Br. J. clin. Pharmac. (1977), **4**, 57S–68S

REVIEW OF THE PHARMACOLOGY OF EXISTING ANTIDEPRESSANTS

P.S.J. SPENCER

Welsh School of Pharmacy, University of Wales Institute of Science and Technology, Cardiff, UK

Introduction

It is almost 20 years since Geigy introduced the archtype antidepressant imipramine. It is remarkable—perhaps even a little alarming–that this symposium should devote itself to describing yet another new antidepressant. The pharmacotherapy of depression today, however, remains significantly less than ideal, and there is a clear need for new antidepressant drugs.

With his description of the clinical effects of imipramine, Kuhn (1958) anticipated that other antidepressants would be found in due course, and that some of these might be suitable for treating specific subgroups of the depressive disorders. It is not possible, however, to define precisely or classify individual types of depression, so that rational selection of the most appropriate drug for a given patient has not been feasible. The rank order of depressive treatments, with electroconvulsive therapy (ECT) coming first, followed successively by the tricyclic, antidepressants monoamine oxidase (MAO) inhibitors and placebo (Klerman, 1971) reflects their relative lack of precision or specificity as methods of treatment.

The purpose of this first paper is to present a general review of those agents currently available to treat depression, to discuss their pharmacological properties and the methods available for the detection and evaluation of new antidepressant agents. Subsequent papers in this symposium will describe the pharmacological properties of nomifensine. Taken together, the reader should be able to assess the scientific and possible clinical impact of nomifensine as an antidepressant drug.

To find and evaluate new drugs of any type, the experimental pharmacologist needs to know two things: first, he must have a clear concept or working hypothesis of the aetiology of the disease he seeks to treat. Second, he requires as tools, one or more existing clinically useful drugs, possibly with a known pharmacological profile which can be related to the pathophysiological changes associated with the target clinical condition. Together, these data enable the pharmacologist to formulate a series of model conditions or illnesses in animals with which the effects of new potential drugs can be evaluated (Spencer, 1976).

Today's ever-increasing list of antidepressant drugs is not really a testament to our knowledge of depression, nor to the skill of the pharmacologist. Instead, their diverse pharmacological properties, coupled with the remaining inadequacies of the pharmacotherapy of depression, are simply a reflection of the poor understanding of the disease itself, and the poor baseline data from which the experimental pharmacologist has had to work.

History of the pharmacotherapy of depression

For many years, drugs such as the barbiturates, chloral hydrate and the bromides, were used empirically to treat the insomnia, anxiety, agitation and related features of depression. In the late 1930s, a number of amphetamine-like agents were introduced for the symptomatic relief of the milder depressive states (Alexander, 1953), and ECT was introduced in 1938 for selected cases of severe depression (Kalinowsky & Hoch, 1961). With the arrival of the phenothiazines and reserpine in the early 1950s came attempts to alleviate agitation, insomnia, anxiety and restlessness with these agents (Denber & Bird, 1956), but the consensus was that they were relatively ineffective against the 'core' symptoms of depressive illness.

In 1957, imipramine (the first tricyclic antidepressant) and iproniazid (the first MAO inhibitor) were introduced almost simultaneously. Animal studies with imipramine and a number of analogues, all closely related chemically to chlorpromazine, had shown them to be weakly acting neuroleptics. They were therefore examined for antipsychotic activity in man. Although significantly inferior to chlorpromazine as a neuroleptic, Kuhn recognized an improvement in the depressive overlay of a number of schizophrenic patients receiving imipramine. A subsequent specific clinical trial confirmed the presence of antidepressant activity, and imipramine was officially introduced in 1958 (Kuhn, 1957; 1958).

Iproniazid was originally studied in 1951 for activity against tuberculosis but it was observed that patient improvement exceeded the mycobacteriological or pathological improvement. Iproniazid's 'beneficial' effects were attributed to central stimulant properties and it was withdrawn as a

tuberculostatic agent. In 1952, Zeller *et al.* showed that iproniazid was an inhibitor of mammalian MAO (Zeller *et al.*, 1952). With growing awareness of the significance of this enzyme in the metabolic pathways of monoamines generally (and catecholamines in particular), Kline (1958) carried out successful trials with iproniazid in depressed patients, whereupon the drug was introduced for general psychiatric use.

Subsequently, Sulser *et al.* (1962) showed that the depressive syndrome in rodents produced by the acute administration of reserpine was abolished by the tricyclic agents imipramine and desipramine. In fact, the reserpine model was quickly recognised to be sensitive to MAO inhibitors and amphetamines (Askew, 1963; Spencer, 1967). With the availability of a drug-sensitive model for the depressive condition in experimental animals, further antidepressant agents quickly became available. The majority of the newer antidepressants have been close chemical derivatives or analogues of the earlier ones, but the so-called second generation tricyclic antidepressants, such as clomipramine and maprotiline, have more specific properties (Iversen, 1974; Waldmeier *et al.*, 1975). Also, MAO inhibition has been observed in a number of non-hydrazine structures—for example, pargyline and tranylcypromine. Some of the more recent additions to the antidepressant armoury—for example, iprindole, viloxazine, mianserin and nomifensine—may elicit profiles of pharmacological activity somewhat different from the two main groups, the tricyclic antidepressants and MAO inhibitors. What can be said by way of a general review is this: with the exception of the lithium salts (lithium is more of a mood stabilizer than an antidepressant), all clinically useful antidepressants interact significantly with the metabolism and function of one or more biogenic amines—dopamine (DA), noradrenaline (NA) and 5-hydroxytryptamine (5-HT)—to increase and/or prolong their availability at postsynaptic receptor sites in the CNS. Current views on the biochemical lesion(s) underlying the symptoms of depressive illness suggest that there is a relative deficiency of one or more of the biogenic amines (DA, NA and/or 5-HT), and it seems likely (and logical) that new antidepressant agents will pursue in various ways, the process of promoting the function of these amines at central sites.

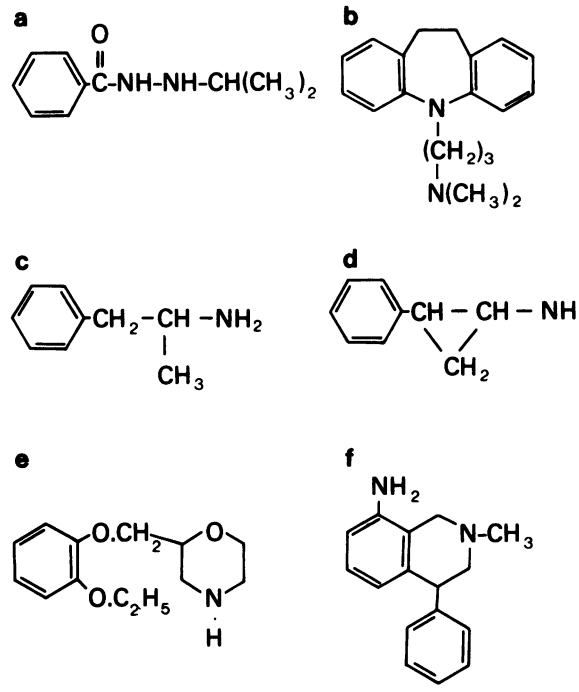

Figure 1 Chemical structures of representative antidepressant drugs. a, Iproniazid (MAO inhibitor); b, imipramine (membrane-pump inhibitor, MPI); c, amphetamine; d, tranylcypromine (MAO inhibitor); e, viloxazine (MPI); f, nomifensine (MPI and/or stimulant).

