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Review

The validity of animal models of depression

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Abstract. Eighteen animal models of depression are reviewed in relation to three sets of validating criteria. Of the 18 models, five could only be assessed for predictive validity, seven could be assessed for predictive and face validity, and six could potentially have predictive, face and construct validity. Some traditional models (reserpine reversal, amphetamine potentiation) are rejected as invalid; the models with the highest overall validity are the intracranial self-stimulation, chronic stress and learned helplessness models in rats, and the primate separation model.

Key words: Animal models – Depression – Validity

Introduction

Until recently, relatively few behavioural procedures had been investigated as potential animal models of depression. Most of the models in use were based on pharmacological interactions between antidepressants and other drugs, and are of minimal psychological interest. Two recent developments have contributed to a change in this situation. Firstly, the recognition that supposedly "endogenous depressions" may have environmental precipitants (Brown and Harris 1978; Lloyd 1980 a, b) has led to vigorous attempts to use animal models to specify the relationship of stress to depression (e.g. Anisman and Zacharko 1982). Secondly, the discovery that chronic treatment with antidepressant drugs produces interesting and potentially significant biochemical changes, which are not apparent on acute administration (e.g. Segal et al. 1974; Sulser et al. 1978) has led to attempts to discover situations in which behavioural effects having a similar course may be observed. Under the impetus of this renewed interest, a number of animal models of depression have been proposed; this review examines their validity.

The validity of animals models of human mental disorders is usually assessed by a set of criteria proposed by McKinney and Bunney: the model should resemble the condition it models in its aetiology, biochemistry, symptomatology and treatment (McKinney and Bunney 1969). It should be noted, however, that in relation to animal models of depression, similarity of aetiology and biochemistry are unsuitable as validating criteria since they are themselves the subject of intense research and speculation. The McKinney and Bunney criteria assess face validity: the phenomenological similarities between the model and the condition being modelled. As a result of recent developments in the literature, it is now possible to assess the predictive validity and construct validity of animal models, in addition to their face validity: predictive validity concerns the success of predictions made from the model, and construct validity concerns its theoretical rationale.

In this review, the following criteria have been used to assess animal models of depression for these different types of validity. Predictive validity is assessed by whether a model correctly identifies (1) antidepressant treatments of pharmacologically diverse types (2), without making errors of omission (3) or commission (4), and whether potency in the model correlates with clinical potency (5). Face validity is assessed by whether antidepressant effects are only present on, or are potentiated by, chronic administration (1), and whether the model resembles depression in a number of respects (2), which are specific to depression (3), and do actually coexist in a specific sub-group of depressions (4); also, the model should not show features which are not seen clinically (5). Construct validity is assessed by whether both the behaviour in the model (1) and the features of depression being modelled (2) can be unambiguously interpreted, and are homologous (3), and whether the feature being modelled stands in an established empirical (4) and theoretical (5) relationship to depression. The rationale behind these three sets of criteria for validating animal models of human mental disorders, and problems associated with their use, have been discussed in more detail elsewhere (Reference Note).

The technique of correlating potencies between a model and the condition it models, which is used as one of the tests for predictive validity, has been used to the best effect to examine the relationship between neuroleptic drugs and dopamine receptors (Creese and Snyder 1978). Correlation of potencies is likely to be more difficult for antidepressants than for neuroleptics, owing to their restricted dosage range (Table 1); whereas the range of clinical doses for neuroleptics spans three orders of magnitude (Creese and Snyder 1978), most of the antidepressant drugs in common clinical use are effective in the 75–150 mg range. With the exception of the beta-receptor agonist salbutamol, the antidepressant efficacy of which is still under investigation (Belmaker et al. 1982), all are effective in the 40–400 mg range. Moreover there are a variety of factors which militate against a perfect correlation of potencies (Reference Note). Nonetheless, the order of potencies in an animal model should approximate to that shown in Table 1: at the very least, tranylcypromine should be more potent than trazodone, with the tricyclics

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Table 1. Antidepressant drugs – approximate clinical dosage range

300 – 600	Buproprion; Trazodone
200 – 300	Amoxapine; Butriptyline; Opipramol; Viloxazine; Zimelidine
100 – 200	Desmethylimipramine; Imipramine; Nialamide
75 – 150	Amitriptyline; Chlorimipramine; Doxepin; Maprotiline; Trimipramine
50 – 100	Iprindole; Iproniazid; Mianserin; Nomifensine; Nortriptyline; Phenelzine
20 – 50	Isocarboxazid; Protriptyline; Tranylcypromine
3 – 6	Salbutamol

Dosages (mg/day) were compiled from information in the Physicians' Desk Reference (1982), Paykel and Coppen (1979) and Costa and Racagni (1982). Information in the table is presented solely in order to relate clinical practice to animal models, and should not be used as a guide to prescribing without further reference to appropriate sources

somewhere in between. In discussing the models, correlations (Spearman rank-order correlation coefficient) have been calculated between published data and the data in Table 1, where there is sufficient information for this to be a useful exercise.

For convenience, this review is organized according to the type of validation procedures applicable to each model. The five models in the first group make no claims to either face validity or construct validity, but aspire only to predictive validity. The majority of animal models of depression lay claim to some degree of face validity, however. The second section will discuss seven such models, beginning with the two classical animal models of depression based on pharmacological interventions. Finally six models are described which may have some degree of construct validity. The first five of these models involve behavioural states generated by stressors of different kinds. The sixth model comprises a group of studies of reward mechanisms, which it is convenient at present to examine as a group, but which might differentiate into separate models in due course.

Models which aspire only to predictive validity

1. Predatory behaviour

One of the earliest empirical models of depression was based on the discovery that the tricyclic antidepressant imipramine blocked the mouse-killing behaviour of rats (muricide) (Horovitz 1965). Subsequent work showed that this effect was shared by monoamine oxidase inhibitors (MAOIs) and other tricyclics (Delina-Stula and Vassout 1979; Horovitz 1965; Horovitz et al. 1966; Sofia 1969 a, b; Ueki 1982), maprotiline (Delina-Stula and Vassout 1979), mianserin, an atypical antidepressant missed by many screening prodedures (Ueki 1982; van Riezen et al. 1975), and electroconvulsive shock (ECS) (Ueki 1982; Vogel and Hambrich 1973).

However, one study found that only four out of ten antidepressants tested blocked muricide at doses significantly lower than those which caused motor debilitation, measured by the rotarod test (Sofia 1969). Additionally, there are discrepancies in the relative potencies of different antidepressants; for example, iproniazid, whilst slightly more potent clinically than the tricyclics, and eqipotent with phenelzine (Table 1), was 20 – 30 times less potent than the other drugs in the muricide test. Moreover, a number of other classes of drug have also been found to block muricide, including psychomotor stimulants, and some anticholinergics and antihistamines (Barnett et al. 1969; Horovitz 1965; Horovitz et al. 1966). The test therefore has only moderate predictive validity.

The antidepressants imipramine, desmethylimipramine (DMI) and chlorimipramine have also been found to block the attack on an anaesthetized rat elicited by hypothalamic stimulation in cats. This effect has been much less extensively studied than muricide. The anticholinergic atropine was ineffective, but so also was the atypical antidepressant iprindole (Dubinsky and Goldberg 1971; Dubinsky et al. 1973).

