HUMAN PHARMACOLOGY OF ANTIDEPRESSIVES

M. LADER

Department of Psychiatry, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK

1 As both the tricyclic antidepressives and the monoamine oxidase (MAO) inhibitors were discovered accidentally, their pharmacology has been established on an empirical *post hoc* basis only. There are no convincing models of depression in the normal human. The classification of depression remains controversial; also the relationship between clinical depression, depressive reactions and pessimistic personality traits is unresolved. Antidepressive effects are demonstrable in lugubrious normals.

2 Pharmacokinetic and drug interaction data are important in the usage of a drug and are available from studies in normals. Secondary psychotropic effects such as sedation can be readily studied both in normals and in patients. The antidepressives produce characteristic changes in the electroencephalogram (EEG). Unwanted effects are often related to autonomic actions which can be readily quantified, salivation being most extensively studied. Psychological impairment is dose related in normals but lessens over a course of treatment in patients.

3 Biochemical measures have been little explored despite their obvious relevance. MAO activity in platelets is diminished by MAO inhibitors. Tricyclic drugs inhibit the uptake of amines into neurones and platelets, and this inhibition can be assessed in various ways.

4 Drug experiments in normal subjects provide data which complement, amplify and elucidate observations in patients without ever substituting for them.

Introduction

This review will outline measures of the pharmacological effects of antidepressive drugs other than the main therapeutic action—namely, the amelioration of psychiatric depression. Other psychotropic actions are germane to this outline. The measures will be presented in a practical way as an attempt will be made to answer the research question: “What sort of information is obtainable from studies, acute or chronic, of antidepressives in normal subjects?”

First, it is chastening to recall that both major groups of antidepressives, the ‘tricyclics’ and the MAO inhibitors were discovered by chance (Ayd & Blackwell, 1970). The Swiss company Geigy were investigating a series of tricyclic compounds (iminodibenzyls) for antihistaminic properties but found them relatively weak. Later, when chlorpromazine was introduced and it was realized that its chemical structure resembled the test compounds, one, G22355, now known as imipramine, was tried as a tranquillizer. Again it proved disappointing but one investigator, Dr Roland Kuhn, discerned its quite unexpected antidepressive properties. This was confirmed in a series of controlled trials. Only later were particular pharmacological properties—the blockade of amine uptake—asccribed to the tricyclics, and even these properties are not unique to this class of compounds.

Iproniazid, the first MAO inhibitor, was introduced as an antituberculous compound and was found to make patients euphoriant. Early clinical trials were unpromising but after the MAO-inhibiting properties were demonstrated, the drug was tried again in a variety of depressed, retarded and withdrawn patients, and antidepressive actions uncovered.

Thus, in one group, discovery of clinical effects led to intensive pharmacological studies to elucidate its mode of action; in the other, putatively relevant biochemical effects stimulated clinical evaluations.

The corollary of this serendipity was that at no time during the development of the antidepressives was recourse made to an adequate animal model. Instead, retrospective models were elaborated. Thus, the newly discovered drugs were administered in a wide dose range to animal preparations, behavioural, biochemical and physiological, and effects sought. Actions which seemed characteristic of clinical antidepressives but not of other types of psychotropic agents were incorporated into a battery of tests in the search for new antidepressives. An example is the reversal of reserpine-induced sedation. The relevance of such actions to the clinical effects could not be firmly established, and the biochemical and other mechanisms in depressive illnesses remained unclear. Consequently, later antidepressives would inevitably have similar profiles to the prototypes. As a corollary,

it is not unexpected that some clinically active compounds display an incomplete animal profile.

No convincing normal human models of depression exist. For example, whereas laboratory-induced anxiety in normals is an appropriate phenomenon on which to evaluate anxiolytics, the production of depression is hardly feasible ethically and probably unedifying. Thus, there is still no obvious niche for normal human studies in the development of promising antidepressives. Nevertheless, as outlined later, useful and even crucial, information on the actions of antidepressives can be extracted.