Classification of existing antidepressant drugs

Although antidepressant drugs may be subdivided into groups according to the types of depression for which they are most appropriately used, it is far more acceptable to classify them according to their principal pharmacological properties. One such classification is set out below in Table 1.

This classification is based on the main or principal pharmacological property of each drug. This is not to suggest that these agents are devoid of other potentially useful (or harmful) contributing properties; indeed, these secondary properties may well determine the further subclassifications. Figure 1 illustrates the structures of typical agents in each main class.

Many authors would not include the centrally acting sympathomimetics amongst such a classification, but this is because the amphetamines have potentially dangerous side-effects rather than any lack of antidepressant action.

Previous authors have described the imipramine-like drugs simply as 'tricyclics', but this is to deny the inclusion of chemically dissimilar drugs that are pharmacologically related (for example, viloxazine). At the same time, one should recognize that not all tricyclics resemble imipramine in interfering with physiological re-uptake of transmitter amines (for example, iprindole). Accordingly, it is more appropriate to name or classify those agents whose primary pharmacological action is to interfere with re-uptake, as 'membrane pump inhibitors'. The

Table 1 A classification of antidepressant and related drugs

Amphetamine-related sympathomimetic stimulants:		
(a)	Releasers of non-granular amine stores	(+)-amphetamine methamphetamine ephedrine cocaine
(b)	Releasers of granular and non-granular amine stores	methylphenidate phenmetrazine fencamfamin
(c)	Agents exerting postsynaptic agonist action at dopamine receptors	apomorphine piribedil
(d)	Agents acting by inhibiting re-uptake of DA (and NA)	nomifensine?
MAO inhibitors:		
(a)	Hydrazines with acute stimulant effects	iproniazid isocarboxazid pheniprazine phenelzine
	without acute stimulant effects	nialamide
(b)	Non-hydrazines with acute stimulant effects	tranylcypromine α-ethyltryptamine
	without acute stimulant effects	pargyline
Membrane-pump inhibitors:		
(a)	Tricyclics: first generation (tertiary amines)	imipramine amitriptyline
	(secondary amines)	desipramine nortriptyline protriptyline
	second generation agents	clomipramine maprotiline
(b)	Non-tricyclics	viloxazine nomifensine?
Naturally occurring agents:		
(a)	Amino acid precursors of transmitter amines:	L-3,4-dihydroxyphenylalanine L-tryptophan L-5-hydroxytryptophan
(b)	Lithium salts	for example, lithium carbonate
Miscellaneous agents:		
	Relatively recent synthetic agents	iprindole mianserin tandamine

Not all agents are practical antidepressants, nor is the Table intended to be exhaustive. Agents have been classified according to the major pharmacological property believed to be responsible for (where applicable) the observed clinical activity.

consensus is that this property (applied to re-uptake of NA and/or 5-HT, and possibly DA) is the basis of their antidepressant action in man. Until such time as this is categorically disproved, their description as membrane pump inhibitors seems appropriate.

The MAO inhibitors are subdivided, not only according to structure (hydrazine or non-hydrazine) but also according to the presence or absence of inherent amphetamine-like activity. Thus high doses of iproniazid, pheniprazine, phenelzine and tranylcypromine directly increase motor activity, whereas nialamide and pargyline do not. As the subgroups (or isoenzymes) of the enzyme MAO become better known, then one should expect new MAO inhibitors whose actions are directed towards individual isoenzymes.

Many authors argue that lithium salts are more 'mood stabilizers' than antidepressants, but they are correctly included here because of their undoubted therapeutic effect in bipolar or manic-depressive states.

Finally, the precursors of the transmitter amines dihydroxyphenylalanine (DOPA), tryptophan (TP) and 5-hydroxytryptophan (5-HT) are included, not because they have demonstrated unequivocal antidepressant activity in man but instead to signify the widespread concern for these agents and their amines in the aetiology of depression. The equivocal clinical results with these agents might largely be explained on their relative failure to cross the blood-brain barrier and gain access to central neurones before being decarboxylated and rendered sensitive in the amine condition to biological inactivation. The simultaneous administration of an MAO inhibitor or a peripherally acting decarboxylase inhibitor certainly renders these amino acids pharmacologically more useful in animal studies.

Biochemical basis of depressive illness

The vast majority of psychotropic or psychoactive drugs are not pharmacologically specific, either in their locus or site of action, nor in their actions. Instead, they usually possess several quite distinct properties, one or more of which may contribute to their useful (or adverse) clinical effects.

Therefore in describing some of the more important pharmacological actions of the existing antidepressants, and (further) in attempting to outline some of the techniques used in their detection and evaluation in laboratory animals, one must lay some pathophysiological foundation for depression, on which (theoretically at least) the therapeutic action may be based. A brief consideration of the biochemical changes underlying (or perhaps merely accompanying) depressive illness is therefore appropriate.

Alterations in man's affective state induced by environmental events are a normal and familiar occurrence. The biochemical changes of clinical depression are therefore unlikely to be qualitatively different (Ridges, 1975); instead, they are likely to be quantitative changes, perhaps highly localized within the brain, reflecting merely the exaggerated intensity or duration of depressive reaction which is typical of the clinical condition.

A working hypothesis in depression is orientated towards the lack of effective levels of NA and/or 5-HT at central neuronal synapses. With the contents of this present symposium, a major or at least a significant role for DA should also be considered.

Brain amines have many roles in relation to mammalian behaviour (Bryson, 1971; Baldessarini, 1972), including the states of consciousness and sleep, reaction to stress (including pain) and feeding. In turn, the vast majority of psychotropic drugs can be shown to affect in the brain one or more of the following agents: acetylcholine (ACh), DA, NA and 5-HT.

