MONOAMINES, MONOAMINE OXIDASE INHIBITORS and DEPRESSION

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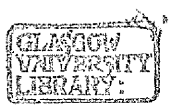

INTRODUCTION and DISCUSSION OF RELEVANT PUBLISHED WORK

It is difficult to determine the frequency of depressive illness. This is partly because of the difficulty of defining affective disorder. There is no clear boundary between the milder manifestations of affective illness and the "well founded moodiness of health" (Kraepelin, 1913). The point at which lowered mood becomes depressive illness is arbitrary and for this reason estimates of the incidence of the condition are bound to vary. Many patients with depressive illness do not come into contact with the hospital services but are treated by their general practitioners. In a study in general practice in Birmingham Crombie (1957) found an incidence of 10 cases of endogenous depression and 5 cases of endogenous depression per 1000 of the population per annum. Working in a country general practice in Leicestershire Watts (1966) found an average of 12 new cases of depression and 4.5 chronic cases of depression per 1000 of the population per annum. Studies in hospital practice give a much lower incidence. Norris (1959) estimates the lifetime's risk, for people living in London, of being admitted to hospital with an affective illness, which in 88% of cases would be a depressive illness, as 11.2/1000. From these figures it may be concluded that the milder forms of depressive illness are very common and the more severe forms are not rare.

The cause of depressive illnesses is not known,

although there are many theories concerning their aetiology. Prominent among the theories which assert that depression is a biological disorder is the monoamine theory. According to this theory certain neuronal systems in the brain are important in the control of mood. Monoamines are thought to act as transmitters or to modify transmission in these systems. Deficiency of monoamine at the synapses in these neuronal systems is said to result in depression and excess in mania. This theory was originally put forward in the late 1950's (Schildkraut, 1965). It has been reviewed more recently by various authors and both catecholamines, principally noradrenaline although dopamine is mentioned at times, (Schildkraut, 1965; Schildkraut & Kety, 1967; Goodwin & Sack, 1973) and the indolalkylamine, 5-hydroxytryptamine (Curzon, 1969; Lapin & Oxenkrug, 1969) have been regarded as important.

It is not possible to confirm or refute this theory on the basis of currently available evidence. Confirmation of the theory must ultimately depend upon direct demonstration of deficiency or excess of the relevant substances at appropriate sites in the brain in the naturally occurring illness. At present such a demonstration is not possible. Pharmacological studies in animals and in man have however produced findings which are compatible with this theory. These concern two main topics :-

1. Substances which deplete monoamines at synapses are associated with sedation in animals and depression in man.

2. Drugs which elevate mood have properties which enable them to increase the amount of monoamine available at synapses.

The information concerning the first of these topics is as follows :-

Reserpine has been shown to deplete the brains of animals of 5-hydroxytryptamine (Pletscher, Shore and Brodie, 1956) and of noradrenaline (Holzbauer & Vogt, 1956; Shore, 1962). Administration of the drug produces a state of sedation in animals (Shore, 1962). Tetrabenazine, a synthetic analogue of reserpine, has been shown to deplete the brains of animals of 5-hydroxytryptamine and noradrenaline and to produce sedation in animals (Quinn, Shore and Brodie, 1959). Reserpine is a derivative of rawolfia the sedative properties of which have been known for many centuries. The first reference to the curative properties of this drug in Western literature was contained in a Portuguese work published in Goa in 1563 (Bein, 1956). In the 1950's reserpine began to be used in fairly high doses as a hypotensive agent and it was found that administration of this drug was associated with the development of depression. This may be severe, may require electro-convulsive therapy and may occur in up to 15% of patients treated with reserpine

(Freis, 1954; Achor, 1955; Bunney and Davis, 1965). Tetrabenazine has sedative properties in man and its administration has occasionally appeared to give rise to severe depression (Ashcroft, McDougall & Barker, 1961; Lingjaerde, 1963).

Drugs which elevate mood fall into three classes: monoamine oxidase inhibitors, amphetamines and tricyclic antidepressants. The evidence concerning these drugs relevant to the monoamine theory of depression is as follows:

Iproniazid was shown in 1952 to inhibit monoamine oxidase in the liver and brain in rats and guinea pigs (Zeller and Barsky, 1952). This drug was later shown to be an effective antidepressant (Loomer, Saunders & Kline, 1957) and it was suggested by these authors that the fact that iproniazid acted as a monoamine oxidase inhibitor might "in part explain its effect upon nervous and mental function, i.e. by altering the metabolic degradation of epinephrine, norepinephrine and serotonin". It was then shown that iproniazid increased brain levels of noradrenaline and 5-hydroxytryptamine in animals (Spector, Prockup et al, 1958) and it was later demonstrated that iproniazid, isocarboxazid and nialamide administration increased the levels of monoamines in human brain (Ganrot, Rosengren & Gottfries, 1962; Maclean et al, 1956). The state of sedation produced in animals by administration of reserpine is at times used as an animal analogue of depression in

man (Schildkraut & Kety, 1967). Monoamine oxidase inhibitors have been found to counteract this reserpine induced sedation in animals (Chessin, Kramer and Scott, 1957; Stein and Ray, 1960). It was largely on the basis of the effects of reserpine and monoamine oxidase inhibitors that the monoamine theory of depression was evolved (Jacobsen, 1964).

Amphetamines were introduced in the 1930's for the treatment of depression. In some depressed persons they produce a temporary alertness and euphoria (Klerman, 1972). There is evidence that amphetamines are able to increase the amount of monoamines available at synapses. Amphetamine releases noradrenaline from nerve cells and blocks its inactivation by cellular re-uptake in animals (Iversen, 1964; Glowinski and Axelrod, 1965).

In 1958, the antidepressant properties of imipramine were demonstrated (Kuhn, 1958). Various studies have shown this and related drugs to be at least as effective antidepressants as MAOIs and probably rather more so (Klerman & Cole, 1965). The fact that imipramine and similar compounds do not inhibit the monoamine oxidase or catechol-O-methyl-transferase systems which control monoamine degradation at synapses (Pletscher and Gey, 1962) initially cast doubt upon the monoamine hypothesis of the affective disorders. In one of the early formulations of the hypothesis Jacobsen (1964) said "Where the effect of

imipramine stands in this matter is still a complete riddle which must await elucidation. Here our present ignorance is such that not even a preliminary hypothesis can be offered". Imipramine was then shown to interfere with the uptake of infused noradrenaline. This blocking action by imipramine of the uptake of noradrenaline was first shown in peripheral tissues (Axelrod, Whitby & Hertting, 1961) and in brain slices (Dengler, 1961). Glowinski and Axelrod (1964) then demonstrated inhibition of uptake of tritiated noradrenaline in intact rat brain by the antidepressants imipramine, desmethylimipramine and amitriptyline thus demonstrating that tricyclic antidepressants have the ability to increase the amounts of monoamine available at synapses in the brain. It therefore became possible to reconcile the mode of action of imipramine and other tricyclic antidepressants with the monoamine theory of the affective disorders.

