ANIMAL MODELS FOR SCREENING NEW AGENTS: A BEHAVIOURAL VIEW

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The evaluation of drug-induced behavioural changes in laboratory animals poses some especially difficult problems for psychopharmacologists. Laboratory findings are more easily assessed when new substances are examined for spectra of effects on 'physical' systems as for example for antibiotic or anti-inflammatory actions, or for effects on the cardiovascular or respiratory systems. In such cases the criteria for measuring change can be specified with relative clarity; this is lacking in interspecific comparisons of behaviour.

The aim in behavioural comparisons is therefore to choose indices that give roughly equal weighting to information which has been obtained from each of the species. A failure to do so invites the criticism made by White, Juhase & Wilson (1973) that 'it is as senseless to study the comparative abilities of man and spider to run a T-maze as it is to compare their performances at web-spinning'.

The search for general principles underlying motivation, learning and conditioning can be regarded as a means of establishing some common ground for comparative studies of acquired behaviour. However, as most relevant behaviour patterns have not recently been acquired by individual animals but have gradually evolved as species have adapted to their particular ecological conditions, one may question the overall relevance of 'laws of behaviour' which have been derived from laboratory tests.

Beach (1950) highlighted tendencies among researchers to overlook inherent species differences when he drew attention to the pre-eminent position held by the laboratory rat in departments of experimental psychology, where much of the emphasis is still on studying learning mechanisms in situations that are very artificial for the animals. This methodology aims to reduce the likelihood of confusion with complex innate patterns of responses, but at the same time it inevitably lends weight to the earlier controversies about the relative importance of instinctive and acquired behaviours. The significance of such distinctions is diminished in the light of observations that different animal species can develop specialized propensities and abilities to learn which correspond to their own particular ecological demands (Bolles, 1970; Lockard, 1971; Seligman, 1970). For these reasons generalizations across species may not be very meaningful when they are based primarily on comparisons of acquired behaviour in analogous laboratory tests. The hazards multiply when the scope

of comparative analyses of behaviour is extended to include 'aberrance' and psychopathology.

The notion of a *scala naturae*, an ordered hierarchy of organisms with man occupying the highest rank, has its origins in early scientific and philosophical thinking (see review by White *et al.*, 1973). Although the concept of such a phylogenetic continuum has for some time been accepted as untenable (cf. Hodos & Campbell, 1969), the idea dies hard. It would seem that much comparative research is conducted as though the animal subjects are simpler or incomplete versions of man. The emphasis in research tends to be anthropocentric for a variety of reasons, of which ethical considerations are only one. But it has been cogently argued that '... rodents and primates either nearly or completely fail to share a common ancestor; the fossil record leaves the matter unclear. Their remoteness (100 million years or so) of relationship makes them irrelevant to each other for all comparative purposes. The place of rodents in psychology is for the study of rodent behaviour...' (Lockard, 1971). How likely is it then, that studies of drug-behaviour interactions most of which are performed in rodents, will both illuminate aspects of human behaviour, and also generate viable predictions about the clinical applications of psychotropic drugs?

Very little is known of naturally-occurring behaviour disorders in animals and the aetiology of most psychiatric conditions is obscure. Thus the identification and development of animal models of psychiatric disorders is a form of interspecific comparison where most of the basic information is lacking. The choice of human criteria in a given condition is made from an amalgam of clinical observations and associated physiological and metabolic findings, which are frequently cast within the framework of a tentative aetiological hypothesis. Assigning equal weighting to behavioural criteria in animals cannot therefore be anything but a biased process; it consists usually of attempts to transpose and translate miscellaneous human observations into an animal setting. Not surprisingly, apparent similarities acquire special importance even though it is recognized that analogous forms of behaviour may have arisen in distantly related species as a result of ecological convergence—that is through pressures of selection which may be broadly similar, but with the underlying mechanisms presumably remaining very different.

Thus, for example, there is no *a priori* reason for supposing that an analogous 'treatment' will have similar effects on the reactions of the individual members of pairs of certain birds or mammals which happen to form monogamous relationships. These issues arise whenever behaviour is investigated as the dependent variable, but they apply also to the nature of the independent variable or treatment, especially if this is some form of behavioural manipulation. It follows that imposing analogous treatments on analogous behavioural substrates must increase the likelihood of error in comparisons of phylogenetically distant species. There have nevertheless been some notable cases where false analogies resulted in major advances, such as the introduction of lithium for the treatment of mania (see review by Cade, 1970).

In a document which set out the primary goals and issues in preclinical psychopharmacology, Russell *et al.* (1962) have this to say about extrapolation from animals to man: 'This is a very old question in those biological and medical disciplines which use the comparative method . . . Ideally to be confident that this type of generalization is valid, however, would require that the behaviour patterns in the species compared be homologous and not merely analogous. By "homologous" is meant that the behaviour patterns are alike in both origin and fundamental structure. At the present stage of the behavioural sciences it is difficult to establish that apparently similar behaviour patterns are truly homologous.' Consequently, Russell *et al.* (1962) suggested the adoption of the following general strategy whenever behaviour was studied as a dependent variable:

- (a) The analysis of a human aberrant behaviour pattern for its basic characteristics.
- (b) The selection of aspects of animal behaviour as similar as possible to these characteristics.
- (c) A search for chemical agents which might affect these characteristics in animals.
- (d) Tests of these agents on the human behaviour patterns originally analysed.