The impulse to study brain amines in relation to depressive illness was provided by pharmacological observations made in the 1950s with the widespread use of reserpine in psychiatry and hypertension. Reserpine induced depression in about 15% of patients (Harris, 1957) and it was possible that this side-effect of reserpine (like the beneficial effects) was due to a substantial depletion of brain biogenic amines. At the same time, it was shown that the MAO inhibitor, iproniazid, alleviated some forms of depression possibly through its known ability to raise tissue monoamine levels. During the ensuing years, DA, NA, 5-HT and ACh have all been investigated in relation to depression. Rosenblatt *et al.* (1960) were amongst the first to suggest that changes in catecholamine or indoleamine function might be involved in the appearance, as well as the abolition, of depression. A functional deficit of brain DA or NA was clearly behind the attempt by Pare & Sandler (1959) to treat depression with the catecholamine precursor DOPA, and later the pharmacological triangle was completed by the demonstration that the depressive syndrome produced by reserpine in laboratory animals could be abolished by treatment with the antidepressants imipramine (Sulser *et al.*, 1962), (+)-amphetamine (Askew, 1963) and the MAO inhibitors (Spencer, 1967).

Substantial increases in our knowledge of the biochemical pathways of transmitter amines were made in the early 1960s, and a brief summary of the position today is given in Figure 2. The effect of antidepressant drugs on brain amines has been effectively reviewed by Iversen (1974).

Schildkraut's (1965) classic catecholamine hypothesis of affective disorders proposed that "some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly

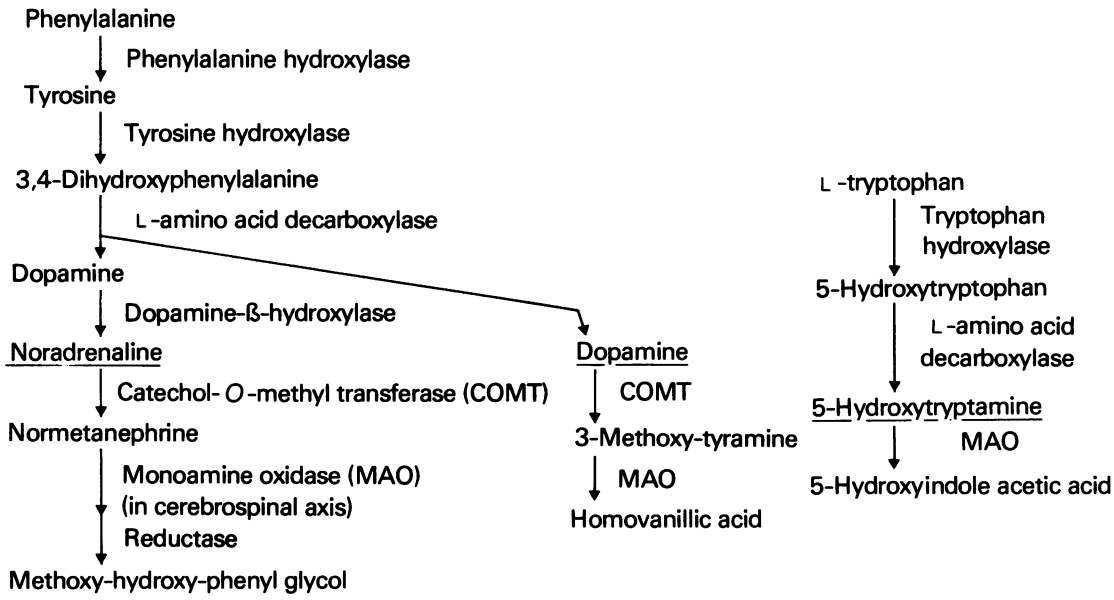

Figure 2 Brief review of the major metabolic pathways of NA, DA, and 5-HT. Transmitter amines are underlined; major breakdown products are listed, together with their normal abbreviations.

NA at functionally important adrenergic receptor sites in the brain. Elation conversely may be associated with an excess of such amines".

Yet reserpine, which it might be argued was father to this hypothesis, also depletes the brain of 5-HT, and it was reasonable to add a second hypothesis (Coppen, 1972) implicating a functional deficit of brain indoleamines.

Two major research strategies were then used to test the catecholamine and indoleamine hypotheses. The first might be called the 'precursor loading technique', since it involved the selective administration of precursor amino acids (for example L-DOPA, tryptophan and 5-hydroxytryptophan) and observing the therapeutic response. The second strategy involved the measuring of amine metabolites in the brains (post mortem) and body fluids of depressed patients.

Although by no means unequivocal, considerable therapeutic success has been observed by Coppen *et al.* (1972) and Prange *et al.* (1974) using the indoleamine precursor L-tryptophan, whereas attempts at treatment with the catecholamine precursor L-DOPA have been disappointing (Bunny *et al.*, 1972).

Measurement of biogenic amine metabolites in the tissues and body fluids of depressed individuals presents formidable methodological problems, especially the problem of determining precisely the source of the biochemical change detected. Shaw *et al.* (1967) and Bourne *et al.* (1968) showed that brain 5-HT levels of depressed suicides were reduced, whereas hind-brain 5-hydroxy indole acetic acid (5-HIAA) levels were also lower than in controls (dying from other causes). Yet Pare *et al.* (1969) found no changes in the NA levels of suicides. It has been shown that cerebrospinal fluid (CSF) levels of the acid end-products of amine metabolism (that is, 5-HIAA, 3-methoxy-4-hydroxyphenolglycol, homovanillic acid and VMA) may under certain circumstances reflect changes in the metabolism of the catecholamines and 5-HT in the brain. Most workers have shown 5-HIAA levels to be reduced (especially in unipolar depressives), whereas equivocal data have been obtained in studies of the catecholamine metabolites (Ridges, 1975).

It might be stated therefore that there is considerable evidence for a role of lowered 5-HT levels in depression, whereas the relationship of catecholamines to depression is a more controversial topic.

A third amine hypothesis, the so-called "permissive amine hypothesis of affective disorders" (Prange *et al.*, 1974) is perhaps more elegant and a better summary of existing data. Briefly, it states that central 5-HT deficiency may represent a *vulnerability* to affective

illness, and this predisposition may separate the depressive patient from the normal individual. Lowered catecholamines may then correlate with the depressive episode (but in this respect, there would be no difference between the clinical depressive and momentarily depressed normal individual. Schildkraut (1973) put it another way. Certain changes in biogenic amine metabolism (alterations in normetanephrine and MHPG excretion) may occur in association with changes in affective state, whereas other abnormalities in monoamine metabolism (as reflected by decreased 5-HIAA levels in the CSF) may represent enduring constitutional factors in some patients with affective disorders (see also Akiskal & McKinney, 1975).

We do know that both the catecholamines and indoleamines play significant roles in modulating the function of the medial forebrain bundle and the periventricular system, the neuroanatomical substrates of 'reward' and 'punishment', respectively. Biogenic amines are important transmitters in both areas. Disturbances in the functional level of biogenic amines, however caused, would disrupt the individual's ability to respond to reinforcement and to experience pleasure and consummatory reward, with the resultant impairment in psychomotor functions and biological drives (Stein, 1971).