Although this theory was originally based upon evidence connected with the effects of drugs, further pieces of information relevant to the theory but not associated with the effects of drugs have come to light. They concern investigations designed to show whether or not there is evidence of reduced cerebral monoamine metabolism in depressed patients. This evidence is as follows:

Firstly, numerous studies have been conducted

to investigate the concentrations in cerebro spinal fluid of 5-hydroxy indole acetic acid (5HIAA), a metabolite of 5-hydroxytryptamine (5HT), homovanillic acid (HVA), a metabolite of dopamine, and 3-methoxy 4-hydroxyphenylglycol (MHPG) the major metabolite of noradrenaline in the brain (Maas & Landis, 1968). CSF 5HIAA levels have been shown to be lower in depressed patients than in neurological controls (Ashcroft et al, 1966), than in normal volunteers (Dencher et al, 1966) and than in non-affectively disturbed controls (Van Praag and Korf, 1971; Coppen et al, 1972). CSF HVA levels have been shown to be lower in depressed patients than in neurological patients (Papeschi & McClure, 1971). CSF MHPG levels have been shown to be lower in depressed patients than in manic patients or in a mixed group of normals and neurological patients (Post et al, 1973).

Probenicid inhibits the transport of acid monoamine metabolites from the central nervous system to the blood stream (Neff, Tozer & Brodie, 1967), the resulting accumulation of 5HIAA and HVA in the lumbar cerebro spinal fluid is used as an index of the central turnover of the corresponding parent amines. It has been shown that in depressed patients as compared with normals (Roos and Sjostrom, 1969) and as compared with non-affectively disturbed controls (Van Praag and Korf, 1973) there is a reduction in the increase in 5HIAA following probenicid.

Concentrations of tryptophan, the precursor of 5-hydroxytryptamine, in the CSF have been found to be lower in depressed patients than in neurological patients (Coppen, Brooksbank & Peet, 1972).

Studies of blood and urine levels of some of these substances have also been undertaken. Levels of free tryptophan in plasma have been shown to be reduced in currently depressed patients as compared with patients who had recovered from a depressive illness (Coppen, Eccleston and Peet, 1973). Urinary excretion of MHPG has been shown to be low in depressed patients as compared with normal controls (Maas, Fawcett, Dekirmenjian, 1968) and in patients in the depressed state as compared with a proportion of the same patient sample when well (Shaw et al, 1973). Urinary tryptamine excretion has been shown to be low in depression and to rise with recovery to approximately normal levels (Coppen et al, 1965). It was thought by the authors that this finding probably reflected a disturbance of tryptophan metabolism in the kidney but that there might be a similar disturbance in the brain during depression.

The levels of monoamines and their metabolites have been studied in the brains of suicides as compared with those of persons dying from other causes. 5HT levels (Shaw, Camps & Eccleston, 1967; Pare et al, 1969) and 5HIAA levels (Bourne et al, 1968) were found to be low in the brains from suicides.

These are the positive findings from direct studies of monoamines and their metabolites which support the monoamine theory but they have by no means always been confirmed by other workers. Bowers, Heninger & Gerbode (1969) found that CSF 5HIAA and HVA levels were no lower in depressed patients than in non-depressed patients. Roos and Sjostrom (1969) did not find CSF 5HIAA to be lower in depressed patients than in normal controls. Nordin, Ottosson and Roos (1971) in a study of depressed patients before and after treatment found that the pre-treatment levels of 5HIAA in the CSF of depressed patients did not differ from those of normal controls. Moreover the pre-treatment levels did not differ from those after treatment despite considerable clinical improvement. Ashcroft et al (1973) studied CSF levels of HVA and 5HIAA in depressed patients before and after recovery. Unipolar depressed patients had lower values of both HVA and 5HIAA than neurological controls but the levels did not alter significantly on recovery. Bipolar depressed patients had levels within normal limits. In this study CSF tryptophan was also measured. There was no significant difference in level between any of the groups of patients studied nor was there any alteration on recovery. Goodwin et al (1973) did not find any difference in the increase in 5HIAA following probenicid between depressed patients, manic patients and non-affectively disturbed controls.

Wilk et al (1972) found the CSF MHPG levels of depressed patients to be within the normal range and did not find that the levels changed with treatment.

While Bourne et al (1968), Pare et al (1969) and Shaw et al (1973) all found reductions in 5-hydroxy-tryptamine or 5-hydroxyindole acetic acid in the brains of suicides as compared with those of persons dying from other causes their results conflict. Bourne et al found that 5HIAA was reduced but that 5HT was not. Pare et al found that 5HT was reduced but that 5HIAA was not. Shaw et al found that 5HT was reduced and did not examine their specimens for 5HIAA.

The evidence provided in support of the monoamine theory of depressive illness by direct studies of monoamines and their precursors or metabolites in samples obtained from depressed patients is therefore somewhat equivocal. The results from pharmcological studies are less open to question but are only of any relevance to the theory that depressive illnesses are based upon lowered concentrations of transmitter amine at synaptic junctions if it can be shown that the drugs involved have undoubted antidepressant activity. The value of the evidence would be greatly enhanced if it could be shown that not only do antidepressant drugs have the ability to increase the amount of monoamine available at synaptic junctions but also that this is the means by which they act in naturally occurring depression. The antidepressant

effect of imipramine is well-established. Multicentre trials carried out both in Britain (Clinical Psychiatry Committee, 1965) and in the United States of America (Raskin et al, 1970) showed imipramine to be more effective than placebo and the majority of the many other trials of tricyclic antidepressants show them to be effective drugs (Klerman & Cole, 1965; Morris & Beck, 1974). The animal experiments in which it was demonstrated that imipramine has the ability to prevent re-uptake of monoamines (Glowinski & Axelrod, 1964) could not be repeated in depressed patients and so it is not possible to determine whether or not it is by this means that imipramine exerts its antidepressant effect.

There are few controlled clinical trials of amphetamines and those which have been carried out do not demonstrate that they are more effective as antidepressants than placebo (Hare, Dominian & Sharpe, 1962; General Practitioner Research Group, 1964). The fact that they are able to increase the amount of monoamine available at synapses cannot therefore be used as evidence for the monoamine theory of depressive illness.