As an additional step before proceeding to tests in man, it is also necessary to check whether the behavioural indices in animals discriminate between existing drugs that are known to be effective clinically and those that are ineffective or irrelevant. This broad method, which can be described as a criterion behaviour approach, is not generally followed in the pharmaceutical industry where the emphasis is on comparisons of empirically-derived profiles of new substances with those of established drugs.

Lasagna (1971) has listed five principal routes by which new drugs might eventually reach the stage of tests in clinical trials; these are theoretical constructs, molecular modification, empirical screening, folk-remedies and animal models. The theoretical construct approach aspires most closely to an eventual rational basis for the therapeutic use of psychotropic drugs (Miller, 1964). The models are usually neurochemical

and physiological, and tests of animal behaviour are assigned secondary importance. The ultimate criterion is nevertheless, in its widest sense, behavioural—that is alleviation of symptoms. One feature of this type of research has been that many of the advances in brain functions themselves sprang from the initially serendipitous discoveries of the central effects of drugs such as reserpine and the amine oxidase inhibitors.

Molecular modification of existing drugs is another potentially valuable technique, but here the main difficulty lies in discriminating between 'me-too' and 'me-different' relatives. Similarly, when empirically derived screening procedures are used to define 'profiles' of new drugs there is a major risk of excluding substances with novel and unexpected profiles. There is a tendency to choose only those compounds which resemble the 'standard' drugs, and it is also possible that standard profiles can contain component indices that may be irrelevant to the desired actions of given drugs. The presence on the market of large families of drugs the individual members of which scarcely differ suggests that the direction of research in the pharmaceutical industry can be greatly influenced by short-term commercial pressures.

Such factors may largely account for the adoption by industry of the criterion-drug strategy, as opposed to the criterion-behaviour approach which was embodied in the proposals of Russell *et al.* (1962). However, another important reason may be that the behaviourally-oriented method is inherently suspect because of its inevitable reliance on similarities and analogies. The search for behavioural homology, or approximations to it, was implicit in the first two steps that were proposed by Russell *et al.* (1962), yet selection of basic characteristics from a given human syndrome can hardly ignore questions of origin or of fundamental structure. Lack of this knowledge on the one hand determines the need for such research, and paradoxically, it also underlines the fallacy of trying to seek homologies along unspecified parameters.

Movement away from the empiricism of profile-testing must be in the direction of animal models and associated theoretical constructs of putative underlying 'lesions'. The most strikingly successful example of such work can be seen in the introduction of L-DOPA for the treatment of Parkinson's disease. This research has also emphasized how successful extrapolations from animal studies depended critically on research into the distribution and levels of dopamine and its metabolites in both normal and in affected human subjects.

Some models of schizophrenia and manic-depressive disorders

The lack of any clearly identified 'lesions' in most psychiatric disorders has handicapped attempts to develop rationally derived treatments for states such

as schizophrenia and affective disorders. Some recent developments illustrate ways in which neurochemical and behavioural analyses in animals can be combined to generate testable hypotheses about human disorders.

Schizophrenia It has been suggested that disorders of dopamine may underlie aspects of schizophrenic illnesses. The evidence is derived from the possible relationship between the therapeutic potency of neuroleptic drugs and the induction of extrapyramidal effects through some common central action such as blockade of dopamine receptors (Van Rossum, 1966; Randrup & Munkvad, 1972; however for contrary evidence, see Crow & Gillbe, 1973, 1975). Animal studies suggesting that amphetamine-induced stereotyped behaviour is mediated by dopamine (Randrup & Munkvad, 1970) are linked with observations of similar patterns of behaviour in amphetamine psychosis. Similarities between the relative potencies of the stereoisomers of amphetamine in producing stereotypy in animals (Snyder, 1972) and psychosis in human subjects have led Angrist, Shopshin & Gershon (1971) to suggest that 'animal stereotypy ... should be utilized as an animal model for the human stimulant psychoses', and to point to 'the striking clinical similarity of amphetamine psychosis to paranoid schizophrenia'. The question remains whether there are common underlying disturbances in these two conditions, which are very similar but not identical.

On the basis of neurophysiological studies in rats responding to electrical stimulation of certain pathways in the brain, Stein & Wise (1971) have proposed that schizophrenic disorders may occur following the accumulation of an endogenous 'toxin' such as 6-hydroxydopamine. This might result in the deterioration of nonadrenergic 'reward' pathways and hence cause deficits of capacities such as goal-directed thinking and the capacity to experience pleasure, which would in turn lead to 'a regression to primitive and less goal-directed modes of behaviour regulation' (Stein, Wise & Berger, 1972).