Normal and abnormal

Without becoming embroiled in the contentious topic of the classification of depression, some remarks on normality and abnormality are apposite. Is there a true biological distinction between normal and depressed individuals or are we observing a continuum? Few would dispute the obvious clinical differences between the normal and the profoundly depressed and there are definite biological abnormalities also. Nevertheless, milder illnesses merge imperceptibly with the non-depressed state, so that quite complex conceptual models are needed.

The habitual tendency to feel depressed, either spontaneously or in response to life's slings and arrows, constitutes the personality trait of depression. Such a pessimistic, lugubrious individual can be used to show antidepressive drug effects despite not being a 'patient' in the formal, operational sense. For example, Dimascio *et al.* (1968) selected 20 healthy young men who scored 2 s. d. above the mean on the depression (D) scale of the Minnesota Multiphasic Personality Inventory and compared them with 20 men scoring 2 s.d. below the mean. All subjects had been interviewed by a psychiatrist who excluded any with significant neurotic or psychotic symptoms or undergoing psychotherapy. Half the subjects in each group were placed on imipramine 50 mg three times daily for a week, the other half on matching placebo, under double-blind safeguards. Neither drug nor placebo had any effect on depression scores in the low depression subjects; placebo made the morose subjects somewhat worse, whereas imipramine lessened the scores to a significant extent. Anxiety ratings were also made and the pattern was more complex. Imipramine had no appreciable effect on anxiety in the two groups. As depression and anxiety ratings seemed independent in the initial assessment, however, the groups were re-classified on the basis of their pretreatment anxiety scores: imipramine was found to exert an appreciable anxiety-reducing effect in the high anxiety subjects but not in the calm group. It was concluded that imipramine could be shown to have antidepressive and anxiolytic properties in appropriately selected normal, asymptomatic subjects.

Pharmacokinetics

Pharmacokinetics—the effect of the body on the drug—is one major area where studies in normal subjects throw direct light on the situation in patients. The absorption, distribution, metabolism and excretion of tricyclic drugs can all be usefully elucidated in normal subjects. The most thorough work in this respect was that carried out by the late Dr Balzar Alexanderson and his colleagues on nortriptyline.

In one study, nortriptyline was administered to three normal subjects, as a single dose, both orally and intramuscularly (Alexanderson *et al.*, 1973). First, as the amount of metabolite was the same for the two modes of administration, absorption from the gut was judged complete. Second, as the amount of nortriptyline itself in the body after oral administration was only 56–70% of that present after parenteral injection, about a third must have been metabolized 'first-pass' by the liver on absorption from the gut, thus lowering the biological availability.

A useful pharmacokinetic stratagem is to be able to predict steady-state plasma concentrations on chronic administration from plasma concentration curves after a single dose. With nortriptyline, Alexanderson (1972a; b) found that the clearance of the drug from the plasma after a single dose was a fair predictor of the eventual steady-state plasma concentration. Complex factors, however, including differences among individuals in bodily distribution patterns of nortriptyline and plasma binding, precluded any high degree of predictability.

The study of a special type of normal subject, namely twins, has also been profitable. Nineteen monozygotic and 20 dizygotic twin pairs were administered nortriptyline 0.2 mg/kg three times daily for 8 d (Alexanderson *et al.*, 1969). In monozygotic twins not taking any other drugs, plasma concentrations after 8 d showed great within-pair similarity. In such twins receiving other drugs, the concentrations were dissimilar, especially if a barbiturate was administered simultaneously. Dizygotic twins had dissimilar within-pair plasma concentrations of nortriptyline, whether or not they were taking other medication. Barbiturate lowered the levels of the tricyclic antidepressive.

In a later and more sophisticated study, Alexanderson & Borgå (1973) described the complexities of nortriptyline metabolism but showed convincingly that the metabolic pattern was very constant within individual and also within monozygotic twin pair. The plasma half-life averaged 19.6 h, and this parameter of the drug is, of course, of importance in recommending rational dosage schedules.