Cyclic AMP is the second messenger for each of the amines DA, NA and 5-HT, receptor stimulation causing an activation of adenylate cyclase and cyclic AMP formation. Some psychotropic agents may attenuate the activity of phosphodiesterase, with much the same effects on cyclic AMP levels. The involvement of cyclic AMP in the affective disorders is currently under considerable investigation. Eccleston (1973) has shown that the production of cyclic AMP in CSF might be used as an index of the functional state of adrenergic neurones.

Finally, attention has been re-focused recently on the possible involvement of acetylcholine in depressive illness, particularly the functional balance between ACh and the catecholamines in the brain. It has been shown (Bogdanski *et al.*, 1961) that there is an excess of central cholinergic activity in reserpinised animals, whereas anticholinesterases may precipitate depression in manic depressives. The tricyclics such as imipramine do possess central anticholinergic activity (Domenjoz & Theobald, 1959), and will attenuate the activity of the centrally acting muscarinic agents tremorine and oxotremorine in rodents (Halliwell *et al.*, 1964; Spencer, 1966), although this is true also of centrally acting sympathomimetics (Spencer, 1965; 1966). The fact remains that we should not forget that raised central cholinergic function is consistent with depressive symptoms, and further work on the role of acetylcholine in the affective disorders is clearly indicated (see Janowsky *et al.*, 1972).

Methodology of the discovery and evaluation of antidepressant drugs

Because the aetiology of depressive illness is still poorly defined (and furthermore, because depression seems to be simply the final common path of several related affective disorders), it is inevitable that the experimental pharmacologist does not rely on any single technique or series of techniques in animals to evaluate new antidepressant drugs. The variety of pharmacological properties displayed by the existing classes of antidepressant agents will also ensure that the philosophy behind the procedures used will remain broad and largely uncommitted; individual groups of workers have their own views about the most appropriate collections of animal tests. Almost the only common theme amongst a vast array of animal tests used in the evaluation of new antidepressants is the fact that most data yield some information about the performance in the brain of one or more neuronal transmitters. This data in turn is an effective supporter of the various amine theories of the affective disorders.

Sequentially, industry-based pharmacological studies in animals might be subdivided into three main stages. These are: (1) detection of activity; (2) confirmation of activity, and determination of relative potency (comparisons with other agents, and attempts to elucidate mechanism(s) of action); (3) miscellaneous studies, including estimates of duration of effects; subacute and chronic properties (presence/absence of tachyphylaxis); and interactions with other drugs. The actual sequence of events will alter from drug to drug, and certainly differ between different laboratories. For psychotropic drugs generally—and antidepressant drugs in particular—the first stage usually consists of a series of tests, from which an initial neuropharmacological profile can be constructed. A decision to proceed further will depend more on the individual profile than the presence/absence of activity or level of activity in any individual test (Spencer, 1976).

The individual pharmacological procedures may be specific (to the detection and evaluation of antidepressants), or *general* (providing a wider range of information about a drug's neuropharmacological properties in general). The specific tests may be:

imitative: attempt made to make a 'true' model of depression, for example by the administration of reserpine or tetrabenazine (agents which produce depressive syndromes in a range of species).

empirical: over a number of years, novel drug–behaviour interactions have been observed which are specific to one class of drugs, yet the underlying mechanism of behavioural change bears no obvious resemblance to the clinical condition (an example, is the common ability of the amphetamines,

tricyclics and MAO inhibitors to potentiate the effects of the convulsant picrotoxin in rodents).

biochemical: in recent years, more emphasis has been placed on *in vitro* and *in vivo* biochemical studies (for example, the effects of drugs on the synthesis, storage and metabolism of transmitter substances).

When these procedures have been carried out—and they have certainly been carried out on nomifensine—a vast amount of experimental data will have been accumulated. The feedback of well documented, objective, clinical data is vital to the experimental pharmacologist if he is to attach importance and significance to the various common and unique features that exist in the neuropharmacological profiles of different antidepressant drugs.

Pharmacological properties of existing antidepressant drugs

Space does not permit a description of the pharmacological properties of all existing antidepressants, but it is necessary to help place the properties of nomifensine in perspective as a potential antidepressant. Consequently, it seemed appropriate to review the properties of the major drugs in each of the pharmacological classes listed previously—for example, the amphetamines (including methylphenidate), the MAO inhibitors, imipramine and second generation tricyclics, and viloxazine.

Amphetamine-like sympathomimetic stimulants

Amphetamine itself is no longer a practical antidepressant in man because of the many attendant adverse effects, but recent work on the site and mechanism of action of pharmacologically related stimulants does suggest that certain members of this group could prove to be clinically important antidepressants.

Amphetamine is a widely acting central nervous stimulant in all mammalian species. The most obvious effects on behaviour are increases in general activity and alertness (arousal), accompanied by appetite suppression and interference with body temperature control. In small animal experiments, amphetamine is a potent antagonist of the depressive syndromes produced by reserpine and the synthetic, shorter-acting tetrabenazine. Amphetamine also potentiates the effects of the convulsants, leptazol and picrotoxin, but against electroshock convulsions amphetamine enhances the effects of anticonvulsants such as barbiturates (in most other aspects, amphetamine is a potent antagonist of the pharmacological effects of the barbiturates). Against the tremorgenic-agent, oxotremorine, amphetamine markedly attenuates the hypothermia, but exerts only a weak antitremor effect. Amphetamine is antinociceptive in most analgesic tests, excluding the unmodified hot-plate test in rodents. Finally (and again typical of all drugs with a central sympathomimetic stimulant action), the effects of amphetamine are markedly potentiated in crowded animals.

(+)-Amphetamine is several times more potent than (-)-amphetamine. Other agents with qualitatively similar properties are methamphetamine, ephedrine, fencamfamin, phenmetrazine, pipradol, methylphenidate, apomorphine, piribedil, and, as will be demonstrated later in this symposium, nomifensine.

When rats are injected with amphetamine, the type of behaviour produced is dose dependent. Low doses (for example, 0.5–2.0 mg/kg) stimulate locomotor activity, whereas higher doses (5.0–10 mg/kg) produce a stereotyped pattern of behaviour. These dual effects are typical of all drugs in this series and differentiate them from other types of antidepressant drug. There is now conclusive evidence to show that amphetamine produces these effects primarily by the release of (and to some extent the inhibition of re-uptake of) DA and NA in the brain (see, for example, Fuxe & Ungerstedt, 1970; Glowinski, 1970; Van Rossum, 1970). The release of DA seems to be correlated with increases in locomotor activity and the appearance of stereotypic behaviour (Costa *et al.*, 1972; Thornberg & Moore, 1973), with mesolimbic DA release being associated with locomotor activity and nigrostriatal DA release being associated with stereotypic behaviour (Kelly *et al.*, 1975).