There is a great deal of controversy regarding the antidepressant efficacy of monoamine oxidase inhibitors (MAOIs). Iproniazid, on which much of the early work was done, is not now used because of its association with serious side effects, principally

liver damage. What evidence there is concerning nialamide does not suggest that this is an effective antidepressant (Table I). The evidence regarding isocarboxazid, tranylcypromine and phenelzine is conflicting (Tables 2, 3 and 4). From these results it may be concluded that some patients recover from their depressive symptoms while they are on monoamine oxidase inhibitors and some do not. While some of this variability may be a dosage effect this does not explain it all. In one study it was shown that patients either responded well to MAOIs or did not respond at all (Hamilton, 1974). It has been suggested that it is in various subgroups of depressed patients referred to as "atypical depressive states", "hysterical depression" or "patients suffering from neurotic or reactive depressive illnesses or even sometimes anxiety hysteria" that MAOIs are effective (West and Dally, 1959; Dally and Rohde, 1961; Sargant, 1961). It is not always easy to define these subgroups and attempts to differentiate on clinical grounds those patients who will respond from those who will not have not been successful (Hamilton, 1974). It is possible that the responders differ from the non-responders in some way other than that of clinical presentation. It has been said that the mode of response to antidepressant drugs may be an inherited characteristic (Pare, Rees and Sainsbury, 1962; Pare and Mack, 1971). This could be because the illnesses from which patients suffer vary on a genetic basis or because their modes of responding

to drugs vary on a genetic basis. If the first alternative is true then some depressive illnesses have characteristics which cause them not to respond to drugs which have properties enabling them to increase the amount of monoamine available at synapses. It would follow from this that for some depressive illnesses at least the monoamine theory is inapplicable. The alternative explanation is certainly possible. Although in the past it tended to be assumed that the variability of drug metabolism and response was of the unimodal continuous type, it has become increasingly apparent that for numerous drugs this is not so - their dose-response curves are of a discontinuous type with two or more modes. These modes represent two or more genetically determined phenotypes and when this position occurs the term polymorphism is used. It is known that there is a polymorphism for the acetylation of certain drugs. Acetylation polymorphism was first studied with reference to the anti-tuberculous drug isoniazid which was shown to be effective in the treatment of tuberculosis in 1952 (Robitzek, Selikoff & Ornstein, 1952). Shortly afterwards it was found that patients differed greatly in the way in which they metabolised isoniazid (Hughes, Schmidt, & Biehl, 1955). This and other studies suggested that the variability in the inactivation of isoniazid is of the discontinuous kind, i.e. that the population is divided into two classes, rapid and slow inactivators.

Twin studies and racial studies (Bonicke & Lisboa, 1957; Harris Knight and Selin, 1958) suggested that there was a genetic basis for this polymorphism and a detailed study of 484 subjects (Evans, Manley & McKusick, 1960) offered definite evidence that this was the case. Intestinal absorption, protein binding, renal glomerular clearance and renal tubular absorption were found to be irrelevant to the polymorphism (Jenne, McDonald & Mendoza, 1961) and it seemed likely that the difference between rapid and slow inactivators was metabolic. The fact that the proportion of free unchanged drug excreted varied inversely with the proportion of acetylated drug (Hughes, Schmidt and Biehl, 1955) tended to suggest that the difference lay in speed of acetylation. This idea was confirmed when it was shown that the livers of rapid inactivators of isoniazid have greater acetylating powers than those of slow inactivators (Evans & White, 1964) and when it was demonstrated that acetylation was the primary metabolic reaction determining inactivator status for isoniazid (Peters, Miller & Brown, 1965). This polymorphism was shown to be of practical relevance by studies indicating that slow inactivators of isoniazid had a greater liability than fast to develop isoniazid induced peripheral neuropathy (Hughes et al, 1954; Devadatta et al, 1960). It is a reasonable assumption that the effects of any drug metabolised by polymorphic acetylation would vary as a result of it. In fact acetylation polymorphism accounts for little

C O R R E C T I O N

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The sentence:

"Sulphadimidine is polymorphically acetylated (Peters, Gordon & Brown, 1965) as are phthivazid (Smirnov & Kozulitzina, 1962) hydrallazine (Jenne, 1965) phenytoin (Butt et al., 1970) and dapsone (Gelber et al., 1971)."

should be deleted and replaced with the following passage:

"Sulphadimidine is polymorphically acetylated (Peters, Gordon & Brown, 1965) as are phthivazid (Smirnov & Kozulitzina, 1962) hydrallazine (Jenne, 1965) and dapsone (Gelber et al., 1971). Polymorphic acetylation may also be relevant for the metabolism of phenytoin (Butt et al., 1970)."

of the widespread variability in the response of human subjects to the vast range of drugs which they ingest as few drugs are metabolised by this means. Sulphadimidine is polymorphically acetylated (Peters, Gordon & Brown, 1965) as are phthivazid (Smirnov & Kozulitzina, 1962), hydrallazine (Jenne, 1965), phenytoin (Kutt et al, 1970) and dapsone (Gelber et al, 1971). It seems possible that other hydrazine derivatives might be metabolised in a similar way. Several MAOIs are hydrazine derivatives. If they were inactivated by acetylation the slower inactivation among slow acetylators might lead to a much higher effective dose in them than in fast acetylators and this might explain the very variable results which have been found with these drugs (Tables 1-3). Furthermore, acetylator status is genetically determined and if inactivation of hydrazine MAOIs was dependent upon it an explanation for the genetic tendency of the response would be provided. The possibility that the response of depressed patients to a hydrazine MAOI might depend upon acetylator status was studied by Evans, Davison & Pratt (1965). This was an uncontrolled study of 24 patients with neurotic depression and 23 with endogenous depression who were given phenelzine in a dosage of 15 mg. t.i.d. for 4 weeks. No significant differences in antidepressant effect were found between slow and fast acetylators but severe side effects were reported only by slow acetylators. In this study the mean age of the

endogenously depressed slow acetylators was 48.59 ± 2.87 years while that of the endogenously depressed fast acetylators was 38.38 ± 3.47 years. This may have some bearing upon the results. It is well established that the clinical course and symptomatic picture of depressions varies with the age of the patient (Klerman, 1972). Depressed patients under 40 respond significantly better to treatment with drugs than those over 40 (Greenblatt, Grosser & Wechsler, 1962). The placebo response of patients under 40 is greater than that of those over 40 (Raskin et al, 1970). All of these factors may have contributed to the negative result and a placebo controlled study in which the fast and slow acetylators were matched for age as well as other factors would be required to resolve this question. Although there is no doubt that monoamine oxidase inhibitors have the ability to increase the amount of available monoamine by inhibiting monoamine oxidase, evidence which links the degree of inhibition of the enzyme with antidepressant effect is somewhat lacking. An uncontrolled study of six depressed patients showed that monoamine oxidase inhibition, as measured by increase in urinary tryptamine and decrease in urinary VMA was greater in those patients with a good clinical response than in those in whom the clinical response was poor (Dunlop et al, 1965). In an uncontrolled study of a group of 21 depressed