Pharmacokinetic processes in patients are usually very similar to those in normal subjects providing certain precautions are observed. Most important is

the avoidance of drug interactions. Patients usually, but by no means always, take more drugs by number and by quantity than normals so that interactions are more likely. Barbiturates are notorious for lowering plasma concentrations of antidepressives but a wide range of drugs, psychotropics and others, can interfere in this way. Conversely, major tranquilizers probably increase the body concentrations of antidepressives.

Another possible site of interaction is in the gut as compounds like aluminium hydroxide tend to adsorb other drugs and hinder their absorption. Whether the changes in gastro-intestinal mobility which accompany states of severe depression alter drug absorption has never been systematically investigated.

Pharmacodynamics

Primary psychotropic effects

This topic—the effect of the drug on the body—is of more direct interest to the clinician. The main psychotropic action of these drugs is their antidepressive effect. Although the work of Dimascio outlined earlier demonstrated some antidepressive effects in lugubrious individuals, it is doubtful whether major actions of this type are demonstrable in normal subjects. Thus, like many other classes of therapeutic agents—for example, anticancer drugs, anticonvulsants and cardiac glycosides—the primary effect is only demonstrable on patients suffering from the condition. One cannot gainsay this limitation of studies in normal subjects.

Secondary psychotropic effects

Nevertheless, secondary psychotropic effects can be evaluated, especially those of a simple sedative or stimulant nature. Tricyclic antidepressives usually have marked actions of this type with, for example, amitriptyline being sedative and protriptyline being stimulant. Information of this sort is useful in deciding which antidepressive to use. The agitated patient is more appropriately treated with a sedative compound like amitriptyline, especially when given as a single hypnotic dose at night.

Over ten years ago, differences in the psychotropic profiles of imipramine and desipramine were sought (for example, Dimascio *et al.*, 1964; Idström & Cadenius, 1964). In both studies, subjective reports suggested that imipramine was associated with a greater incidence of drowsiness, tiredness and sedation than was desipramine. In our own recent study (Bhanji & Lader, 1977), imipramine was administered in single doses of 0.67 and 1.0 mg/kg to 12 healthy volunteers and its effects compared with placebo. Imipramine significantly increased ratings of drowsiness, feebleness, muzziness, clumsiness, lethargy, mental slowness, dreaminess, incompetence,

sadness, withdrawal and calm. Thus, it was both diminishing general alertness and anxiety, the type of effect seen with anxiolytic drugs like the benzodiazepines. In patients given imipramine as a course of treatment, reports of tiredness tended to diminish over time.

With amphetamine and caffeine, stimulant effects can be reliably demonstrated but these drugs are not usually considered as true antidepressives but rather euphoriant agents.

Central effects

These essentially refer to drug effects on the EEG and the electroencephalographic averaged evoked response (AER). The tricyclic antidepressives produce characteristic alterations in the EEG, namely increase in slow and fast wave activity, and decrease in alpha activity. By contrast, chlorpromazine increases slow activity but reduces fast activity. The EEG remains an almost entirely empirical measure as the underlying neuronal mechanisms are poorly understood. Nevertheless, even within these limitations, the EEG can be a useful predictor. Mianserin was originally noted to have anti-5-hydroxytryptamine (5-HT) activity in laboratory studies. After giving it to man, it was reported to have a profile most resembling amitriptyline, and clinical trials as an antidepressive were recommended. Such properties were confirmed and the drug marketed (Fink, 1975).

To give another example, trazodone has a chemical structure distinct from other psychotropic drugs and preliminary animal screening suggested it might be sedative. Its full profile, however, was atypical of antipsychotic, antidepressive and anti-anxiety agents, although it had elements of each class. Thus it suppressed the conditioned avoidance response without inhibiting amphetamine-induced stereotyped behaviour in rats; it potentiated tryptophan but not L-DOPA nor did it antagonize reserpine sedation; it had atypical profiles of action on brain monoamines.