Other studies (Kornetsky & Eliasson, 1969) have tested whether states of excessive cerebral excitation or overarousal might underlie some aspects of schizophrenic disturbances. The experimental model consisted of tests of 'attention' in rats which were intermittently subjected to electrical stimulation of the mesencephalic reticular formation through implanted electrodes. The rats' performance was impaired by both electrical stimulation and by doses of chlorpromazine. However, when the two types of treatment were combined they appeared to antagonize each other with a resultant improvement in performance. This effect was interpreted in terms of the inverted-U model of arousal.

The experimental paradigms cited here are open to

criticism because the putative neurophysiological 'lesions' are unlikely to be unitary and discrete, and, by the same token, the behavioural models may only touch on particular aspects of complex clinical syndromes. The validity or otherwise of the animal models is examined principally at the neurochemical and physiological level and the behavioural tests provide adjunctive sets of measures. In all three examples some overt similarity with aspects of human state can be discerned, but too great an emphasis on this would be misleading for the reasons discussed earlier.

Manic-depressive disorders Animal models of manic-depressive disorders also rely in varying degrees on manifest analogues of human symptoms. Hyperactivity in mice induced by doses of morphine (Carroll & Sharp, 1971), and in rats by combinations of drugs such as amphetamine and chlordiazepoxide (Davies, Sanger, Steinberg, Temkiewicz & U'Prichard, 1974) has been used as a behavioural substrate for testing the effects of lithium and of manipulations of levels of biogenic amines in the brain.

Ashcroft *et al.* (1972) have explored some of the very complex ways in which biogenic amine systems may be involved in recurrent depressive illnesses and in bipolar manic-depressive states. In their discussion of behavioural indices they draw attention to the usefulness of tests of exploratory behaviour and of stereotypy in animals (rats) and postulate that changes of similar nature can be discerned clinically in both depression and in hypomania. Parallels are likewise drawn in many other studies of experimentally induced 'depression' in animals.

Treatments such as disruption of mother-infant bonds, isolation and separation of infant monkeys can induce 'despair' characterized by self-clasping, motor-retardation and prolonged behavioural disturbances (Harlow & Harlow, 1971). Repetitive non-contingent punishment given to dogs produces a syndrome of 'helplessness' in a proportion of the subjects (Seligman, Maier & Solomon, 1971). Pharmacological treatments have also been extensively tested. Monkeys chronically medicated with reserpine show reduced motor activity and exploration and increased huddling (McKinney, Eising, Moran, Suomi & Harlow, 1971).

Depletion of catecholamines by α -methyl-*p*-tyrosine produces similar results, whereas depletion of 5-hydroxytryptamine (5-HT) by *p*-chlorophenylalanine does not (Redmond, Maas, Kling, Graham & Dekirmenjian, 1971). Intraventricular injections of 6-hydroxydopamine in monkeys (Breese, Prange, Howard, Lipton, McKinney, Bowman and Bushnell, 1972) reduce locomotion and increase social withdrawal, but interestingly, these effects are temporary despite the permanent depletion of noradrenaline. Interactions between dopaminergic and serotonergic systems have been investigated in rats

(Grahame-Smith & Green, 1974a and b) using the syndrome of hyperactivity and hyperpyrexia as a model.

These studies suggest that an important action of lithium may be not only to increase the synthesis of 5-HT, but also somehow to increase its availability and release; in this way it becomes possible to interpret the observation that doses of lithium and associated inhibition of monoamine oxidase result in *hyperactivity* in rats. As the parts played by the amine systems are progressively clarified (cf. Ashcroft *et al.*, 1972) it will become possible to test whether the 5-HT system does indeed antagonize and exert a modulating influence on some aspects of behaviour that are principally thought to be sustained by dopamine and noradrenaline. The experiments of Grahame-Smith and his colleagues show how necessary it is to study underlying neural mechanisms in detail before interpreting behavioural changes such as hyperactivity and thus, hopefully, avoiding specious analogies with man.

Many of the behavioural changes described here were, however, evocative of depression in man and a

statement by Ashcroft *et al.* (1972) has a bearing on such observations. 'The feeling state and cognitive aspects can only be examined in man because he is the only species to communicate feelings by language. It seems likely, however, that certain of the behavioural and autonomic changes may have much in common in man and other species.' It is assumed that since such changes covary with disturbances of emotion and of thinking in man, analogous indices in animals may serve as useful tools for research.

The question which was discussed at the beginning of this article would seem once again to be thrown open. Allowing for phylogenetic divergences, is it possible to identify in animals some sorts of 'common denominators', structural and functional, that can be applied to the study of psychiatric disorders? On the other hand can it be that certain human disorders are a function of novel aspects of the evolution of the human brain—for example, do the abilities to think, talk, symbolize, experience and communicate feelings themselves generate the possibility of disturbances of these faculties? There seems, at present, to be no ready answer to these questions.

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