2, 3. Yohimbine potentiation

The yohimbine potentiation test vies with muricide as the most distasteful animal model of depression. Quinton (1963) observed that the lethality of yohimbine, which is an alpha$_2$-receptor antagonist, was increased in mice by tricyclic antidepressants and MAOIs, but also by a variety of other drug classes, including neuroleptics. In a recent reevaluation of this model, neuroleptics were ineffective, but yohimbine lethality was potentiated by tricyclics, the MAOI paragyline, and a variety of newer "atypical" antidepressants, including iprindole, mianserin, nomifensine, buproprion, viloxazine and zimelidine (Malick 1981). However, electroconvulsive shock (ECS), administered acutely or chronically, was ineffective, and stimulants, anticholinergics and antihistamines gave false positive responses (Lapin 1980; Malick 1981). In one study (Lapin 1980), the most potent drug in this test was the experimental compound AW-151129, which was not found to be a clinically effective antidepressant (Stille et al. 1968). Although the test does successfully identify effective antidepressants drugs, the correlation between their potency in the test and their clinical potency is only 0.2 (calculated using LD-50 values in Malick 1981).

In a less offensive version of this test, yohimbine was administered to dogs at low doses, and the cardiovascular (increased blood pressure) and behavioural (restlessness and body tremors) changes were measured. The tricyclics imipramine, amitriptyline and nortriptyline, and the MAOI nialamide, potentiated the effects of yohimbine (Johnsson et al. 1970; Lang and Gershon 1962, 1963; Sanghvi et al. 1969). However, with the exception of iprindole, which was found to be effective (Sanghvi et al. 1976), "second-generation" antidepressants and ECS do not appear to have been tested. The psychostimulants amphetamine and cocaine, which, with anticholinergics and antihistamines, appear as false positives in a number of other models, were ineffective (Sangvi and Gershon 1969), as were three agents which had been tested clinically as potential antidepressants, but found not to work (Sanghvi and Gershon 1969; Sanghvi et al. 1969). Anticholinergics and antihistamines do not appear to have been tested. Thus, unlike the mouse yohimbine lethality potentiation test, which has very little predictive validity, the dog yohimbine potentiation test has a fair degree of predictive validity, which is limited, however, by the narrow range of drugs examined.

4. Kindling

The daily application of low-intensity electrical stimulation to certain brain areas leads to the development of electrical and behavioural seizure activity, which may eventually be elicited by as little as a few seconds stimulation. This phenomenon is known as kindling (Goddard et al. 1969). Babington and Wedeking (1973) observed that seizures elicited from the amygdala were suppressed by tricyclic antidepressants at doses lower than those required to suppress cortical seizures; anticonvulsant and anxiolytic drugs also suppressed seizure activity, but failed to show selectivity. However although ECS was effective in this test, showing a greater suppression of amygdaloid than cortical seizures (Babington 1975), MAOIs were ineffective, as were iprindole and mianserin (Babington 1981). Moreover, Knobloch et al. (1982) were unable to confirm the selective action of impramine on amygdaloid seizures, and also found that after subacute treatment (2 or 5 days), neither imipramine nor amitriptyline showed selectivity. There is therefore serious doubt as to the ability of this test to identify antidepressant treatments successfully and to eliminate false positives.

5. Dopa-potentiation

If dopa, the precursor of the catecholamines dopamine (DA) and noradrenaline (NA) is administered following pretreatment with an MAOI to protect newly synthesized amines, signs of adrenergic stimulation are seen, including pilloerection, locomotor activity, irritability and aggression. These effects are potentiated by pretreatment with tricyclic antidepressants (Everett 1967; Sigg and Hill 1967). This test is essentially an assay system for "me-too" drugs with adrenergic stimulating activity, and should not be considered an animal model of depression (Reference Note). Theoretical considerations apart, the test does not discriminate well: by its nature, it cannot detect MAOIs; some antihistamines and anticholinergic drugs show positive (Sigg and Hill 1967); and newer non-adrenergic antidepressants such as mianserin (van Riezen et al. 1975) and trazodone (Silvestrini 1982) give negative results.

Models which claim face valitity

6. Reserpine reversal

Reversal of the behavioural and physiological effects of reserpine was the earliest animal model of depression to be developed (Costa et al. 1960). The syndrome induced by reserpine and related agents such as tetrabenazine and Ro-4-1284 is characterized by ptosis (eye closure), hypothermia and catalepsy. The reversal of ptosis and hypothermia by tricyclic antidepressants and MAOIs is very well established, and was the first clear demonstration of a difference in pharmacological activity between tricyclic antidepressants and neuroleptics, which potentiate, rather than counteracting, the effects of reserpine-like drugs (Costa et al. 1960; Maxwell and Palmer 1961; Theobald et al. 1964). Consequently, these effects have been very widely used as a screening test for potential new antidepressants (Hill and Tedeschi 1971; Barnett and Taber 1971; Askew 1963; Howard et al. 1981).

However, the test fails to detect some newer antidepressants, which differ structurally from the tricyclics and MAOIs, such as mianserin (van Riezen 1972), and trazodone (Silvestrini 1982). Conversely, a wide range of non-antidepressants are detected by the test, including stimulants, dopa, alpha-methyl-dopa, alpha-adrenergic agonists, beta-adrenergic blockers, antihistamines and LSD (Carlsson et al. 1957; Day and Rand 1963; Duvoisin and Marsden 1974; Colpaert et al. 1975; Grabowska et al. 1974; Sigg et al. 1965; Sigg and Hill 1967). Correlation between reserpine reversal and clinical potency (Table 1) is in the right direction, but not statistically significant ($r_s = 0.48$, 0.43, $P > 0.1$, calculated from data of Howard et al. 1981 and Colpaert et al. 1975).

If the predictive validity of this test is poor, its face validity is worse. The claim to face validity rests upon two foundations: that reserpine induces depression in people, and that reserpine-induced catatonia is normalized by antidepressant drugs. The first of these claims is questionable. Despite the many published studies of supposed reserpine-induced depressions which appeared in the 1950's and 60's, it has been argued that the incidence of true depressions may have been as low as 5%, and that these patients usually had a prior history of depression (Goodwin et al. 1972). It is possible that true depressions might be induced more frequently by very high doses of reserpine (Peterfy et al. 1976), but this remains to be confirmed. The second claim, that reserpine-induced catatonia is normalized by antidepressants is simply false. Whilst reversal of the physiological effects of reserpine-like drugs is always reported, antidepressants frequently fail to reverse the behavioural effects (e.g. Colpaert et al. 1975; Willner and Clark 1978). When antidepressant-treated animals do awaken from their drug-induced stupor, it is to take up a highly stereotyped and abnormal behaviour, consisting of continuous sniffing and incessant, inexorable forward locomotion, which continues unabated for a period of hours (Brodie et al. 1961; Sulser et al. 1964; Willner and Clark 1978). There is no evidence that antidepressants are able to reverse the suppression by reserpine-like drugs of normal instrumental behaviour (Willner and Clark 1978). Finally, the fact that in order to work, the antidepressant must be given first, further detracts from what little face validity remains.