We have administered trazodone 0.33 and 0.67 mg/kg (≈ 23 and 46 mg per average man) to ten healthy volunteers and compared the effects with those of imipramine 0.05 mg/kg (35 mg), diazepam 0.067 mg/kg (4.6 mg) and placebo (Karniol *et al.*, 1976). At both doses trazodone increased EEG slow (4 - 7.5 Hz) activity, whereas imipramine had no effect, and diazepam decreased this wave-band. Both trazodone and imipramine increased alpha wave band activity, diazepam again having a reducing effect. With respect to fast-wave activity, diazepam produced its typical augmentation, whereas the other drugs, trazodone in particular, lowered this waveband activity. Together with the results of other tests, it was concluded that trazodone's properties differed from both diazepam and imipramine, but of the two, it more closely resembled imipramine. This

accorded with recent general clinical impressions (Ban & Silvestrini, 1974).

The EEG responses in normals to somatosensory stimulation have also shown differences among antidepressives. The latencies of early components of the waves were decreased and of the later components increased by amitriptyline and imipramine (Saletu *et al.*, 1973). The amplitude of the AER was diminished. Amitriptyline was more potent than imipramine in diminishing amplitude and increasing latencies and it was suggested that this reflected its greater sedative propensities.

Autonomic effects

Many unwanted effects of the tricyclic antidepressives relate to their autonomic actions. As these can be estimated in normal subjects useful predictions regarding clinical side-effects can be made. Even so, effects can be complex. Imipramine in single dose has been reported to produce a slight dilatation of the pupil, amitriptyline a slight constriction (Lauber *et al.*, 1967). As both drugs enhance sympathetic activity and are anticholinergic, marked pupillary dilatation is only to be expected. In our own studies, this did indeed occur in patients on repeated administration of imipramine but not in normal volunteers after single doses.

Salivation has been extensively used as an index of the autonomic effects of imipramine. For example, Palmi *et al.* (1967) gave imipramine 50 mg four times daily for 10 weeks to eight nurses. Salivation rate decreased to a third of initial values by day 7 but then gradually increased until by 10 weeks it attained two-thirds of the initial level. Thus, either tolerance supervened or the nurses were taking the medication less regularly.

Blackwell *et al.* (1972) compared dimethacrin, a developmental drug known to have few anticholinergic effects in animals, with imipramine, with respect to salivary flow. As expected, imipramine, but not dimethacrin, diminished salivation in a dose-related manner. Only imipramine, however, produced consistent sedative effects which led the authors to speculate whether sedation was mediated by central anticholinergic effects.

Psychological effects

As might be expected from the subjective reports, both imipramine and amitriptyline impair psychological performance of various kinds. In one study (Dimascio *et al.*, 1964), imipramine but not desipramine decreased tapping speed, accuracy in an aiming task and visuomotor coordination. These effects, however, occurred after fairly hefty single doses of the drugs (200 mg). In another study

(Ideström & Cadenius, 1964), no such effects followed the administration of 50 mg. Even in repeated daily dosage (25 mg three times daily), no psychomotor impairment was apparent. Indeed, one report even claimed that imipramine given over 2 weeks to normal subjects (25 mg 4 times daily) reduced reaction time, and this was attributed to an increase in alertness secondary to enhanced catecholamine activity (Keeler *et al.*, 1966).

The psychological sequelae of drug interactions are obviously important. Psychotropic drugs are often prescribed in conjunction by the doctor or are taken by the patient unknown to the prescriber. Alcohol is probably the commonest psychotropic substance taken by patients maintained on antidepressives and the potentiation of effects may be considerable. Often, however, such interactions are difficult to demonstrate in normal subjects, especially with acute administration of the drug (for example, Milner & Landauer, 1973).

Biochemical indices

Most of the measures outlined so far have been difficult to interpret, like the EEG, or have reflected drug effects which are secondary or peripheral. Although they are of some utility in monitoring side-effects, they leave the researcher dissatisfied that he might be working in unimportant areas and the clinician still without alternative assessments to his clinical judgements. Are there any pharmacodynamic effects of the antidepressives which would facilitate adequate monitoring of clinical treatment?