Recent work on the subcellular actions of these agents (see, for example, Sayers & Handley, 1973; Gerhards *et al.*, 1974; Kelly & Iversen, 1976) will enable the amphetamine-like stimulants to be subdivided into four groups:

(+)-Amphetamine, metamphetamine, ephedrine and cocaine. This group acts predominantly by the release of non-granular (reserpine-resistant) stores of DA (and NA) (Scheel-Krüger & Randrup, 1967).

Methylphenidate, phenmetrazine and fencamfamin. This group acts through the release of both granular and non-granular pools of catecholamines (Handley & Sayers, 1973).

Apomorphine and piribedil. These agents do not act through the release or potentiation of endogenous amines, but exert an agonist action directly at DA (and perhaps NA) postsynaptic receptors (Anden *et al.*, 1967).

Nomifensine. There is evidence that this agent exerts a dual action at DA and NA synapses in the brain, causing both a release of DA (Braestrup & Scheel-Krüger, 1976) and—perhaps much more important—an inhibition of the re-uptake of both DA and NA (Hunt *et al.*, 1974; Gerhards *et al.*, 1974). There seems

to be no effect on 5-HT re-uptake mechanisms (Samanin *et al.*, 1975). There is also some evidence for a direct agonist action on DA receptors by the hydroxylated metabolite of nomifensine (Costall *et al.*, 1975).

Further specific evidence for locus and mechanism of action of nomifensine is presented in later papers. It is already possible to say, however, that nomifensine has properties intermediate to those of amphetamine (predominantly a releaser of both catecholamines) and imipramine (predominantly an inhibitor of NA and 5-HT uptake). The neuropharmacological profile of nomifensine lies between these two extremes, and the combination of properties (release of DA with inhibition of uptake of both DA and NA) should provide a drug with interesting clinical properties.

MAO inhibitors

The MAO inhibitors comprise a rather heterogeneous collection of drugs which, as their name implies, are potent and effective inhibitors of the mitochondrial enzyme MAO. Although agents exist which produce a relatively short-acting, reversible inhibition of MAO (for example, the Harmala alkaloids), those agents in clinical use produce irreversible, and therefore long-lasting inhibition. In fact, on cessation of treatment, recovery of MAO activity parallels the synthesis of new enzyme. MAO is involved in the intracellular breakdown of the amines, DA, NA and 5-HT, its function being to control neuronal pools of these transmitters. It follows that inhibition of MAO is accompanied by an increase in tissue levels of all three amines. It is believed that antidepressant activity results from the spontaneous spilling over of these amines into the neuronal synapse, but it can also be argued that more amines are available for release by specific neuronal activity, particularly if previously amine synthesis and/or storage was impaired (for reviews, see Pletscher *et al.*, 1960; Pletscher, 1968; Costa & Sandler, 1972).

In small animals, MAO inhibitors do not increase locomotor activity, nor produce stereotypic behaviour or exhibit greater acute toxicity in crowded conditions, but these amphetamine-like effects are elicited by large doses of certain hydrazines (for example, iproniazid and pheniprazine) or tranylcypromine, and they precede the inhibition of MAO activity. Nialamide (hydrazine) and pargyline (non-hydrazine) are examples of MAO inhibitors which do not exhibit amphetamine-like activity. Thus, nialamide does not enhance leptazol convulsions (Spencer & Turner, 1968), nor effect electroshock convulsions, but does potentiate picrotoxin. There is only minimal antinociceptive activity, and nialamide does not antagonize either the tremor or hypothermia of tremorine (Spencer, 1965). All MAO inhibitors also enhance the behavioural effects of amphetamine-like stimulants and amino acid precursors of biogenic amines.

Bearing in mind the current views of the involvement of biogenic amines in depression, and the well-documented effects of MAO inhibitors on tissue stores of these amines, the concensus is that MAO inhibitors exert their antidepressant effects in man by increasing the amounts of catecholamines and/or 5-HT available at adrenergic and/or tryptaminergic receptor sites.

Apart from the mechanism of this effect, MAO inhibitors differ from the imipramine-like drugs in one other major aspect; MAO inhibitors also promote the effects in the brain of DA, a property not possessed by first and second generation tricyclics.

Imipramine and related tricyclic membrane-pump inhibitors

The original pharmacological evaluation of imipramine revealed a weakly acting central nervous depressant, structurally and pharmacologically similar to the phenothiazines (Grünthal, 1958). Thus, imipramine depresses spontaneous and induced animal behaviour, depresses body temperature and is antinociceptive in the less specific analgesic tests. It prevents amphetamine hypertoxicity in crowded conditions. In rodents, these effects are elicited at doses of about 50 mg/kg and above, a potency approximately 1/20th of that of chlorpromazine. After Kuhn's (1957; 1958) observations in man, attempts were made to find a pharmacological basis for its clinical antidepressant activity.

Sulser *et al.* (1962) and other workers showed that very much lower doses would prevent the depressive effects of reserpine in rodents. The subsequent studies at these lower doses were reviewed by Gyermek (1966). In addition to its anti-reserpine and anti-tetrabenazine effects, low doses of imipramine (3–15 mg/kg) will enhance the motor effects of amphetamine; potentiate yohimbine (Halliwell *et al.*, 1964); and inhibit tremorine- and oxotremorine-induced tremor and hypothermia; in this last respect imipramine's activity is greater against the hypothermia, so that it more closely resembles the centrally acting sympathomimetic stimulants than the anticholinergics (Spencer, 1965; 1966).

The pharmacological effects of these lower doses of imipramine are largely, if not wholly, explained by their ability to inhibit the presynaptic uptake of transmitter amines, thereby enhancing their postsynaptic activity (for reviews, see Glowinski & Axelrod, 1966; Iversen, 1974). Activity is most marked against NA and 5-HT uptake, and relatively weak against DA. Imipramine is a tertiary amine, and the secondary amine (metabolite), desipramine, shows greater potency against NA uptake. This is true of all secondary amines. Some second generation tricyclics

have been introduced with greater specificity of action, clomipramine being the most potent 5-HT uptake inhibitor, whereas maprotiline is an almost 'pure' inhibitor of NA uptake (Waldmeier *et al.*, 1976).

Imipramine (and the majority of its tricyclic analogues) possesses significant antimuscarinic activity, peripherally and centrally, which is an acknowledged source of certain tricyclic side-effects. The value of this antimuscarinic property in combating depressive illness has been only partially unexplored (Blackwell *et al.*, 1972), although in animal neuropharmacological tests this effect is not conspicuous (Spencer, 1965; 1966).

Benesova & Nahunek (1971) have attempted to relate the pharmacological effects of the tricyclics with observed clinical actions, dividing the clinical response into three temporal phases:

Phase 1. Psychomotor activation or increase in drive seems to correlate with inhibition of NA uptake. Effects are most marked with desipramine, protriptyline and maprotiline.

Phase 2. Brightening of mood in depressed patients, seems to correlate with increased 5-HT function. Effects are marked with imipramine, amitriptyline and clomipramine.