patients consisting of 10 psychoneurotics, 8 manic-depressives, 2 schizophrenics and 1 reactive depressive who were variously treated with phenelzine, isocarboxazid and nialamide, inhibition of monoamine oxidase was estimated by the conversion of orally administred 5HTC^{14} to 5HIAA-C^{14} (Feldstein et al, 1965). In those patients whose clinical improvement as based upon global impressions and ward observations was said to be marked or moderate the mean MAO inhibition was 37%. Of those showing slight or no clinical improvement the mean MAO inhibition was 22%. Against these positive studies are the negative findings of Resnick et al (1960) and Dewhurst and Pare (1961). In a study of schizophrenic, manic-depressive, psychoneurotic and involutional melancholic patients, numbering 12 in all, treated with various MAOIs Resnick et al did not find any correlation between MAO inhibition and antidepressant effect. Dewhurst and Pare treated 18 patients with nialamide and found no relationship between antidepressant effect and inhibition of MAO. Robinson et al (1973) carried out a trial of phenelzine /placebo in 60 patients with depressive-anxiety states. Phenelzine was shown to be significantly more effective than placebo, the dosage of phenelzine being adjusted to maintain MAO inhibition at 80%. No information was obtained about the effects of phenelzine when inhibition of this degree was not produced.

It was against this background that the studies to be described were designed. In summary, the aetiology of the common and disabling disorder depressive illness is unknown. A theory which postulates that depression is associated with a deficiency of monoamine transmitter at synaptic sites has been put forward. The evidence for this is in two sections. Some is based on pharmacological studies and some on more direct studies of monoamines and their metabolites. The results given by the direct studies of monoamines are by no means unequivocal. The pharmacological evidence concerns the fact that both major groups of antidepressants, the tricyclics and the monoamine oxidase inhibitors, have properties which enable them to increase the amount of monoamine available at synapses. This evidence can only be used to support the monoamine theory of depressive illness if it can be shown that these drugs are effective antidepressants and that their antidepressant efficacy is related to their ability to increase monoamine at synaptic sites rather than to some other property of the drug. The evidence that tricyclics are effective antidepressants is convincing. The direct demonstration, in human subjects, of the block of re-uptake of monoamine at synaptic sites, which these drugs have been shown to produce in animals, is not possible. There is therefore no means of relating their antidepressant efficacy to increase in available monoamine at

synaptic sites. The evidence that MAOIs are effective antidepressants is less convincing. From the point of view of the monoamine theory of depressive illness this is disappointing. Very variable results have been obtained by different groups of investigators and it has not been possible to determine on clinical grounds which depressed patients will respond to these drugs. Several MAOIs are hydrazines. Other hydrazines have been shown to be inactivated by acetyl transferase, an enzyme for which there is a human genetic polymorphism approximately half the population being fast acetylators and half slow. The clinical effects of these other hydrazine drugs have been shown to relate to acetylator status. In the one existing study relating the antidepressant effects of MAOIs to acetylator status the groups were ill-matched for age so that it is difficult to interpret the results. The mechanism by which MAOIs are able to increase the amount of monoamine available at synapses is by inhibition of monoamine oxidase. It is technically possible to estimate the degree of inhibition of monoamine oxidase in depressed patients but evidence relating the antidepressant efficacy of MAOIs to inhibition of monoamine oxidase is somewhat scanty and again the results of different investigators are variable. The studies to be described have been designed to test the hypothesis that the effects of a hydrazine MAOI are dependent on acetylator status, this drug being metabolised by acetylation, a

mechanism for which there is a genetic polymorphism.

If the hypothesis is true it is predicted that :-

a) the antidepressant effect of the drug would be greater in slow acetylators than in fast.

b) the difference between the efficacy of phenelzine and placebo would be greater in slow acetylators than the same difference in fast.

c) the side effects of phenelzine would be greater in slow acetylators than in fast.

d) slow acetylators would achieve a greater degree of inhibition of monoamine oxidase than would fast acetylators.

e) slow acetylators would achieve higher levels of free phenelzine than would fast acetylators.

The findings of this study will provide needed evidence for or against the monoamine theory of depressive illness.

MATERIALS and METHODS: 1st STUDY.

The initial step in examining this hypothesis was to find out if acetylator status was a significant determinant of the antidepressant effect of hydrazine MAOIs and the first experiment was designed for this purpose. The results of this part of the study have already been published (Johnstone & Marsh, 1973). In designing this project the following factors were taken into account.

PATIENT SELECTION

The antidepressant effect of MAOIs is open to question (Tables 1-4). There is evidence to suggest that it is in patients with 'atypical' depression that MAOIs are effective (Sargant, 1961; West & Dally, 1959; Dally & Rohde, 1961; Robinson et al, 1973). They have however been shown to be no more effective than placebo in samples of inpatients containing a proportion of cases of endogenous depression (Tables 1-4). It was therefore decided to confine the study to outpatients whose depressive illness was not of the endogenous type. It is not possible to define clear clinical characteristics of those patients who are likely to respond to phenelzine (Hamilton, 1974) nor indeed is it easy to define the concept of atypical depression. The criteria for including a patient in the study were therefore somewhat arbitrary. They were as follows:-

All patients with a complaint of depression referred from all sources to the psychiatric department, Eastern District Hospital between 1st December, 1971 and 1st October, 1972 were interviewed by one of the two psychiatrists concerned in the project to see if they were suitable for the study. They were included in the study if they had a depressive illness not secondary to any other psychiatric or physical disorder, if that depressive illness did not have endogenous characteristics and if they consented to participate. Clearly the interviews required to be standardised. Standardised psychiatric interviews have been in use for a number of years (Overall & Gorham, 1962; Wing et al , 1967). These tend to emphasize psychotic features and would be inappropriate for the majority of the patients who would be seen. The Standardised Psychiatric Interview devised by Goldberg et al (1970) seemed suitable for this purpose. It was intended for use in community surveys and for this reason is designed to be acceptable to individuals who may not see themselves as psychiatrically ill. Although our patients were attending a psychiatric clinic for many of them this would be a first such attendance and they might well resent any implication that they were out of touch with reality. An interview designed to have this type of acceptability therefore seemed appropriate. The Goldberg interview incorporates a past medical and psychiatric history

together with questions to detect all reasonably common psychiatric disorders and was therefore a convenient instrument for identifying patients with depressive illness which was not secondary to any other physical or psychiatric disorder. It was used modified only by questions regarding previous alcohol and drug ingestion. The neurotic/endogenous rating scale devised by Carney, Roth and Garside (1965) was administered to the patients who had been found to have a primary depressive illness in order to eliminate those with endogenous depression. By these means we defined a population of patients with primary depressive illness of neurotic type and if they consented they were included in the study.