7. Amphetamine potentiation

Most antidepressants enhance most actions of amphetamine, including, among others, hypothermia (Morpurgo and Theobald 1965), weight loss (Claasen and Davies 1969), locomotor activity (Halliwell et al. 1964) stereotyped behaviour (Halliwell et al. 1964) and enhancement of shock avoidance performance (Carlton 1961; Scheckel and Boff 1964). However, the mechanism for these effects appears to be the impairment of amphetamine metabolism by the liver, which effectively increases the dose of amphetamine reaching the brain (Sulser et al. 1966; Valzelli et al. 1967; Lewander 1968). Not surprisingly, this action is shared by representatives of many other classes of drug, including, inter alia, stimulants, anticholinergics, antihistamines, neuroleptics, beta-blockers and local anaesthetics. Conversely, newer antidepressant agents structurally dissimilar to the tricyclics, such as mianserin (van Riezen 1972) and trazodone (Silvestrini 1982), do not potentiate amphetamine.

The claim to face validity arises from the fact that in addition to the other actions of amphetamine noted above, antidepressants also potentiate the rate-increasing effect of amphetamine in animals pressing a lever to receive brain stimulation reward (Stein and Seifter 1961; Stein 1962). Since the effect is non-specific, both behaviourally and pharmacologically, and artefactual in origin, the claim that this effect confers face validity is untenable.

8. 5-HTP-induced behavioural depression

Another drug interaction model involves the reversal by antidepressant drugs of the behavioural depression induced by 5-HTP, the precursor of 5-HT, in rats working for milk reinforcement. Behavioural depression was attenuated by acute pretreatment with imipramine, amitriptyline, iprindole, mianserin or trazodone (Nagayama et al. 1980, 1981; Aprison et al. 1982). However, behavioural depression was potentiated by fluoxetine, which appears to be an effective antidepressant in some patients (Shopsin et al. 1981); conversely, the most potent blocker of behavioural depression was the 5-HT-receptor blocker methysergide, which is not known to have antidepressant properties (Nagayama et al. 1980, 1981).

Aside from the effects of antidepressants, the decrease in activity is the only other point of resemblance between the model and depression, so the model is extremely weak in both predictive and face validity. In fact, the model was explicitly developed as a behavioural system within which to test the effects of drugs on 5-HT neurotransmission. In this role, it serves a useful function. It is included here as another example (cf. model 5) of the way in which behavioural bioassay systems are sometimes mistaken for animal models (see Reference Note for further discussion).

9. Olfactory bulbectomy

Rats subjected to bilateral lesions of the olfactory bulbs show a variety of behavioural changes, including irritability, hyperactivity and an elevation of circulating levels of plasma corticosteroids; as a result of their hyperactivity, the animals are also deficient in passive avoidance learning. All of these changes can be reversed by antidepressant drugs (Cairncross et al. 1977, 1978, 1979). The specificity of the effects is variable, however: whilst all of the effects of bulbectomy were reversed by amitriptyline, mianserin and viloxazine, irritability and the hormonal changes were also reversed by the neuroleptic chlorpromazine and the anxiolytic chlordiazepoxide. Of the three changes, therefore, the passive avoidance deficit appears to be the only one which is reversed specifically by antidepressants. The effectiveness of antidepressants in the passive avoidance paradigm has been confirmed in other laboratories, and extended to imipramine, doxepin, viloxazine, mianserin, fluoxetine, trazodone, buproprion and zimelidine (Broekkamp et al. 1980; Leonard 1982; Lloyd et al. 1982; Noreika et al. 1981).

In some cases (imipramine, viloxazine, mianserin), effects of antidepressants are only seen after subchronic treatment (5–10 days) (Lloyd et al. 1982; Noreika et al. 1981); other drugs, however (fluoxetine, zimelidine, trazodone), were effective after a single injection. Dosage relationships are difficult to assess from the published data, but what little clinical evidence is available does not suggest that the drugs which are effective acutely in this model have a more rapid clinical onset than those which require chronic treatment. Amphetamine was ineffective in reversing the olfactory-bulbectomy-induced passive avoidance deficit (Cairncross et al. 1978, 1979; Noreika et al. 1981), as was the anticholinergic atropine (Lloyd et al. 1982). However, the 5-HT agonist quipazine was effective (Lloyd et al. 1982), whereas the only MAOI to have been tested, tranylcypromine, was not (Cairncross et al. 1978, 1979; Noreika et al. 1981).

With the exception of tranylcypromine, and, possibly, other MAOIs, the model appears sensitive to all typical and atypical antidepressants. However, a very narrow range of non-antidepressants have been tested, and two important questions, concerning the requirement for chronic drug treatment and the specificity of antidepressant effects on the hormonal changes induced by bulbectomy, remain to be answered.

In addition to the effects described, olfactory-bulbectomy induces muricide in non-killer strains of rat (Ueki 1982); both spontaneous and bulbectomy-induced muricide are blocked by lesions of the cortico-medial portion of the amygdala (Horovitz 1967; Ueki 1982). Moreover, both types of muricide, and the bulbectomy-induced passive avoidance deficit, were blocked by injection of antidepressant drugs directly into this region of the amygdala (Horovitz 1967; Watenabe et al. 1979; Lloyd et al. 1982). Hence, the bulbectomy model is closely related to the muricide model described above (Model 1).

Whereas the muricide model can make no claim to face validity, the bulbectomy model can do so, on two counts. Firstly, hyperactivity is a symptom shown by a significant proportion of depressed patients (Kupfer and Detre 1978; Nelson and Charney 1981). Although the learning of a passive avoidance task is the usual paradigm for studying the bulbectomized rat, it is likely that the learning deficit simply reflects hyperactivity, since it has been observed that chronic treatment with amitriptyline or mianserin reduces locomotor activity in bulbectomized animals, but not in sham operated controls (van Riezen et al. 1977; Leonard 1982). Secondly, like the bulbectomized rat, depressed people frequently have elevated circulating corticosteroid levels (Sacher et al. 1973; Carroll et al. 1976).

These observations raise the question of what exactly is being modelled by bulbectomy. The inactivity of the MAOI tranylcypromine, and elevation of plasma corticosteroids, point strongly to endogenous rather than neurotic depression. Whilst MAOIs have been found to be effective in neurotic depression, there is little or no evidence that they are efficacious in endogenous depression (Tyrer 1979). Similarly, abnormalities of the pituitary-adrenal system are seen in the majority of endogenous depressions, but not in neurotic depressions (Carroll 1978). It would appear, therefore, that the bulbectomized rat models a specific subgroup of depressions – endogenous depressions with psychomotor agitation. Factor and other multivariate analytic studies support the concept of this diagnosis as a nosological entity, distinct from anxious depression, which also involves hyperactivity (Gersh and Fowles 1979; Nelson and Charney 1981). However, there are two potentially important discrepancies between this clinical sub-group and the model. Firstly, elevated levels of plasma cortisol are seen in most, perhaps all, endogenous depressions (Sachar et al. 1973; Carroll 1978); the abnormality is not confined to agitated depressions. Secondly, and perhaps more important, in clin-

ical use, fluoxetine and zimelidine, which are the most potent drugs in the model, acting after a single administration (Lloyd 1982), may actually make psychomotor agitation worse (Shopsin et al. 1981).