Phase 3. Relief of anxiety, tranquillizing action, effect most readily elicited by amitriptyline and certain neuroleptics Benesova & Nahunek (1971) have queried whether this last effect is related to central atropine-like effects.

In summary, a variety of *in vivo* and *in vitro* studies show that imipramine and its close analogues are able to potentiate the central (and peripheral) effects of NA and/or 5-HT, that this is their overwhelming pharmacological property, and seems to correlate with our current knowledge of the biochemical basis of depressive illness. The tricyclics do not stimulate NA and 5-HT receptors, nor do they release endogenous amines; at high doses they may even exert a postsynaptic receptor-blocking action, reminiscent of the neuroleptics.

Viloxazine

Viloxazine was first synthesized in 1967, and its pharmacology briefly reported in 1972 (Mallion *et al.*, 1972) and 1975 (Greenwood, 1975). Brief reports of its clinical pharmacological activity have been given by Kirby & Turner (1974), Bayliss & Duncan (1974) and Turner *et al.* (1975).

Although structurally different to the imipramine-like drugs, viloxazine possesses a number of pharmacological similarities. Thus, viloxazine reverses an established reserpine depressive effect, as well as preventing the onset of reserpine effects by previous treatment. Viloxazine likewise antagonises the effects of tetrabenazine.

Like imipramine, viloxazine does not exhibit increased toxicity in crowded conditions; alone, it produces generally CNS depressant effects; protects mice against electro-shock convulsions; potentiates the effects of amphetamine-like stimulants; and antagonises the effects of oxotremorine. Viloxazine is a potent inhibitor of NA re-uptake, with minimal activity against 5-HT uptake.

Viloxazine also exhibits a number of differences from the imipramine group. Thus, it possesses no anticholinergic activity, and causes moderate transient increases in the brain levels of all three amines, DA, NA and 5-HT. On the electroencephalogram (EEG) of the rat, viloxazine produces an arousal effect more reminiscent of the amphetamines, yet in the septal rat preparation viloxazine affords significant protection against the typical violent aggressive episodes, a feature reminiscent of the benzodiazepines (minor tranquillizers generally) and not found in any other antidepressant group (Greenwood, 1975).

The long-term importance of viloxazine as a clinically useful antidepressant remains to be confirmed. From animal studies, it has a pharmacological profile reminiscent of both the amphetamines and the imipramines with additionally some evidence of minor tranquillizer properties. Viloxazine epitomises the earlier suggestion that new drugs should go forward for clinical evaluation, not because of presence/absence of activity in one or two specific tests of antidepressant activity, but because of an interesting and unique profile of neuropharmacological activity.

Summary

Clear-cut differences and similarities can be discerned between each major class of antidepressant. Their major common property is to enhance in the brain the functional activity of one or more of the biogenic amines DA, NA and 5-HT. The importance of the coexistence of central anticholinergic activity (imipramine-like drugs) or anxiolytic activity (viloxazine) remains to be explored further. The most appropriate way of summarizing the differences and similarities of their pharmacology is to diagrammatize their neuropharmacological profiles, as described by a few pertinent pharmacological techniques (Figure 3)

General conclusions

Existing antidepressant drugs share just one major property: the ability (by a variety of mechanisms, admittedly) to enhance the functional state in the

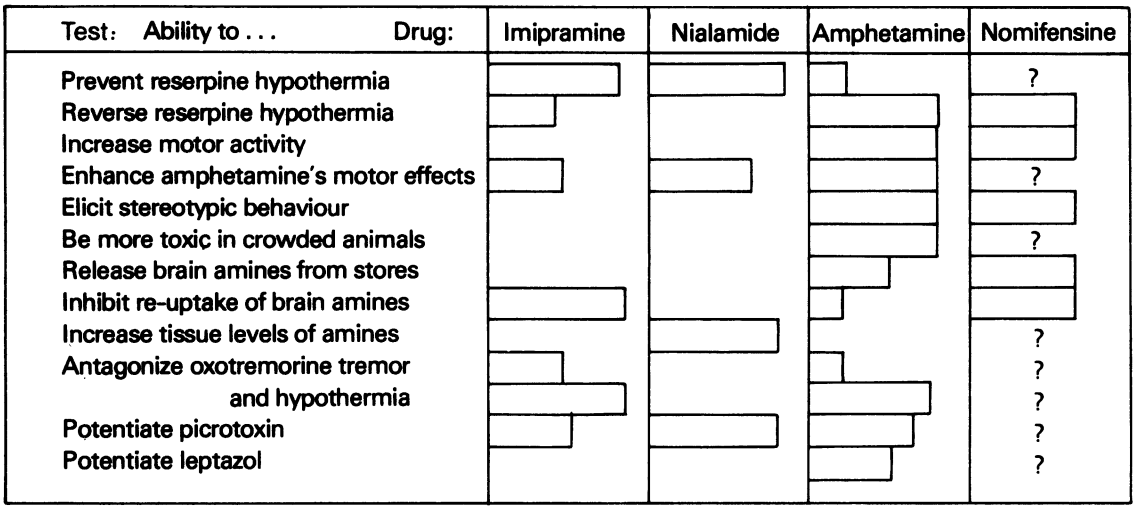

Figure 3 Simple neuropharmacological profile (incomplete) for nomifensine, compared with profiles for imipramine, nialamide and amphetamine. The histograms refer to data obtained in rats and/or mice. The length of each histogram indicates the approximate relative potency of each drug, data being obtained by converting the various ED50 to their reciprocals.

brain of one or more of the amines DA, NA and 5-HT. Bound inextricably into this property are the various amine hypotheses of affective disorders, which suggest that NA and/or 5-HT may be functionally deficient before and/or during a depressive episode in man.

Although the amphetamine-like drugs are effective antidepressants, a number of important side-effects preclude their clinical use. A property which the amphetamines and MAO inhibitors possess, which the tricyclics do not, is the ability to enhance brain DA activity; yet very little is known of the involvement of DA in clinical depression.

Nomifensine thus becomes an interesting drug for a number of reasons. First, it presents a new and unique profile of neuropharmacological activity. Second, it may release DA from stores, a property not shared by the tricyclics or viloxazine. Third, it is a potent inhibitor of DA and NA uptake in the brain. Pharmacologically, therefore, nomifensine slots in between the amphetamines and the secondary amine tricyclics, and a full and in-depth study of nomifensine's clinical properties is important to the long-term development of pharmacotherapy of the depressive disorders.

References

AKISKAL, H.S. & MCKINNEY, W.T. Jr. (1975). Overview of recent research in depression. *Arch. gen. Psychiat.*, **32**, 285-305.

ALEXANDER, L. (1973). *Treatment of Mental Disorder.* Philadelphia: Saunders.

ANDEN, N.E., RUBENSON, A., FUXE, K. & HÖKFELT, T. (1967). Evidence for dopamine receptor stimulation by apomorphine. *J. Pharm. Pharmac.*, **19**, 627-629.