With the MAO inhibitors the obvious index would seem to be some estimate of MAO inhibition. Surprisingly, this has rarely been attempted. One problem is the lack of direct estimates of MAO inhibition in the brain, presumably the relevant site of action. Estimates of urinary tryptamine have been suggested as indirect or whole-body indices. Alternatively, platelet MAO activity can be measured. We are at present monitoring a trial of antidepressives at St Thomas' Hospital using platelet MAO activity. But we are not too sanguine, as the relationship between the clinical and the biochemical effects of the MAO inhibitors has never been convincing. For example, iproniazid is euphoriant but a poor MAO inhibitor. Also, marked MAO inhibition occurs within an hour or two of administering tranylcypromine yet clinical improvement may be delayed for up to 6 weeks, if it occurs at all.

Biochemical techniques also exist to assess the effects of the tricyclic antidepressives. One of their properties is the block of uptake of monoamines into presynaptic nerve endings. Tertiary amines like imipramine and amitriptyline tend to block 5-HT uptake preferentially; secondary compounds such as desipramine and nortriptyline act more against

Figure 1 Effects of single doses of imipramine 0.67 mg/kg (□) and 1 mg/kg (■) as compared with those of placebo (●) on mean skin conductance of normal subjects. The vertical line labelled CD represents the 0.05 critical differences, 'means further apart than this statistic being significantly different.

noradrenaline uptake. The issue becomes complicated because tertiary compounds are dealkylated to secondary compounds *in vivo*.

In human studies synaptosomes are not feasible preparations, so the human platelet is used as a model (Sneddon, 1973). Blockade can be demonstrated *in vitro* but is often difficult to interpret. For example, doxepin is only about one-fifteenth as potent as imipramine in blocking 5-HT uptake (Lingjaerde, 1976), yet the clinical dosage ranges are similar.

Our studies initially involved single dose administrations in normals. *In vivo*, our data suggest that imipramine reduces 5-HT and dopamine (DA) uptake by about one-third while leaving metaraminol (equivalent to noradrenaline, NA) unaffected. Trazodone inhibited 5-HT uptake by about one-quarter and both DA and metaraminol by 10% only. Tranlycypromine and lithium had no effects. These studies have now been extended to patients and we are hoping to evaluate this technique for its clinical usefulness.

Figure 2 Effect of treatment with imipramine 50 mg three times daily for 4 weeks on mean skin conductance of depressed patients. CD as in Figure 1.

The attraction of platelet techniques is that they could be developed into routine assay procedures. They involve radio-isotopes but central clinical chemistry laboratories are usually equipped for such assessments. Thus, if the clinical utility was established, a practical aid to the clinician might be produced.

Other techniques are less easy to apply. The infusion of tyramine produces an easily quantifiable pressor response. Blockade of uptake of NA by a tricyclic antidepressive also blocks uptake of tyramine, an indirectly acting sympathomimetic. Consequently, an estimate of this blockade is provided by the extent to which tyramine dose-pressor response curves are shifted to the right (for example, Ghose *et al.*, 1976). This is, however, a time-consuming technique and only applicable to those tricyclic antidepressives preferentially blocking NA uptake. Even less generally practicable are estimations of amine metabolites, for example, 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (Asberg *et al.*, 1973).

Extrapolation from normals to patients

I will conclude by assessing the value of studies in normal subjects with respect to clinical relevance. First, one point needs emphasizing, namely, that

many measures of antidepressive drug action are measures which are already abnormal in depressed patients. For example, skin conductance (sweating) is decreased in normal subjects when imipramine or amitriptyline is administered (Figure 1). In patients, the level also decreases after these drugs are given but over the course of a few weeks, the level increases again (Figure 2). The immediate explanation is that 'tolerance' has occurred to the anticholinergic effects of the drug. As conductance, however, is diminished in depression, especially if the patients display some retardation, as a corollary, improvement in mental state might be expected to be associated with an increase in conductance. An alternative explanation for the decrease and then increase in conductance would suggest that the initial decrease does reflect direct pharmacodynamic actions, namely the anticholinergic effect, whereas the increase does not reflect tolerance, whatever that might be, but an improvement-related increase. In other words, the drug and the patient's mental state are exerting separate effects on such measures.