A further limitation on the face validity of the model arises from the observation that following chronic treatment with a variety of antidepressants, effects on passive avoidance in bulbectomized rats were seen after 48 or 72 h of withdrawal, but not after 4 h of withdrawal (Noreika et al. 1981). If, as suggested by this study, it should transpire that the effects of antidepressants in the model can only be demonstrated after a period of withdrawal, then the face validity of the model would be seriously undermined.

10. Isolation-induced hyperactivity

If rats are reared in social isolation from an early age (2–3 weeks), they show a marked hyperactivity when compared to group-reared controls (Einon et al. 1975; Sahakian et al. 1975, 1977). Unlike the olfactory bulb lesioned animal described above, the hyperactivity appears not to be accompanied by any signs of aggression, either towards the experimenter or towards other animals (Garzon et al. 1979; Garzon and Del Rio 1981). The time of isolation appears to be critical to the development of this syndrome, since isolation of 2-month-old animals results in aggression towards the experimenter, and muricide, but not hyperactivity (Sofia 1969 a; Valzelli and Bernasconi 1971).

Garzon and colleagues have reported that the activity difference between isolated and group-reared animals was abolished by acute treatment with tricyclic antidepressants (amitriptyline, chlorimipramine, DMI, doxepin). MAOIs (phenelzine, clorgyline), atypical antidepressants (mianserin, iprindole, nomifensine, viloxazine, trazodone), and the beta-receptor agonist salbutamol. The 5-HT-receptor blocker and antihistamine cyproheptadine, which does not appear to have been tested clinically, was also effective. However, neuroleptics (chlorpromazine, haloperidol) and anxiolytics (chlordiazepoxide, diazepam) did not abolish the activity difference between isolated and group-reared animals except at neurotoxic doses. Anticholinergic drugs were not tested. Comparison of drug potencies is difficult from the published data, but one striking result is that salbutamol was clearly the most potent drug tested (cf. Table 1) (Garzon et al. 1979; Garzon and Del Rio 1981).

With two possible exceptions, the test appears to be rather specific. The effect of noradrenaline receptor antagonists is controversial; Garzon and Del Rio (1981) reported that the beta-blocker propranolol did not affect hyperactivity, but blockade of hyperactivity with propranolol or phenoxybenzamine, an alpha-receptor blocker, has also been observed (Weinstock et al. 1976). The effect of amphetamine is also unclear; on acute administration, isolated animals are hypersensitive to amphetamine (Garzon et al. 1979; Sahakian et al. 1975), but chronic amphetamine administration appears to abolish the activity difference between isolated and grouped animals (Weinstock et al. 1978). As the Garzon experiments employed acute treatments, it should probably be concluded that amphetamine is ineffective in this test.

Other than the fact of hyperactivity, which is seen in a significant proportion of depressions (Kupfer and Detre 1978), there is little information on which to judge the face validity of this model. One potential problem is that in operant tasks, isolated animals may show greater persistence (Morgan et al. 1975), which depressed people certainly do not (Weingartner and Silberman 1982). The effects of chronic antidepressant treatment could not be determined, since the activity difference between isolated and group-reared animals was abolished by repeated daily handling and saline injections (Garzon and Del Rio 1981), a fact which itself does not augur well for the model's face validity.

11. Exhaustion stress

Female rats, reared in revolving cages, show a cyclical activity pattern tied to the estrous cycle. Forced running in the wheel, to the point of exhaustion, killed about half the animals. Of the survivors, half resumed running within several days; the others, however, showed a very low spontaneous locomotor activity, with no cyclicity, for several weeks, accompanied by constant diestrous. Normal activity was restored by daily imipramine treatment (Hatotani et al. 1982). There is as yet virtually no information on which to judge either the predictive validity of the model, or its face validity as a model of retarded depression. However, two features of the model are potentially of interest: the effect was all-or-none, only appearing in some of the subjects, and long-lasting. This model may be related to other models involving response to stress, which are discussed below.

12. Circadian rhythms

Rats are nocturnal animals; their locomotor activity is high at night and low during the day. Readjustment to a normal circadian cycle of locomotor activity following reversal of the light-dark cycle was expedited by moderate doses of the antidepressants imipramine, maprotiline and pargyline, administered daily for 10 days prior to the phase-shift, and 16 days subsequently. Chlordiazepoxide, chlorpromazine, reserpine and amphetamine were all ineffective (Baltzer and Weiskranz 1975), Imipramine and clorgyline have also been found to cause a lengthening of the circadian period of hamsters shifted from a normal light-dark cycle to constant darkness (Goodwin et al. 1982).

Lietle work has been carried out using this model, and at first sight, the results might appear to have little face validity in relation to depression. However, disturbance of circadian rhythms appears to be a characteristic feature of depression. In addition to the well-established decrease in the latency of the first period of rapid eye movement (REM) sleep (Akiskal 1980; Kupfer 1976), phase-advance of most other circadian rhythms has also been found in depression (Goodwin et al. 1982). The significance of these changes is obscure. However, a number of authors have suggested that changes in circadian rhythms may be of etiological significance in depression (Wehr and Wirz-Justice 1982), and there is evidence that a variety of sleep deprivation procedures are effective as antidepressant treatments (Gillin 1983).

A related model has been advanced, based on the suppression by antidepressants of (REM) sleep in cats (Scherschlicht et al. 1982). Amphetamine and morphine had a similar effect, but also suppressed non-REM sleep. The only other non-antidepressant for which results were reported was phenobarbital, which had an effect similar to the antidepressants. No relationship is apparent between the ability of antidepressants to suppress REM sleep and their clinical potency.

Models with potential construct validity

13. Learned helplessness

The learned helplessness phenomenon, originally described by Seligman and co-workers in dogs, and subsequently extended to a large number of other species, including people, is that exposure to uncontrollable stress produces performance deficits in subsequent learning tasks, which are not seen in subjects exposed to the identical stressor but able to control it (reviewed by Garber et al. 1979; Maier and Seligman 1976; Miller et al. 1977; Seligman 1975). Learned helplessness could be reversed by sub-chronic treatment (4–7 days) with a variety of antidepressants; including tricyclics, monoamine oxidase inhibitors, atypical antidepressants and ECS (Dorworth and Overmeier 1977; Leshner et al. 1979; Petty and Sherman 1980; Sherman et al. 1982). Acute treatment with imipramine was ineffective in reversing helplessness (Petty and Sherman 1980), as was chronic treatment with neuroleptics, stimulants, sedatives and anxiolytics (Sherman et al. 1982). Reversal of helplessness by catecholamine receptor stimulants and by the anticholinergic scopolamine have also been reported (Anisman et al. 1979), but it is difficult to compare this study directly with the preceding literature, owing to a large number of procedural differences, including use of acute drug treatment.

The current position, therefore, is that the model has good predictive validity, insofar as it responds to a wide range of clinically effective treatments and there are no false negatives. However, the drugs examined do not differ greatly in their clinical potency, so the correlation test cannot be applied. Also, the effects of chronic anticholinergic treatment on learned helplessness have not yet been assessed; neither have the effects of antihistamines.