ASKEW, B.M. (1963). A simple screening procedure for imipramine-like antidepressant agents. *Life Sci.*, **10**, 725-730.

BALDESSARINI, R.J. (1972). Biogenic amines and behaviour. *A. Rev. Med.*, **23**, 343-354.

BAYLISS, P.F.C. & DUNCAN, S.M. (1974). The clinical pharmacology of viloxazine hydrochloride - a new antidepressant of novel chemical structure. *Br. J. clin. Pharmac.*, **1**, 431-437.

BENESOVA, O. & NAHUNEK, K. (1971). Correlation between the experimental data from animal studies and therapeutical effects of antidepressant drugs. *Psychopharmacologia Berl.*, **30**, 337-347.

BLACKWELL, B., LIPKIN, J.O., MEYER, J.H., KUZMA, R. & BOULTER, W.V. (1972). Dose responses and relationships between anticholinergic activity and mood with tricyclic antidepressant. *Psychopharmacologia Berl.*, **25**, 205-217.

BOGDANSKI, D.F., SULSER, F. & BRODIE, B.B. (1961). Comparative action of reserpine, tetrabenazine and chlorpromazine on central parasympathetic activity: effects on pupillary size and lacrimation in rabbit and on salivation in dog. *J. Pharmac. exp. Ther.*, **132**, 176-182.

BOURNE, H.R., BUNNEY, W.E. Jr., COLBURN, R.W., DAVIS, J.M., DAVIS, J.N., SHAW, D.M. & COPPEN, A. (1968). Noradrenaline, 5-hydroxytryptamine, and 5-

hydroxyindoleacetic acid in hind brains of suicidal patients. *Lancet*, **ii**, 805-808.

BRAESTRUP, C. & SCHEEL-KRÜGER, J. (1976). Methylphenidate-like effects of the new antidepressant drug nomifensine. *Eur. J. Pharmac.*, **38**, 305-312.

BRYSON, G. (1971). Biogenic amines in normal and abnormal behavioural states. *Clin. Chem.*, **17**, 5-26.

BUNNEY, W.E., GOODWIN, F. & MURPHY, D. (1972). The 'switch process' in manic-depressive illness: III. Theoretical implications. *Arch. gen. Psychiat.*, **27**, 312-317.

COPPEN, A. (1972). Indoleamines and affective disorders. *J. psychiatr. Res.*, **9**, 163-171.

COPPEN, A., SHAW, D.M. & FARRELL, J.P. (1963). Potentiation of the antidepressant effect of a monoamine-oxidase inhibitor by tryptophan. *Lancet*, **i**, 79-81.

COSTA, E., GROPPETTI, A. & NAIMZADA, M.K. (1972). Effects of amphetamine on the turnover rate of brain catecholamines and motor activity. *Br. J. Pharmac.*, **44**, 742-751.

COSTA, E. & SANDLER, M. (1972). Monoamine oxidases - new vistas. In *Advances in Biochemistry and Psychopharmacology*. New York: Raven.

COSTALL, B., KELLY, D.M. & NAYLOR, R.J. (1975). Nomifensine: a potent dopaminergic agonist of antiparkinson potential. *Psychopharmacologia Berl.*, **41**, 153-164.

DENBER, H.C.B. & BIRD, E.G. (1956). Chlorpromazine in the treatment of mental illness: III. The problem of depression. *Am. J. Psychiat.*, **112**, 1021.

DOMENJOZ, R. & THEOBALD, W. (1959). Zur Pharmakologie des Tofranil (N-(3-dimethyl-aminopropyl)-iminodibenzyl hydrochlorid). *Arch. int. Pharmacodyn. Ther.*, **120**, 450-489.

ECCLESTON, D. (1973). Adenosine 3', 5'-cyclic monophosphate and affective disorders: animal models. *Biochem. Soc. Spec. Publ.*, **1**, 121-126.

FUXE, K. & UNGERSTEDT, U. (1970). Histochemical, biochemical and functional studies on central monoamine neurons after acute and chronic amphetamine administration. In *Amphetamine and Related Compounds*, ed. Costa, E. & Garattini, S. New York: Raven.

GERHARDS, H.J., CARENZI, A. & COSTA, E. (1974). Effect of nomifensine on motor activity, dopamine turnover rate and cyclic 3', 5'-adenosine monophosphate concentrations of rat striatum. *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.*, **286**, 49-63.

GLOWINSKI, J. (1970). Effects of amphetamine on various aspects of catecholamine metabolism in the central nervous system of the rat. In *Amphetamine and Related Compounds*, ed. Costa, E. & Garattini, S. New York: Raven.

GLOWINSKI, J. & AXELROD, J. (1966). Effect of drugs on the disposition of ^{3}H-norepinephrine in rat brain. *Pharmac. Rev.*, **18**, 775-786.

GREENWOOD, D.T. (1975). Animal pharmacology of viloxazine ('Vivalan'). *J. Int. med. Res.*, **3**, suppl., 18-30.

GRÜNTHAL, E. (1958). Untersuchungen über die besondere psychologische Wirkung des Thymoleptikums Tofranil. *Psychiat. neur. Wschr.*, **136**, 402-408.

GYERMEK, L. (1966). The pharmacology of imipramine and related antidepressants. *Int. Rev. Neurobiol.*, **9**, 95-143.

HALLIWELL, G., QUINTON, R.M. & WILLIAMS, F.E. (1964). A comparison of imipramine, chlorpromazine and related drugs in various tests involving autonomic functions and antagonism of reserpine. *Br. J. Pharmac.*, **23**, 330-350.

HARRIS, T.H. (1957). Depression induced by rauwolfia compounds. *Am. J. Psychiat.* **113**, 950.

HUNT, P., KANNENGIESSER, M.H. & RAYNAUD, J.P. (1974). Nomifensine: a new potent inhibitor of dopamine uptake into synaptosomes from rat brain corpus striatum. *J. Pharm. Pharmac.*, **26**, 370-371.

IVERSEN, L.L. (1974). Monoamines in the mammalian central nervous system and the actions of antidepressant drugs. In *Biochemistry and Mental Illness*, ed. Iversen, L.L. & Rose, S. *Biochem. Soc. Spec. Publ.*, **1**, 81.

JANOWSKY, D.S., EL-YOUSEF, M.K., DAVIS, J.M. & SEKERKE, H.J. (1972). A cholinergic-adrenergic hypothesis of mania and depression. *Lancet*, **ii**, 632-635.

KALINOWSKY, L.B. & HOCH, P.H. (1961). *Somatic Treatments in Psychiatry*. New York: Grune & Stratton.

KELLY, P.H. & IVERSEN, S.D. (1976). Selective 6-OHDA-induced destruction of mesolimbic dopamine neurons: abolition of psychostimulant-induced locomotor activity in rats. *Eur. J. Pharmac.*, **40**, 45-56.