Support for this view comes from our data on the effects of imipramine on psychological functioning in normal subjects and depressed patients. In the former, single administrations of imipramine produce dose-

related impairment of simple behavioural tests such as symbol copying. In depressed patients, however, the repeated administration of imipramine in a therapeutic course of treatment is associated with a steady increase in psychological functioning. Furthermore, this improvement parallels the amelioration of depressive symptoms, quantified by rating scales. The most reasonable interpretation is that the drug produces a clinical improvement and that this is associated with a lessening of the psychological disabilities well known to occur in depression. This improvement outweighs any direct drug-induced impairment.

The implication for research is that drug experiments in normal subjects provide essential information for the interpretation of drug effects in patients. Without such data, drug-associated changes cannot be confidently ascribed to direct effects of the drug or to indirect effects mediated through clinical improvement. Thus, although I agree with Poldinger's (1963) view that there is no close relationship between antidepressive drug actions in normal subjects and in patients, I do not automatically dismiss studies in normals as unprofitable. Instead, they complement, amplify and elucidate those in patients while, of course, never substituting for them.

References

- ALEXANDERSON, B. (1972). Pharmacokinetics of nortriptyline in man after single and multiple oral doses: the predictability of steady-state plasma concentrations from single-dose plasma-level data. *Eur. J. clin. Pharmac.*, **4**, 82-91.
- ALEXANDERSON, B. (1972). Pharmacokinetics of desmethylinipramine and nortriptyline in man after single and multiple oral doses - a crossover study. *Eur. J. clin. Pharmac.*, **5**, 1-10.
- ALEXANDERSON, B. & BORGÅ, O. (1973). Urinary excretion of nortriptyline and five of its metabolites in man after single and multiple oral doses. *Eur. J. clin. Pharmac.*, **5**, 174-180.
- ALEXANDERSON, B., BORGÅ, O. & ALVÁN, G. (1973). The availability of orally administered nortriptyline. *Eur. J. clin. Pharmac.*, **5**, 181-185.
- ALEXANDERSON, B., PRICE EVANS, D.A. & SJÖQVIST, F. (1969). Steady-state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. *Br. med. J.*, **4**, 764-768.
- ASBERG, M., BERTILSSON, L., TUCK, D., CRONHOLM, B. & SJÖQVIST, F. (1973). Indoleamine metabolites in the cerebrospinal fluid of depressed patients before and during treatment with nortriptyline. *Clin. Pharmac. Ther.*, **14**, 277-286.
- AYD, F.J. & BLACKWELL, B. (1970). *Discoveries in Biological Psychiatry*. Philadelphia: Lippincott.
- BAN, T.A. & SILVESTRINI, B. (1974). *Trazodone. Modern Problems of Pharmacopsychiatry*, **9**. Basel: Karger.
- 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 antidepressants. *Psychopharmacologia Berl.*, **25**, 205-217.
- DI-MASCIO, A., HENINGER, G. & KLIERMAN, G.L. (1964). Psychopharmacology of imipramine and desipramine. A comparative study of their effects in normal males. *Psychopharmacologia Berl.*, **5**, 361-371.
- DI-MASCIO, A., MEYER, R.E. & STIFLER, L. (1968). Effects of imipramine on individuals varying in level of depression. *Am. J. Psychiat.*, **124**, suppl., 55-58.
- FINK, M. (1975). Prediction of clinical activity of psychoactive drugs: application of cerebral electrometry in Phase I studies. In *Predictability in Psychopharmacology: Preclinical and Clinical Correlations*, 65-82, ed. Sudilovsky, A., Gerhon, S. & Beer, B. New York: Raven.
- GHOSE, K., TURNER, P. & GRANT, I.N. (1976). The assessment of interactions in man between tyramine and viloxazine hydrochloride, an antidepressant drug. *Br. J. clin. Pharmac.*, **3**, 668-671.
- IDESTROM, C.M. & CADENIUS, B. (1964). Imipramine-desmethylinipramine. A pharmacological study on human beings. *Psychopharmacologia Berl.*, **5**, 431-439.
- KARNIOL, I., DALTON, J. & LADER, M. (1976). Comparative psychotropic effects of trazodone, imipramine and diazepam in normal subjects. *Curr. Ther. Res.*, **20**, 337-348.