In addition to performance deficits in aversively motivated tasks, "helpless" animals show a variety of other behavioural changes, including decreased locomotor activity (e.g. Wagner et al. 1977), poor performance in appetitively motivated tasks (Anderson et al. 1968; Rosellini 1978; Rosellini et al. 1981; Zacharko et al. 1982), decreased aggression (e.g. Maier et al. 1972), and loss of appetite and weight (e.g. Weiss 1968). At first sight, the large number of symptoms induced by inescapable shock, and their obvious similarities to the symptomatology of depression, appear to lend the model considerable face validity. However, this very richness proves an embarrassment when it comes to examining parallels between the two conditions.

The defining feature of learned helplessness is reduced voluntary response initiation. However, passivity and psychomotor retardation are not pervasive in depressive disorders: psychomotor retardation is a key symptom of endogenous depression, but is not present in neurotic depressions (Nelson and Charney 1981), and among endogenous depressions, bipolar depressions are characterized by retardation, whereas agitation is more common in unipolar depressions (Depue and Monroe 1978, 1979). Similarly aggression and hostility, whilst absent in bipolar depressions, are not absent from unipolar depressions or neurotic depressions (Depue and Monroe 1978, 1979; Paykel 1971). Helplessness therefore appears to resemble bipolar endogenous depression most strongly. However, the defining feature of endogenous depressions is their failure to respond to psychosocial intervention (Depue and Monroe 1978; Nelson and Charney 1981). Helplessness does respond to psychosocial intervention, in that performance deficits may be overcome by forcibly exposing the animal to the fact that its responding does produce shock termination (e.g. Seligman et al. 1975). Furthermore, uncontrollable shock generates significantly more anxiety than controllable shock (reviewed by Seligman 1975). However, anxiety is not associated with endogenous depressions (Nelson and Charney 1981), and certainly not with bipolar or retarded endogenous depressions (Depue and Monroe 1978, 1979); conversely, anxious depressions are not characterized by passiveness and lack of hostility (Gersh and Fowles 1979).

The specificity of learned helplessness as a model of depression has also been questioned. In addition to the relationship between uncontrollable stress and anxiety, the similarity of the learned helplessness hypothesis of depression to theories of the aetiology of a number of other psychiatric disorders, including schizophrenia, paranoia and psychopathy, have also been noted (Blaney 1977). Despite its appeal, therefore, there are serious doubts regarding the face validity of learned helplessness as a model of depression. Its specificity is unclear, and the model appears to predict patterns of symptoms which are not found to occur in depression.

The construct validity of the learned helplessness model of depression rests on three assumptions; that animals exposed to uncontrollable aversive events do become helpless; that a similar state is induced in people by uncontrollability; and that helplessness in people is the central symptom of depression. Each of these assumptions has been the source of intense controversy, which may be summarized as follows: the "helplessness" interpretation of the animal experiments has not been conclusively established, the "helplessness" interpretation of the human experiments is even less certain, and the relationship between helplessness and depression remains elusive (see Reference Note, for a full discussion).

14. "Behavioural despair"

If mice or rats are forced to swim in a confined space, after an initially frenzied attempt to escape, they assume an immobile posture. On subsequent immersion, the onset of immobility is much more rapid. This state has been named "behavioural despair"; it is assumed that the animals have "given up hope of escaping", as in the learned helplessness procedure (Porsolt et al. 1977 a, b, 1978 a, b, 1979; Porsolt 1981). The onset of immobility in the second test is delayed by pretreatment with a wide variety of antidepressants, including tricyclics (imipramine, amitriptyline, doxepin, DMI, nortriptyline), MAOIs (clorgyline, deprenyl, iproniazid, nialamide, tranylcypromine), atypical antidepressants (maprotiline, iprindole, buproprion, mianserin, nomifensine, viloxazine), ECS, and rapid eye movement sleep deprivation (Browne 1979; Ferris et al. 1982; Gorka and Wojtasik 1980; Gorka et al. 1979; Martorana and Nitz 1979; Porsolt 1981; Porsolt et al. 1977a, b, 1978a, 1979; Schechter and Chance 1979; Wallach and Hedley 1979). There is, in fact, a significant correlation between clinical potency (Table 1) and potency of antidepressants in the behavioural despair test ($r_s = 0.58$, $P < 0.05$, calculated using data in Porsolt et al. 1977b and Porsolt 1981); this was not found in any other model.

The specificity of this test for antidepressants has been questioned: three effective antidepressants, chlorimipramine, trazodone and salbutamol did not reduce immobility in the rat (Porsolt et al. 1979; Porsolt 1981). Clorimipramine did reduce immobility in the mouse, however; its inactivity in the rat may reflect the fact that the drug is metabolized differently in rats than in mice and people (Nagy 1977). It is possible, though unlikely, that the maximum dose of trazodone (100 mg/kg; Porsolt 1981) was insufficient (cf. Table 1), and it is also possible, though even less likely, that the minimum dose of salbutamol (16 mg/kg; Porsolt et al. 1979) was too high.

A potentially more serious problem arises from the large number of non-antidepressants which also reduce immobility. Whilst the test successfully discriminates antidepressants from neuroleptics and anxiolytics (Porsolt et al. 1977 a, b), false positives have been reported for stimulants, convulsants, anticholinergics, antihistamines, pentobarbital, opiates and other brain peptides, and a number of other drugs (Betin et al. 1982; Browne 1979; Kastin et al. 1978; Porsolt 1981; Schlechter and Chance 1979; Wallach and Hedley 1979). Some of these effects are non-specific, however; it has been demonstrated that stimulants and anticholinergics reduce immobility by an indiscriminate stimulation of motor activity rather than by delaying the onset of immobility, and could be distinguished from antidepressants simply by prolonging the period of the test (Kitada et al. 1981). It is possible that this procedural change might eliminate may of the false positives. Additionally, it has been found that whereas response to antidepressants were potentiated by chronic treatment, the response to an antihistamine disappeared on chronic administration (Kitada et al. 1981). The generality of these effects remains to be established, however.

The effectiveness of acute drug treatments in this model does not correspond to their time course of clinical action, which appears to detract somewhat from the face validity of the model. However, the force of this argument is weakened by the observation that chronic treatment potentiates the effects (Kitada et al. 1981; Porsolt 1981); it has also been observed that immobility is potentiated by repeated exposure to the forced swimming procedure, an effect which could be counteracted by chronic imipramine (Gorka and Wojtasik 1980). Nonetheless, the face validity of the "behavioural despair" model is far from well established. Unlike learned helplessness, "behavioural despair" has not been subjected to extensive behavioural investigation; if it is not taken for granted that the two procedures are equivalent (see below), then the face validity of the model rests largely on the aetiological effects of stress and the analogy between immobility and the passivity seen in retarded depressions. The analogy between the life stresses which precipitate depression and the stress of water immersion goes no deeper, but the analogy between immobility and depression may be slightly enlarged by the observation that "behavioural despair" represents not a generalized hypoactivity, but rather an inability or reluctance to maintain the effort of attempting to escape; depressed subjects have been found to show their most pronounced psychomotor impairments in tests which require the sustained expenditure of effort (Weingartner and Silberman 1982). The model therefore has some small degree of face validity.

