1963; 109: 803–809.
140. Angst J. Switch from depression to mania—a record study over decades between 1920 & 1982. Psychopathol 1985; 18: 140–154.
141. Angst J. Hypomania following tricyclic antidepressants. Special Guest Lecture to Brit Assoc for Psychopharmacol, Spring Meeting, 1986. J Psychopharmacology 1987; 1: 13–20.
142. Kingdon D, Farr P, Murphy S and Tyrer P. Hypomania following cognitive therapy. Br J Psychiatry 1986; 148: 103–105.
143. Dowbiggin I. Degeneration and hereditarianism in French mental medicine 1840–90: psychiatric theory as ideological adaptation. In: Bynum WF, Porter R and Shepherd M (Eds), The Anatomy of Madness. 1985; vol 1; 188–232.
144. Kuhn TS. The Essential Tension. London: University of Chicago Press, 1977; 320–339.
145. Popper K. Normal Science and its dangers. In: Lakatos I and Musgrave A (Eds), Criticism and the Growth of Knowledge. Cambridge: Cambridge University Press, 1970; 51–58.
146. Carlsson A and Lindquist M. Effect of chlorpromazine and haloperidol on formation of 3-methoxy-tyramine and normetanephrine in mouse brain. Acta Pharmacol Toxicol 1963; 20: 140–144.
147. Anden NE, Butcher SG, Corrodi H, Fuxe K and Ungerstedt U. Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. Eur J Pharmacol 1970; 11: 303.
148. Carlsson A. Detection and assay of dopamine. Pharmacol Rev 1959; 11: 300.
149. Stevens JR. An anatomy of schizophrenia. Arch Gen Psychiatry 1973; 29: 177–189.
150. Hokfelt T, Lyungdahl A, Fuxe K and Johansson O. Dopamine nerve terminals in the rat limbic cortex: aspects of the dopamine hypothesis of schizophrenia. Science 1974; 184: 177.
151. Snyder SH. The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. Am J Psychiatry 1976; 133: 197–202.

152. Seeman P. Brain Dopamine Receptors. Pharmacol Rev 1980; 32: 229–313.
153. Carlsson A. Does dopamine have a role in schizophrenia? Biol. Psychiatry 1978; 13: 3–21.
154. Popper K. The rationality of Scientific Revolutions. In: Harre R (Ed), Problems of Scientific Revolution. Oxford: Oxford University Press, 1975; 72–101.
155. Bayer R and Spitzer RL. Neurosis, psychodynamics and DSM-III. Arch Gen Psychiatry 1985; 42: 187–196.
156. Kahneman D, Slovic P and Tversky A. Judgement under Uncertainty: Heuristics and biases. Cambridge: Cambridge University Press, 1982.
157. Ross L and Anderson CA. Shortcomings in the attribution process: on the origin and maintenance of erroneous social assessments. In: Kahneman D, Slovic P and Tversky A (Eds), Judgement under Uncertainty. Cambridge: Cambridge University Press, 1982; 129–152.