- KEELER, M.H., PRANGE, A.J. & REIFLER, C.B. (1966). Effects of imipramine and thioridazine on set and attention. *Dis. Nerv. Syst.*, **27**, 798-802.
- LAUBER, H., HARTMANN, R. & HERMANN, D. (1967). The effects of tranquillizers and thymoleptic drugs on the human pupil. *Germ. med. Mth.*, **12**, 232-234.
- LINGJAERDE, O. (1976). Effect of doxepin on uptake and efflux of serotonin in human platelets *in vitro*. *Psychopharmacologia Berl.*, **47**, 183-186.
- MILNER, G. & LANDAUER, A.A. (1973). The effects of doxepin, alone and together with alcohol, in relation to driving safety. *Med. J. Aust.*, **1**, 837-841.
- PALMAI, G., BLACKWELL, B., MAXWELL, A.E. & MORGENSTERN, F. (1967). Patterns of salivary flow in depressive illness and during treatment. *Br. J. Psychiat.*, **113**, 1297-1308.
- PÖLDINGER, W. (1963). Comparison between imipramine and desipramine in normal subjects and their action in depressive patients. *Psychopharmacologia, Berl.*, **4**, 302-307.
- SALETU, B., SALETU, M. & ITIL, T.M. (1973). Effect of tricyclic antidepressants on the somatosensory evoked potential in man. *Psychopharmacologia Berl.*, **29**, 1-12.
- SNEDDON, J.M. (1973). Blood platelets as a model for monoamine-containing neurones. *Progr. Neurobiol.*, **1**, 151-198.

Discussion

PROFESSOR VALENTINE (Bristol) stated that it was known that histamine had a pronounced effect on duodenal ulcers, but that antihistamines had no therapeutic value. This led to the hypothesis that a second histamine receptor might exist. Subsequently, cimetidine, an effective H_2 receptor blocker had been developed. He wondered, as almost all psychotropic drugs had been derived from antihistamines, whether there was similarly an undetected H_2 receptor in the brain.

DR LADER (London) said that histamine undoubtedly had an important intracerebral role, but was unable to say whether the development of psychotropics from antihistamines was a commercial accident or whether it had greater significance. He nevertheless believed that the evidence implicating 5-HT, NA and DA in brain mechanisms was more substantial than that implicating histamine.

PROFESSOR TURNER (London) said he believed there was real interest in H_2 receptor blockers which could get into the CNS and which would enable Professor Valentine's hypothesis to be tested more realistically. Professor Turner then asked Dr Lader what particular tests can be carried out in normal volunteers to help select worthwhile products which had promising biochemical and pharmacological profiles.

DR LADER did not think any of the normal human volunteer tests were an adequate basis on which to make a commercial decision to further develop an antidepressive, but he believed they could indicate what side effects might be expected. Knowledge of the underlying biochemical mechanisms could be of some future value in the synthesis of new antidepressants.

DR RACK (Bradford) asked Dr Lader to comment on enzyme induction in the context of differing serum levels between individuals and of tolerance.

DR LADER agreed that enzyme studies could be carried out in volunteers but he would normally get this data from patient studies as they necessitated chronic administration of drug, and because such data could usually be obtained from clinical trials.

PROFESSOR HALL (Newcastle) said that when studying the endocrine effects of nomifensine, some elevation of mood was noted in the volunteers.

DR LADER said that it was certainly possible to note stimulant or sedative effects in volunteers, but pointed out that amphetamine, a powerful euphoriant in normal subjects, was of little value therapeutically whereas amitriptyline, which was not a euphoriant, was most useful in the clinic. Significant euphoriant or stimulant actions would alert him to the possibility of the development of dependence.