The construct validity of this test derives entirely from its supposed relationship to learned helplessness. Consequently, the problems discussed in relation to the construct validity of learned helplessness (Reference Note) apply equally to the behavioural despair model. In addition, it is necessary to examine the nature of the relationship between the two models. Surprisingly, the question of escapability has hardly been investigated in relation to behavioural despair. Only one study has addressed the problem directly; immobility was induced to the same extent by escapable or inescapable swimming (O'Neill and Valentino 1982). However, in this study, the "escapable" condition consisted of lowering a ladder into the water at the end of each 3-min trial. In effect, the situation was inescapable for most of the time, and it is questionable whether it would be perceived as escapable by the animals involved. Inescapable immersion has been shown in another study to cause deficits on subsequent water-escape and shock-escape performance, relative to animals allowed to escape, but in this case, the procedure involved total submersion rather than forced swimming (Altenor et al. 1977).

A relationship between behavioural despair and learned helplessness is supported by the observation that inescapable shock increased immobility in the behavioural despair test, either 30 min or 24 h later; escapable shock did not have this effect (Nomura et al. 1982; Weiss et al. 1981). In view of the consistent finding of decreased motor activity following inescapable shock (e.g. Anisman et al. 1979), it would be surprising were this not the case. However, the reciprocal finding has not been demonstrated. With the exception of the submersion experiment described above (Altenor et al. 1977), forced swimming has not been found to impair subsequent escape performance in a water maze (Porsolt 1981) or in shock avoidance responding (O'Neill and Valentino 1982). The task used in the former study may have been too easy, since it has been found that performance deficits following inescapable shock are only seen in rats when difficult tasks are used (Seligman and Beagley 1975; Maier and Testa 1975). However, the shock avoidance task used by O'Neill and Valentino (pressing a lever three times) is one in which inescapable-shock-induced performance deficits are typically seen (e.g. Seligman and Beagley 1975).

In conclusion, therefore, whilst it seems possible that behavioural despair is a milder version of learned helplessness, it remains to be demonstrated that the two procedures do, in fact, constitute different ways of measuring the same thing, and the behavioural despair procedure, which is rapidly gaining in popularity, cannot at present be said to have construct validity.

15. Chronic unpredictable stress

Another model along similar lines has recently been proposed by Katz and colleagues. During a 3-week period, rats were subjected to a variety of different stressors, including, among others, electric shocks, immersion in cold water and reversal of the light/dark cycle. At the end of this period, they received a session of exposure to loud noises and bright lights, followed immediately by an open field test. In unstressed animals, the noise/light session caused an increase in open field activity, but this effect was not seen in chronically stressed animals. The effect was, however, restored by daily antidepressant treatment during the chronic stress period. Restoration of the activating effect of an acute stress was observed with tricyclics (imipramine, amitriptyline), a

MAOI (pargyline), atypical antidepressants (iprindole, mianserin, buproprion) and ECS. A major tranquillizer (haloperidol), an anxiolytic (oxazepam), an antihistamine (tripellenamine), an anticholinergic (scopolamine) and a stimulant (amphetamine) were ineffective; so, also, however, was the MAOI tranylcypromine. In agreement with previous research (Burchfield 1979), chronic stress was also found to increase plasma corticosteroid levels; this effect showed the same spectrum of pharmacological sensitivity, with the exception that the anticholinergic scopolamine was also effective (Katz 1981b; Katz and Hersh 1981; Katz et al. 1981 a, b; Katz and Baldrighi 1982; Katz and Sibel 1982 a, b; Roth and Katz 1981). Similar effects have also been reported in mice (Soblosky and Thurmond 1982). A further effect observed after chronic stress was a failure to increase fluid consumption when saccharine was added to the drinking water. This deficit was partially restored by imipramine; no other drugs were tested (Katz 1982).

This model would appear to have a fair degree of face validity, since the effects observed – increased corticosteroid levels, a lack of reactivity to an acute stress, and a failure to respond to a (presumably) pleasurable stimulus – are all central symptoms of endogenomorphic depression (American Psychiatric Association 1980; Carroll et al. 1976). The observed decrease in locomotor activity is consistent with these effects; a recent review of the symptomatology of major depression found that lack of reactivity tends to characterize retarded, rather than agitated depression (Nelson and Charney 1981). Additionally, the stress regime employed in these experiments appears a somewhat more realistic analogue of the stress of living than a single session of either electric shock or water immersion. It must be emphasized, however, that the requirements for stress to be chronic, varied and unpredictable have not been established; a briefer and more uniform stress regime might have proved equally effective. The requirement for chronic drug treatment has been demonstrated, but only for imipramine. It should also be noted that the model involves prophylactic treatment, since drugs were administered during, rather than following, chronic stress.

There are two sources from which the model might derive construct validity. The first is the learned helplessness literature. To the extent that the model is related to learned helplessness, it is subject to the problems previously noted in relation to the learned helplessness model (see Reference Note). As noted, the importance of predictability in the chronic stress model has not been investigated. In fact, elevation of blood corticosteroids levels, combined with a reduced response to stress, has been observed following daily exposure to a predictable cold stress, and a conditioning model explicitly based upon predictability of the stress was advanced to explain the results (Burchfield 1979).

The second, and more likely, source of construct validity is the literature relating depression to psychological stress. The relationship of stress to diagnostic sub-groups of depression is unclear. The passiveness shown by chronically stressed rats would be more commonly encountered in bipolar than in unipolar depressives (Donnelly and Murphy 1972), and among unipolar in endogenomorphic rather than neurotic depressions (Nelson and Charney 1981). However, stressful life events are equally frequent in neurotic and endogenomorphic depressions (Brown and Harris 1978; Lewinsohn et al. 1977; Paykel 1979); on the other hand, there is some evidence suggesting that bipolar depressives may suffer from a higher level of chronic stress than unipolars (Depue and Monroe 1979).

A number of theoretical approaches have been developed which attempt to explain the supposed aetiological effect of stress in depression (see e.g. Anisman and Zacharko 1982; Depue 1979). However, the definition of "stress" in relation to human studies remains a topic of endless debate (e.g. Anisman and Zacharko 1982), and a number of fundamental questions are unanswered, including the accuracy with which depressed individuals recall stressful life events (e.g. Lishman 1972), the possibility that stress may simply provoke hospitalization in already depressed people (e.g. Hudgens et al. 1967), and the provocative thought that the life style of depressives may be responsible for many of the stressses they experience (e.g. Beck and Harrison 1982). Indeed, a causal relationship between stress and depression, as opposed to a statistical association, has still not been conclusively demonstrated (Tennant et al. 1981). Assessment of the chronic intermittent stress model must therefore await further clarification of the relationship between stress and depression in people.

16. Separation models

For many authors (e.g. Everitt and Keverne 1979; Howard et al. 1981), the only worthwhile animal models of depression are those involving separation phenomena in non-human primates; the evolutionary proximity of primate species seems to afford intuitive insights into their behaviour which are lacking in less closely related animals. In fact, separation phenomena of protest followed by despair are present to some extent in many species, including cats, dogs, rodents and precocial birds (reviewed by Katz 1981a; McKinney and Bunney 1969).