KELLY, P.H., SEVIOUR, P.W. & IVERSEN, S.D. (1975). Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res.*, **94**, 507-522.

KIRBY, M.J. & TURNER, P. (1974). Some preliminary observations of ICI 58, 834, a new psychotropic agent in man. *Br. J. clin. Pharmac.*, **1**, 169.

KLERMAN, G.L. (1971). Chemotherapy of depression. In *Brain Chemistry and Mental Disease*, ed. Ho, B.T. & McIsaac, W.M. London: Plenum.

KLINE, N.S. (1958). Clinical experience with iproniazid (Marsilid). *J. clin. exp. Psychopath.*, **19**, suppl. 1, 72-78.

KUHN, R. VON (1957). Über die Behandlung depressiver Zustände mit einem Iminodibenzylderivat (G-22355). *Schweiz. med. Wschr.*, **87**, 1135-1140.

KUHN, R. VON (1958). The treatment of depressive states with G 22355 (imipramine hydrochloride). *Am. J. Psychiat.*, **115**, 459-464.

MALLION, K.B., TODD, A.H., TURNER, R.W., BAINBRIDGE, J.G., GREENWOOD, D.T., MADINAVEITIA, J., SOMERVILLE, A.R. & WHITTLE, B.A. (1972). 2-(2-ethoxy-phenoxymethyl) tetrahydro-1, 4-oxazine hydrochloride, a potential psychotropic agent. *Nature*, **238**, 157-158.

PARE, C.M.B. & SANDLER, M. (1959). A clinical and biochemical study of a trial of iproniazid in the treatment of depression. *J. Neur., Neurosurg., Psychiat.*, **22**, 247-251.

PARE, C.M.B., YEUNG, D.P.H., PRICE, K. & STACEY, R.S. (1969). 5-Hydroxytryptamine, noradrenaline and dopamine in brain stem, hypothalamus and caudate nucleus of controls and of patients committing suicide by coal-gas poisoning. *Lancet.*, **ii**, 133-135.

PLETSCHER, A. (1968). In *Psychopharmacology, a Review of Progress*, ed. Efron, D.H. Washington: US Dept. of Health, Education and Welfare.

PLETSCHER, A., GEY, K.F. & ZELLER, P. (1960). In *Fortschritt der Arzneimittel-Forschung*. Basel: Birkhäuser.

PRANGE, A., WILSON, I. & LYNN, C.W. (1974). L-Tryptophan in mania: contribution to a permissive

hypothesis of affective disorders. *Arch. gen. Psychiat.*, **30**, 56-62.

RIDGES, A.P. (1975). Biochemistry of depression: a review. *J. Int. med. Res.*, **3**, suppl. 2, 42-54.

ROSENBLATT, S., CHANLEY, J.D., SOBOTKA, H. & KAUFMANN, M.R. (1960). Inter-relationships between electro-shock, the blood-brain barrier and catecholamines. *J. Neurochem.*, **5**, 172-176.

SAMANIN, R., BERNASCONI, S. & GARATTINI, S. (1975). The effect of nomifensine on the depletion of brain serotonin and catecholamines induced respectively by fenfluramine and 6-hydroxydopamine in rats. *Eur. J. Pharmac.*, **34**, 377-380.

SAYERS, A.C. & HANDLEY, S.L. (1973). A study of the role of catecholamines in the response to various central stimulants. *Eur. J. Pharmac.*, **23**, 47-55.

SCHEEL-KRÜGER, J. & RANDRUP, A. (1967). Stereotype hyperactive behaviour produced by dopamine in the absence of noradrenaline. *Life Sci.*, **6**, 1389-1398.

SCHILDKRAUT, J.J. (1965). The catecholamine hypothesis of affective disorders. A review of supporting evidence. *Am. J. Psychiat.*, **122**, 509-522.

SCHILDKRAUT, J.J. (1973). Neuropharmacology of the affective disorders. *A. Rev. Pharmac.*, **13**, 427-454.

SHAW, D.M., CAMPS, F.E. & ECCLESTON, E.G. (1967). 5-hydroxytryptamine in the hindbrain of depressive suicides. *Br. J. Psychiat.*, **113**, 1407-1411.

SPENCER, P.S.J. (1965). Activity of centrally acting and other drugs against tremor and hypothermia induced in mice by tremorine. *Br. J. Pharmac.*, **25**, 442-455.

SPENCER, P.S.J. (1966). The antagonism of oxotremorine effects in the mouse by thymoleptics. *Life Sci.*, **5**, 1015-1023.

SPENCER, P.S.J. (1967). Antagonism of hypothermia in the mouse by antidepressants. In *Proc. First Int. Symp. Antidepressant Drugs*. Amsterdam Excerpta Medica Int. Congr. Series, No. 122, 194-204.

SPENCER, P.S.J. (1976). Animal models for screening new agents. *Br. J. clin. Pharmac.*, **3**, suppl. 1, 5-12.

STEIN, L. (1971). Neurochemistry of reward and punishment: some implications for the etiology of schizophrenia. *J. psychiatr. Res.*, **8**, 345-361.

SULSER, F., WATTS, J. & BRODIE, B.B. (1962). On the mechanism of antidepressant action of imipramine-like drugs. *Ann. N.Y. Acad, Sci.*, **96**, 279-288.

THORNBURG, J.E. & MOORE, K.E. (1973). The relative importance of dopaminergic and noradrenergic neuronal systems for the stimulation of locomotor activity induced by amphetamine and other drugs. *Neuropharmacology.*, **12**, 853-866.

TURNER, P., BAYLISS, P.F.C. & GHOSE, K. (1975). Clinical pharmacology of viloxazine ('Vivalan'). *J. Int. med. Res.*, **3**, suppl. 3, 41-49.

TURNER, T.A.R. & SPENCER, P.S.J. (1968). Effect of pretreatment with monoamine oxidase inhibitors or (+)-amphetamine on leptazol convulsions in mice and rats. *J. Pharm. Pharmac.*, **20** suppl., 122-125S.

VAN ROSSUM, J.M. (1970). Mode of action of psychomotor stimulant drugs. *Int. Rev. Neurobiol.*, **12**, 307-383.

WALDMEIER, P.C., BAUMANN, P., GREENGRASS, P.M. & MAITRE, L. (1976). Effects of clomipramine and other tricyclic antidepressants on biogenic amine uptake and turnover. *Postgrad. med. J.*, **52**, suppl. 3, 33-39.

ZELLER, E.A., BARSKY, J., FOUTS, J.R., KIRCHHEIMER, W.F. & VAN ORDEN, L.S. (1952). Influence of isonicotinic acid hydrazide (INH) and 1-isonicotinyl-2-isopropyl hydrazide (IIH) on bacterial and mammalian enzymes. *Experientia*, **8**, 349-350.