DRUG REGIME

Three hydrazine MAOIs are in ordinary use, nialamide, isocarboxazid and phenelzine. The efficacy of none of these is certain although the evidence suggests that phenelzine and isocarboxazid are more effective than nialamide (Tables 1, 2, and 3). Phenelzine was chosen for the trial because it has been more widely studied than isocarboxazid.

The high incidence of response to placebo in depressed patients (Greenblatt, Grosser & Wechsler, 1964; Friedman et al, 1966; Klerman & Cole, 1965) made a placebo controlled trial essential. A double blind crossover design of phenelzine and placebo was used. This meant that none of the patients was

deprived of active medication and it allowed us to examine any tendency to relapse on cessation of the active drug. It is a common experience that patients are inclined to drop out of drug trials for a variety of reasons (Robinson et al, 1973; Raskin et al, 1970). In an attempt to keep this to a minimum we wanted to avoid undue prolongation of the trial. The duration of published trials of phenelzine is variable but Rees and Davies (1961) found it to be effective given for three weeks in a dosage of 90 mg./day. We decided upon a similar dosage so that the trial period was six weeks, each patient having three weeks of placebo and three weeks of active drug. Although Rees and Davies did not describe a high incidence of severe side effects 90 mg./day seemed a high starting dosage for outpatients and our patients were therefore given 15 mg. phenelzine t.i.d. for the first week of active medication and this was followed by 30 mg. t.i.d. for two weeks.

DETERMINATION OF ACETYLATOR STATUS

In 1969 Evans introduced a much simplified method of determining acetylator status by means of a sulphonamide loading technique.(Evans, 1969). This was used. One week following the initial assessment the patients returned to the clinic in a fasting state and were given a body weight related dose of sulphadimidine according to the following dosage schedule.

TABLE 5

Body Weight (Kg)	Dose Sulphadimidine (mg)
<51	500
51 to 83	750
>83	1000

Six hours later 20 mls of venous blood was removed and the amount of free and total sulphadimidine estimated. From these results the percentage of the dosage which was acetylated was derived and by this means the population was divided into fast and slow acetylators. Urinary excretion of free and total drug can also be used for this estimation but it was felt that among this group of outpatients it would be difficult to collect accurate-timed urine samples. The results of the determination of acetylator status were retained by the biochemist until completion of the study.

EVALUATION OF MENTAL STATE

Many rating scales have been developed to provide objective measurements of depressed mood. Well-known among these are those devised by Hamilton, Beck, Zung and Snaith (Hamilton, 1960; Beck et al, 1961; Zung, 1965; Snaith et al, 1971). These ratings tend to be more applicable to patients with endogenous depression than to patients such as ours. Moreover many depression scales are self-rated and require a degree of verbal sophistication not possessed by our patients. None

of the well-known depression scales appeared suitable. In many studies of depressive illness global impressions are used as an index of change. This has the disadvantage that others have no means of knowing what the ratings used meant to the rater and it was felt that a more standardised mode of rating would be preferable. We initially assessed the patients by means of the Standardised Psychiatric Interview (Goldberg, 1970) in which 10 groups of symptoms (Figure 1) and 12 manifest abnormalities (Figure 2) were each rated on a 5-point scale (0-4). A manual describing the degree of severity which is appropriate to each rating is provided so that the severity described can be understood and replicated. Clearly the whole Goldberg interview was unsuitable for the purpose of rating change as some of the items would obviously be inapplicable. It did however seem that a score derived from those items which were appropriate to our cases would be useful. It would be understandable to the patients and it would be possible for others to know what we meant by the varying degrees of severity. From the symptom areas we omitted somatic symptoms, fatigue, sleep disturbance, irritability, lack of concentration and depersonalisation. The first three were omitted because they are reported side effects of phenelzine. A complaint of irritability tended to reflect changes in the unstable domestic environment of many of our patients rather than a change in mental state. Lack

of concentration was omitted as it was a concept which many of the patients confused with drowsiness and depersonalisation was omitted because it occurred very rarely. We therefore rated only the symptom areas :-

DEPRESSION

ANXIETY

PHOBIAS

OBSESSIONS/COMPULSIONS

With regard to the manifest abnormalities persons showing any of the following :-

ELATED, EUPHORIC

FLATTENED, INCONGRUOUS

THOUGHT DISORDER, DELUSIONS

HALLUCINATIONS

INTELLECTUAL IMPAIRMENT

were excluded at the initial interview on the basis that these are not features of a primary depressive illness. Goldberg (1970) states that the reliability of the item "histrionic" as a description of interview behaviour is questionable and points out that it is at least as much a personality variable as an index of morbidity. For this reason it was omitted as were "lack of spontaneity" and "suspicious". In our non-psychotic population these would never be rated at a high level and seemed inclined to reflect personality variables and initial shyness rather than change in mood. "Excessive concern with bodily

functions" was omitted for the same reason as "somatic symptoms" namely because it seemed possible that change in this item might reflect side effects rather than mood change. This left the three items

DEPRESSED

ANXIOUS/TENSE

DEPRESSIVE THOUGHT CONTENT

"Depressive thought content" was also omitted. This was because the raters found it difficult to separate this variable from the symptom of depression, clinically observable depressed mood and depressive ruminations ratable under obsessions. In view of the fact that so many items were being omitted it seemed best to omit this one also and avoid any confusion produced by the same feature being rated twice. The manifest abnormalities rated were therefore:

DEPRESSED

ANXIOUS/TENSE

In the Standardised Goldberg Interview the overall severity is derived as follows :-

$$\text{OVERALL SEVERITY} = \begin{matrix}\text{TOTAL}\\ \text{SYMPTOMS}\end{matrix} + \left(\begin{matrix}\text{TOTAL MANIFEST}\\ \text{ABNORMALITIES}\end{matrix}\right) \times 2$$

The overall severity of the modified score used in this study was derived in the same way. It was fully realised that this modified score used as an index of rate of change did not have the tested reliability of the Goldberg score but it was felt that it was a simple understandable and replicable method of

assessing the changing mental status of our patients. Ratings were made immediately before medication was commenced and at weekly intervals during the six-week period of the study.

SIDE EFFECTS

It is often difficult to assess the side effects of drugs. Frequently there is no objective means of measurement and one is dependent upon the patient's subjective complaints about the relevant symptoms. Such complaints depend upon factors such as the patient's degree of stoicism as well as upon the severity of the effects. This difficulty can never be entirely overcome but in an attempt to minimise it we devised a list of known side effects of the administration and abrupt withdrawal of phenelzine. Our source of these effects was a standard account of psychotherapeutic drugs (Brucke, Hornykiewicz & Sigg, 1970) (Figure 3).