Infant monkeys respond to maternal separation by an initial stage of "protest", characterized by agitation, sleeplessness, distress calls and screaming, followed after 1 or 2 days by "despair", characterized by a decrease in activity, appetite, play and social interaction, and the assumption of a hunched posture and "sad" facial expression (Hinde et al. 1978; Kaufman and Rosenblum 1967; McKinney and Bunney 1969; Reite et al. 1981; Suomi et al. 1976). The nature of the separation response is sensitive to the environment in which the experiments are carried out, however (Hinde and McGinnis 1977; Kaufman and Stynes 1978; Reite et al. 1981; Suomi 1976), and the incidence of "depressive" behaviours may in some experiments be as low as 15% (Lewis et al. 1976). Similar phenomena are also observed when group-reared animals are isolated from their peers (Bowden and McKinney 1972; Kraemer and McKinney 1979; Suomi et al. 1970). In a recent study it was observed that "depressive" responses during the "despair" phase could be predicted from the size of the elevation of serum cortisol during the "protest" phase (Higley et al. 1982).

Only three published studies have attempted to use antidepressant treatments to modify primate separation behaviour. Chronic DMI has been found to increase social contact and decrease distress vocalization and self-oriented behaviours in maternally-separated infant macaques (Hrdina et al. 1979). Similarly, chronic imipramine was found to decrease self-clasping in peer-separated infant rhesus monkeys, whilst acute treatment had the opposite effect; other separation-induced behavioural changes were

unaffected by imipramine (Suomi et al. 1978). A partial response to ECS in isolated rhesus monkeys has also been reported (Lewis and McKinney 1976). Trifluoperazine, amphetamine and diazepam were not found to affect responses to social isolated in chimpanzees (Menzel et al. 1963; Turner et al. 1969), but some therapeutic effects of chlorpromazine were seen in rhesus monkeys (McKinney et al. 1973). It should be added that although antidepressant drugs are frequently used in childhood depression, there is a conspicuous absence of methodologically sound studies demonstrating their efficacy (Kashani et al. 1981; Pearce 1981).

The primate separation response shows a marked similarity to the state of "anaclitic depression", first described by Spitz (1946) and Robertson and Bowlby (1952); institutionalized children showed the same sequence of protest (agitation, crying, insomnia, and oral stereotypies) followed in approximately 15–20% of cases by despair (retardation, self-clasping, withdrawal from social contact and an increase in the likelihood of succumbing to disease). However, insufficient studies employing diagnostic criteria (Kashani et al. 1981; Poznanski 1982) have been carried out to assess the claim that in children "the sine qua non in acute depressive reactions is the sudden loss of a love object" (McKnew and Cytryn 1973), which obviously has a bearing on the face validity of the separation model.

Furthermore, no consensus exists as to the relationship between infantile anaclitic depression and depression in adults (Ainsworth 1976; Bowlby 1976; Schulterbrandt and Raskin 1977); consequently, the construct validity of the separation model is difficult to assess, despite the apparent homology between primate "depression" and anaclitic depression. Even the assumption that separation from a loved one is a significant cause of adult depression has been questioned; the incidence of clinical depression following bereavement may be as low as 5% (Parkes 1972), and in the case of marital breakdown, it has not been established whether separation precipitates depression, or conversely, whether a prior depression in one partner was the cause of separation (Briscoe and Smith 1975). Thus, the theoretical formulation of depression as a phase of the protest-despair cycle, which is assumed by this model, is at best tenuous at present.

17. Incentive disengagement

A common feature of all of the four stress-based models described above is a biphasic response – activation by acute stress, superceded eventually by passiveness, the time course varying between models. Klinger et al. (1974) have observed that in rats trained in a runway for food rewards, and then switched to non-reward (extinction), non-rewarded trials were followed for the 1st week by heightened locomotor activity, but for the next few days, non-rewarded trials were followed by a reduction in locomotor activity below control levels. It was hypothesized that this "incentive" disengagement" cycle of invigoration followed by depression is characteristic of the period following the loss of a significant source of reinforcement (Klinger 1975); the response to separation in primates, discussed above, would be a special case of this more general mechanism.

The "incentive disengagement" theory can potentially explain a number of features of depression, including the autonomous course of many depressions. Autonomy is perhaps the single most perplexing characteristic of depression, yet most theories are concerned primarily with the aetiology of depression, and do not address the issue of its course. As the theory has attracted little attention in the research literature, and in particular, as there has been only a single relevant animal experiment, the theory will not be discussed in detail here. However, it is noted that the model has potential construct validity, despite having minimal face validity and no predictive validity.

18. Intra-cranial self-stimulation

In several of the models already described, one important effect of the experimental manipulation has been a decrease in the performance of rewarded behaviours (e.g. models 13, 15, 16). A number of recent experiments have attempted to investigate directly the brain systems which mediate reward, by studying brain stimulation reward in animals implanted with intracranial self-stimulation (ICSS) electrodes. Three such paradigms have been found that ICSS rates were reduced, and the threshold for brain stimulation reward was elevated, for a period of weeks following withdrawal from chronic amphetamine treatment (Barrett and White 1980; Kokkinidis and Zacharko 1980; Leith and Barrett 1976, 1980; Simpson and Annau 1977). This effect was alleviated by 2 days of imipramine or amitriptyline treatment, and with continued treatment, normal responding was restored (Kokkinidis et al. 1980). The effects of other agents have not been studied in this model. A second model utilizes the depression of ICSS produced by a lesion of the internal capsule, in the region of the telencephalic-diencephalic border; the deficit was alleviated by subchronic (5–9 days) treatment with tricyclics (impramine, amitriptyline, DMI, protriptyline) MAOIs (tranylcypromine, iproniazid) and atypical antidepressants (maprotiline, mianserin, zimelidine, nomifensine, nisoxetine). Morphine, which may have antidepressant properties (Emrich 1982) was also effective; diazepam, yohimbine, propranolol and "other non-antipressants" were not (Cornfeldt et al. 1982; Szewczak et al. 1982). In a third paradigm, brain stimulation reward is studied without any prior treatment. Wauquier (1976) reported that acute antidepressant treatment prolonged lever pressing for brain stimulation reward in a progressive ratio reinforcement schedule (i.e. one in which more and more responses are required for each successive reward), but these results could not be replicated (Binks et al. 1979). However, it has been found that sensitivity to brain stimulation reward was increased in "normal" rats by chronic (2 weeks) administration of DMI (Fibiger and Phillips 1981). By contrast, amphetamine has been found to decrease ICSS threshold on acute administration, but with chronic treatment, tolerance develops to this effect (Leith and Barrett 1976, 1980).

The first two of these paradigms can claim face validity, since a decrease in the ability to experience pleasure may be the single most important symptom of endogenomorphic depression (American Psychiatric Association 1982; Klein 1974; Nelson and Charney 1981). Additionally, in the case of post-amphetamine depression of ICSS, there is an obvious parallel with the depressions which frequently follow the cessation of chronic amphetamine use (Watson et al. 1972; Schick et al. 1973). These parallels depend on the assumption that the changes in self-stimulation behaviour are brought about by a change in the rewarding value of the

Table 2. Assessment of the models against validating criteria

Models	Responsive to antidepressants	Wide range tested	No false positives	No false negatives	Correlation of potencies	Time course	Similarity of symptoms	Coherence of symptoms	No dissimilarities	Specificity to depression	Clear interpretation of model	Clear interpretation of modelled	Homology	Empirical relationship to depression	Theoretical relationship to depression	Summary P	Summary F	Summary C	Total
1. Muricide	+	++	−	−?	−?											+			1
2. Yohimbine (mice)	+	++	=	−	−														0
3. Yohimbine (dogs)	+	+	+?	+												++			2
4. Dopa	+	+	−	=															0
5. Kindling	+		−	=															0
6. Reserpine	+	++	−	=	+?	−	+		−										0
7. Amphetamine	+	+	−	=		−	−												0
8. 5-HTP	+	+	−	−		−	+												0
9. Bulbectomy	+	++	−	−		?	++	?		?						+	+		2
10. Isolation	+	++	+?	+	+?	−	+			−						+++			3
11. Exhaustion	+					+	+									+	+		2
12. Rhythms	+	+	+	+?		+	+									++	+		3
13. Helplessness	+	++	+	+		+	++	−?	−	−	+?	+?	+?	?	?	++	+	+	4
14. 'Despair'	+	++	?	−?	+	+?										++	+		3
15. Chronic stress	+	++		+	−	+	++	+		−	+			?		++	++	+	5
16. Separation	+					+	++	+	−		+	+	+	?	?	+	+	++	4
17. Disengement							+				+	+	+	+?	+		+	+	2
18. ICSS	+	+	+?	+		+				+	+	+?	+?	+?	+	++	+	++	5

The models are listed (under abbreviated titles) in the other in which they appear in the text. The main body of the table estimates the extent to which a model meets each criterion (+ or ++, model does well; − or =, model does badly). The summary columns on the right estimate predictive (P), face (F) and construct (C) validity on a 4-point scale (blank, +, ++, +++); these scores are summed to give a grand total at the far right.

brain-stimulation, rather than by non-specific sedative or other motor effects. There exist a number of "rate-free" paradigms, in which these two factors may be dissociated (Liebman 1983), but unfortunately, they have not yet been employed in the models under consideration. However, whilst non-specific factors might well be responsible for changes in ICSS rates, this is less likely in the case of the reported changes in ICSS thresholds (Leith and Barrett 1976, 1980; Barrett and White 1980; Fibiger and Phillips 1981).

The ICSS models also have a degree of construct validity. ICSS appears to be controlled by many of the factors which control responding for natural rewards. For example, although the precise effects vary from electrode to electrode (e.g. Gallistel and Beagley 1971), ICSS rates may be increased by food deprivation or by a variety of hormonal manipulations (e.g. Olds 1958), and decreased by pre-loading with food or water (e.g. Hoebel and Teitelbaum 1962). These and other parallels indicate that brain stimulation reward works by activating neural systems which mediate natural rewards (Hoebel 1976). Homology between brain stimulation reward and positive reinforcement in people is suggested by the observation that stimulation of electrodes implanted in medial forebrain sites has been found to evoke pleasurable sensations in human subjects (Heath 1963; Heath et al. 1968; Valenstein 1973), though a variety of other reasons for stimulating, such as curiosity, are also reported (Sem-Jacobsen 1976; Valenstein 1973)

The hypothesis that depression results from a reduction in the activity of reward systems is central to a number of theories of depression (Costello 1972; Ferster 1973; Lewinsohn 1974; Stein 1962). As predicted by all of these theories, there is strong support for the hypothesis that depression is associated with a low frequency of positive reinforcement, particularly social reinforcement (Blaney 1977; Lewinsohn et al. 1979). However, the direction of causality has not yet been established.

Discussion

Information on the validity of each of the 18 models reviewed is summarized in Table 2. In the main body of the table, judgements of validity (+) or invalidity (−) are made on each of the 15 criteria (five for each type of validation procedure) outlined in the Introduction. The four columns at the right of the table offer a summary estimate of the current status of each model, using 4-point scales (0 to +++) for each validation procedure, and a grand total (out of 9). The models which score highest are the self-stimulation (5), chronic stress (5), separation (4) and learned

Table 3. Overall assessment

Model	Validity		
	Predictive	Face	Construct
Group 1 (Good?)			
14. 'Behavioural despair'	++	+	
15. Chronic stress	++	++	+
16. Separation	+	++	+
18. Self-stimulation	++	+	++
Group 2 (Interesting)			
3. Yohimbine (dogs)	++		
10. Chronic isolation	+++		
11. Exhaustion stress	+	+	
12. Circadian rhythms	++	+	
17. Incentive disengagement		+	
Group 3 (Problematic)			
1. Muricide	+		
9. Olfactory bulbectomy	+	+	
13. Learned helplessness	++	+	+
Group 4 (Poor)			
2. Yohimbine (mice)			
4. Dopa potentiation			
5. Kindling			
6. Reserpine reversal			
7. Amphetamine potentiation			
8. 5-HTP reversal			

helplessness (4) models; the ad hoc nature of the scales should, of course be borne in mind.

In Table 3, the models are divided into four groups. Group 1 contains those models which score well on the validating criteria, and have few or no invalidating characteristics. Group 2 contains potentially valid models which have been the subject of limited research. Potentially serious questions have been raised concerning the validity of models in group 3; these models may still be useful, but should be treated with caution. The models in group 4 appear to have little to recommend them as animal models of depression. This of itself does not necessarily render them unsuitable as drug screening tests, since models and screening tests are assessed according to different criteria (Reference Note). It should be noted that all of the traditional models fall into groups 3 (questionable) and 4 (probably invalid), whereas the two models which appear to have the highest overall validity are among the most recent.

The models in groups 1 and 3 are those which (i) have been relatively extensively researched, and (ii) are not clearly invalid. Two of these, olfactory bulbectomy and muricide, as well as the social isolation model in group 2, appear to model agitated depression. The other five models in groups 1 and 3 model retarded depression. These latter are closely related. Four of these models – separation, helplessness, behavioural despair and chronic stress – involve a biphasic activation/inhibition cycle, which has been proposed as the general form of the response to prolonged stress (Engel 1962; Burchfield 1979); in three of them – separation, helplessness and chronic stress – the inhibitory phase has been shown to be associated with a decrease in positively reinforced behaviour, which characterizes the self-stimulation models.

The limitations of a theory which treats depression as a response to stress have already been noted; at best, stressful life events appear to account for only 25–30% of the variability in the incidence of depression (Akiskal 1979; Brown et al. 1973). Increasingly, theories of depression emphasize multidimensional causality, with stress as only one among serveral etiological factors; in these theories, the underactivity of a central reward pathway has been proposed as a "final common path" to which the diverse precipitants lead (e.g. Akiskal and McKinney 1973; Akiskal 1979; Lewinsohn et al. 1979). It is therefore possible that stress-based models might prove to be valid as models of a state of depression, even if they should turn out to be wide of the mark as models of its aetiology.

The object of this paper has been to apply multiple criteria to assess the validity of animal models of depression. It is clear that no one method of validation is sufficient for this purpose; whilst predictive validation and face validation suffer from a number of empirical drawbacks (Reference Note), construct validation rests on a theory of the nature of depression, and current theories of depression are not such as to inspire confidencce in their eventual vindication. In the final analysis, an animal model is a theory of interspecific homology and, like all theories, must be judged ultimately on its power to generate testable hypotheses about the human condition being modelled.

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Reference Note

Some of the theoretical issues in this paper have been discussed at greater length in an unpublished manuscript, which is available on request.

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