The ratings were :-

0 = ABSENT; 1 = PRESENT; 2 = SEVERE.

The total side effects score was devised by addition of the individual scores. Ratings were made immediately before medication was commenced and at weekly intervals during the six-week period of the study. It was thought that the fact that the side effects were rated in this way before commencement of any drugs and while the patients were on placebo

as well as while they were on active drug would make the actual incidence of symptoms resulting from drug ingestion clearer than would dependence upon a spontaneous report of the symptoms from the patients.

FOLLOW-UP

At the end of the six week course of phenelzine/placebo the drugs were stopped. The patient's part in the study terminated at that point and each patient was thereafter treated as seemed appropriate. If the patients were well they were not asked to continue to attend the clinic although if they still had symptoms their attendance was naturally continued. At a mean of 22 weeks from completion of the course of phenelzine/placebo the patients were contacted by letter and asked to attend for a follow-up visit at which the Standardised Psychiatric Interview (Goldberg, 1970) was administered.

OTHER CONSIDERATIONS

Previous drug ingestion:

It was determined to exclude from the study any patients who had had a course of MAOIs in the previous six months. The chronic administration of various hypnotics, tranquillisers and other drugs increases the amount of drug metabolising enzymes in the liver (Evans, 1968(a)) and thus previous drug experience may be relevant to studies of the effects of drugs. The enzymes for acetylation

have been shown to be non-inducible (Levi & Walker, 1966; Evans, 1968(b)) and therefore it was felt that apart from MAOI ingestion previous drug experience was not relevant to the study. As the intention was to study the effects of phenelzine/ placebo alone and not combined with any other drugs patients were advised to stop all drugs at the time of the initial interview, i.e. one week before commencing phenelzine/placebo.

Dietary restrictions:

Hypertensive attacks during treatment with monoamine oxidase inhibitors were first described in tuberculous patients who were being treated with iproniazid (Ogilvie, 1955). Following the introduction of monoamine oxidase inhibitors as antidepressant agents numerous reports were made of the occurrence of these attacks which may be serious and associated with fatal intracranial haemorrhage (Clark, 1961; McClure, 1962; Dorrell, 1963). A detailed study showing the relationship between the consumption of certain dietary articles and the occurrence of hypertensive crises was carried out by Blackwell et al (1967). Many of the earlier reports concern tranylcypromine. In Blackwell's study several MAOIs were used. The incidence of hypertensive attacks was five times greater in patients on tranylcypromine than in those on phenelzine but hypertensive crises did occur in

patients on phenelzine. It was clearly established that the occurrence of hypertensive attacks in patients on MAOIs was associated with the ingestion of tyramine-containing foods. In 1969 it was demonstrated that the ingestion of phenylpropanalamine, a common constituent of proprietary cough and cold remedies, by patients on MAOIs provoked a rapid and potentially dangerous rise of blood pressure (Cuthbert, Greenberg & Morley, 1969). It had previously been shown that MAOIs potentiate the effects of barbiturates by inhibiting barbiturate metabolising enzymes (Laroche & Brodie 1960) and similar effects have been shown to take place with pethidine (Shee, 1960). It is therefore essential that patients on MAOIs avoid tyramine-containing foods and drugs which have not been prescribed for them by a physician who is aware of the MAOI ingestion. As this was an outpatient trial there was particular concern about the necessity of impressing the need for these restrictions upon the patients as this aspect could not be controlled. The dangers were stressed heavily and the patients were supplied with a card explaining about the prohibited substances. The patients were told to take no other drugs during the study without the permission of the trial psychiatrists. The general practitioners of the patients were contacted and informed of this arrangement.

The results of drug trials can have little meaning if the patients do not take the drugs. It has been shown that the percentage of psychiatric outpatients who do not take their drugs is as high as 48% (Willcox, Gillan and Hare, 1965). It was stressed to the patients that they must take the drugs exactly as prescribed. The patients were given one week's supply of tablets at a time and a small excess was provided so that tablet counts would give some measure of the patient's ingestion of the drug. Two urine samples were taken from each patient and tested for phenelzine (Tilstone, unpublished work). These were not taken at any specific week but one was taken during each three-week period of the study so that for each patient one of the two samples should have been positive. Where this did not happen it was put to the patient at follow-up that we had reason to believe that he had not taken his tablets. By these means we attempted to ensure that the patients in the study did take their drugs but it is realised that this may not have been so.

In summary, the regime for the first study was as follows :-

Week-1: initial visit: assessment with Standardised Psychiatric Interview (Goldberg et al, 1970) and neurotic/endogenous rating (Carney, Roth and Garside, 1965). Decision made re

inclusion in study: patient advised to stop all drugs.

Week-0: Estimation of Acetylator Status (Evans, 1969): Administration of side effects score: Administration of modified Goldberg score: One week's supply of phenelzine/placebo given: warning given re dietary and drug restrictions.

Week 1-5: Administration of side effects score: Administration of modified Goldberg score: One week's supply of phenelzine/placebo given: warning re dietary and drug restrictions: urine samples taken on two occasions.

Week-6: Administration of side effects score: Administration of modified Goldberg score: Drug stopped: patient advised to maintain dietary restrictions for ten days: patient's part in trial terminated.

RESULTS OF FIRST STUDY

During the study 257 patients were referred to the clinic because of a complaint of depression. The outcome of these referrals is seen in Table 6. 97 patients who were diagnosed as having neurotic depression according to the criteria previously described began the study. The outcome in these 97 patients is seen in Tables 7 and 8. Of the 79 who finished, 7 were not shown to have phenelzine in either of the urine specimens which were tested. It was put to them that they had not been taking the tablets and they agreed that this was so. Our final population therefore consisted of 72 patients and it is only to these patients that the results refer. An obvious criticism of this study would be that the side effects might make the allocation of placebo/phenelzine apparent to the raters. For this reason each rater independently made a note of at which three-week period he/she thought that the patient was taking the active drug. In 27 of the 72 cases at least one rater was wrong. The final population of 72 patients was found to consist of 33 fast and 39 slow acetylators and they are best considered in 4 groups

FAST ACETYLATORS on PLACEBO FIRST

FAST ACETYLATORS on DRUG FIRST

SLOW ACETYLATORS on PLACEBO FIRST

SLOW ACETYLATORS on DRUG FIRST

Comparisons between the groups were made by Students 't' test (unpaired). The starting scores of the 4 groups were not significantly different from one another (Table 9). There was no significant difference between fast and slow acetylators with regard to placebo response (Tables 10 and 11) and indeed there was no consistent trend (Table 12). On drug, however, the slow acetylators improved more than did the fast and in the first three-week period this difference was statistically significant. In the second three-week period the trend remained but statistical significance was not reached (Tables 13 and 14). When drug was compared with placebo it was found that for fast acetylators the drug was not significantly more effective than placebo but that for slow acetylators phenelzine was more effective than placebo to a highly significant degree (Tables 15 and 16).

In this study the side effects check list previously described was used to assess side effects. The patients achieved high scores before drug treatment was commenced and while on placebo as well as while taking active medication (Figures 4-7). It was felt that the tendency of the patients to complain of the symptoms in the side effects check list while depressed might be obscuring differences in the physical symptoms actually produced by the drug. For this reason, in the second study, a

description of which follows, although the entire score was administered individual side effects were examined and a new score was evolved composed only of those symptoms which showed a tendency to increase at some point while the drug was being taken. Retrospectively this was done with the results of the first study (Tables 17-20). The symptoms which showed a tendency to increase were fairly consistent in the four groups. They were - headaches, insomnia, tremor, ataxia, fatigue, apathy, sweating, constipation, faints/dizziness, micturition difficulty and blurred vision. Scores using these symptoms plus any other new symptoms spontaneously reported by the patients were made and the groups were compared in terms of these (Tables 21 and 22) (Figures 8 and 9).

In general terms the patients improved considerably during the study. On the Modified Goldberg Score, the mean score of all the patients at the outset of the study was 15.2. For those who went on to complete the course it was 14.9 and their mean finishing score was 1.9. The patients were seen for a follow-up visit at a mean of 22 weeks after completing the course of phenelzine/placebo. 85% attendance was achieved and at that time the mean score was 2.2. In view of the fact that this 22 week period was uncontrolled with respect to further treatment, intercurrent illness or changed circumstances this result was not examined in any further detail.

MATERIALS and METHODS: 2nd STUDY

INTRODUCTION

These studies were undertaken to examine the hypothesis that the effects of hydrazine MAOIs, of which phenelzine was used as the most studied example, are dependent upon acetylator status, the drug being metabolised by acetylation. The results of the first study showed that the first two predictions namely:

1) The antidepressant efficacy of the drug will be greater in slow acetylators than in fast

2) The difference between the efficacy of phenelzine and placebo will be greater in slow acetylators than in fast

were correct. The results regarding the third prediction:

3) The side effects of phenelzine will be greater in slow acetylators than in fast

were inconclusive.

These results support the hypothesis and therefore a second study was carried out in which the following variables were examined:

1) Acetylator Status
2) Antidepressant Response
3) Side effects
4) Degree of inhibition of monoamine oxidase
5) Levels of free phenelzine.

Study of these variables would make it possible to determine whether or not the last two predictions namely:

4) Slow acetylators will achieve a greater degree of inhibition of monoamine oxidase than fast

5) Slow acetylators will achieve higher levels of free phenelzine than fast.

were correct.

The studies of MAO inhibition and phenelzine levels necessitated strict control of the timed ingestion of the drug and repeated collections of blood and urine. This study could therefore only be carried out on inpatients. This meant that an opportunity would be provided for checking, in patients known to be taking their medication, the findings of the first study relating antidepressant effect and incidence of side effects to acetylator status. It is known that a high proportion of psychiatric outpatients do not take their drugs (Willcox, Gillan and Hare, 1965). Despite our precautions some of the patients in the first study may not have taken their tablets and this could obviously affect the results. In order that the two studies would be comparable the methods used in the second study closely resembled those of the first.

PATIENT SELECTION

This study concerned depressed patients of

non-endogenous type whose illness was not secondary to any other physical or psychiatric disorder. This trial was confined to patients conforming to these criteria, who agreed at the outset to come into hospital for four weeks. Most of the patients were selected from those referred with a complaint of depression to the psychiatric clinic at Eastern District Hospital, Glasgow or to the outpatient clinic of the Glasgow University Department of Psychological Medicine. Six to eight patients per week were seen from 1.3.73 until 31.7.74. A few other patients were referred by other psychiatrists in both hospitals as possibly suitable and the selection procedures also applied to them. The means of selection were similar to those used in the first study. The Standardised Psychiatric Interview (Goldberg et al, 1970) was used and the Neurotic/ Endogenous rating (Carney, Roth and Garside, 1965) was applied to those who had a depressive illness not secondary to any other physical or psychiatric disorder. The study was explained to those patients who were suitable and if they agreed to participate their admission was arranged and they were included in the study.

DRUG REGIME

As in the first study phenelzine was used. It was felt that the estimation of phenelzine levels would be simplified if the dosage was constant

throughout the period of the study and the drug was therefore given in a dosage of 30 mg. t.i.d. for 21 days. This second study was not placebo controlled. On theoretical grounds placebo control would have been desirable but it was thought to be impracticable in this inpatient study. The depressive illnesses of neurotic type, from which these patients suffered, are frequently treated on an outpatient basis. The patients in this study were being asked to agree to a four-week admission which could possibly have been avoided, at least in some cases. Extending this admission to at least six weeks, which would have been necessary had the phenelzine/placebo crossover design of the first study been used, would have placed an unreasonable burden upon the patients and upon the hospital services. It would have been possible to give half of the patients phenelzine and half of them placebo. This would have meant asking patients, who could possibly have been managed as outpatients, to agree to a four-week period of hospital care during which they would be deprived of effective treatment. It was not felt that patients could be treated in this way. Because of these objections and because the effects of phenelzine/placebo, as related to acetylator status, had already been examined in the first study, all of the patients were given a three-week course of phenelzine 30 mg. t.i.d. without placebo control.

DETERMINATION OF ACETYLATOR STATUS

This was done by means of the sulphadimidine loading technique initially described by Price Evans (1969) and further discussed by Rao et al (1970), Eze and Evans (1972) and Schroder (1972). Using the sulphadimidine loading method either urine or blood samples can be used for estimation of free and total sulphadimidine. In the first study blood samples were used. In the more controlled conditions of this inpatient study it was possible to use urine samples collected for one hour between five and six hours after ingestion of the drug which was given according to the dosage schedule described in Table 5. Urine samples were used in order to minimise the number of venepunctures that would be required. In ten of the patients the estimation was also performed on a blood sample. This was done to confirm that the results with urine are comparable with those with blood and to clarify the result in those patients in whom the percentage acetylated was close to the dividing line between fast and slow acetylators. There is some difference of opinion about the point at which this division should be made, figures of 65% and 70% being used in different studies and in patients whose result fell between these points the test was repeated using a blood sample. The sulphadimidine was estimated both by the method described by Price Evans (1969) and by that described by Schroder (1972).

EVALUATION OF MENTAL STATE

The changing mental states of the patients were

assessed using the modification of the Goldberg (1970) interview earlier described. This rating was made at the time of the initial assessment, following hospital admission but prior to commencing medication and on the 7th, 14th and 21st days of treatment. A further rating was made on the third day after stopping the drug to assess the mental state when the patient was drug-free. Further ratings were made after discharge, four weeks and eight weeks after cessation of the drug, to assess any tendency to relapse. In the initial study many patients stated that they had improved suddenly over a period of about twenty-four hours at some point between the weekly ratings. For this reason it was felt that ratings should be carried out at least once per day. For such frequent assessments to be made the rating required to be very simple: Visual Analogue Scales (Aitken, 1969; Zealley & Aitken, 1969) seemed appropriate. The patients rated themselves on 3 variables: anxiety, tension, and depression, morning and evening throughout the study. This allowed the patients' mental states to be sampled frequently, simply and without causing them any distress. It also meant that a self-rating scale was included in the study. As all of the other assessments were being carried out by the author this was useful as it would combat any personal preconception and prejudice.

SIDE EFFECTS

Side effects were rated using the same side effects

check list as was used in the first study. The rating was made the day before treatment was begun, on the 7th, 14th and 21st days of treatment and on the 3rd day after it was stopped (Day 24). It was evident from the first study that many of the somatic complaints to which the patients admitted when the side effects score was administered reflected depressed mood rather than effects of the drug as many of the patients had higher scores before starting the drug than they had while on it. Therefore, although the score was administered unchanged, it was determined to assess which of the items did in fact show any tendency to increase while the patients were on the drug and to assess the side effects in terms of these.

ESTIMATION OF INHIBITION OF MONOAMINE OXIDASE

Monoamine oxidase (MAO) occurs in many tissues of the body including the liver, the kidney, the plasma and the platelets as well as the nervous system. Some investigators have found that MAO exists in multiple forms in a single tissue. Although there are authors (Houslay & Tipton, 1973) who suggest that these findings may be due to artefact, Youdim et al (1972), studying the brains of deceased persons, concluded that in human brain MAO exists in four forms and that the degree to which each of these is inhibited by various MAOIs is variable. Squires (1972) showed that MAO existed in two forms in various tissues in several mammalian species. Platelet and plasma MAO have been shown in man to differ from each other and

from liver MAO (Robinson et al, 1968) and these authors showed that the degree of inhibition produced by various MAOIs in plasma and platelet MAO is not the same.

From the point of view of considering the relevance of inhibition of MAO to antidepressant activity and the implications of this for the monoamine theory of depressive illness, it is the inhibition of MAO within the brain which is important. At present it is not possible to estimate in living subjects inhibition of total brain MAO and certainly not inhibition of the various forms of brain MAO. There are various methods of estimating inhibition of MAO. The use of these in connection with testing the monoamine theory of depression involves making the assumption that the degree to which MAO is inhibited in the site tested is a measure of the degree of inhibition of MAO in the brain. Methods of estimating inhibition of MAO include the following. Firstly, there are those involving urinary estimation of a monoamine substrate of MAO. The most commonly used substrate is tryptamine. Normally tryptamine is metabolised by MAO to indole-3-acetic acid and if MAO were inhibited this would be expected to lead to increased urinary excretion of tryptamine. This was shown to occur in 1959 (Sjoerdsma et al, 1959) and these authors stated that the level of urinary tryptamine was a sensitive index of monoamine oxidase inhibition. Secondly, there are those involving

urinary estimation of a metabolite of a monoamine substrate of MAO. When MAO is inhibited the normal metabolic path is blocked and the urinary level of the metabolite will fall. 5HIAA and VMA can be used for this purpose but the changes in level are much less marked than the changes in tryptamine level (Dunlop et al, 1965). Moreover the metabolites are present in such low concentrations that estimation is difficult (Dewhurst and Pare, 1961). For this reason a loading dose of enzyme substrate, e.g. 5-hydroxytryptamine, may be given before its major metabolite, in this case 5HIAA, is estimated in the urine (Dewhurst and Pare, 1961; Sjoerdsma, Gillespie and Udenfriend, 1958). Related to this method is that using a loading dose of C^{14} labelled adrenaline (Resnick et al, 1960). In this method the amount of radioactivity in the urine is used as an index of MAO inhibition. All of these methods are indirect. In 1968 a technique of direct assay of MAO in platelets and plasma using radioactive substrates was introduced (Robinson et al, 1968). Of these methods the estimation of urinary tryptamine is the simplest and the method of Robinson et al the most direct. Results with urinary tryptamine correlate well with inhibition of platelet MAO (Robinson et al, 1968). Estimation of platelet MAO could not be undertaken in Glasgow and repeated estimations would have involved repeated venepunctures. Estimation of urinary tryptamine is simple and could be done locally. As only urine samples are required repeated testing could be carried out with minimal

inconvenience to the patients. For these reasons it was decided to use estimation of urinary tryptamine to measure inhibition of MAO. 24 hour urine collections were carried out continuously for the 21 days of phenelzine administration and for 3 days after it was stopped. There was no intention of doing daily estimations but it was felt that it would be less confusing for the patients if continuous collections were carried out than if collections were carried out some days but not others. The urine was frozen following collection and 100 ml. aliquots stored at -20°C without preservative until the estimations could be carried out. This was done by the method described by Sjoerdsma et al (1959).

ESTIMATION OF PHENELZINE LEVELS

Estimation of monoamine oxidase inhibitors in biological samples is difficult. A method of detecting monoamine inhibitors in biological samples was published in 1970 (Curry and Mercier, 1970). This method is based on the inhibitory action of these drugs on the activity of MAO. This being the case this method was unsuitable for this study as it was hoped to examine the levels of the drug and the degree of inhibition of MAO separately and see if there was a relationship between these two variables. During the initial study a gas chromatographic method of detecting phenelzine in the urine was developed (Tilstone unpublished). Samples from poisoning cases are dealt with in the same laboratory and at the time of the first study samples

were obtained from a man who had successfully committed suicide by ingesting an unknown quantity of phenelzine tablets. This man was not in the study and was not known to the doctors involved. In blood from this patient a level of phenelzine of 2 ug/ml was detected by the method evolved in this laboratory from the initial urine studies. This method was further developed so that free phenelzine was detected and it was decided that it was practicable to make the determination of free phenelzine levels part of the second study. This method involves the conversion of free phenelzine to phenelzine acetonide and the measurement of this substance by gas chromatography. Acetylated phenelzine is not detectable by this method which was devised by Caddy & Tilstone (unpublished). The method is as follows :-

Phenelzine was assayed by gas liquid chromatography as the acetonide derivative on 10% apiezon - L on gas chrom Q at 180°C. 20 ml of urine was added to 10 ml of a 1:1 mixture of ether and acetone and shaken. 1 ml of phendimetrazine bitartrate 11.2 ug/ml was added as an internal standard and 3 drops of saturated sodium carbonate were also added. Phenelzine acetonide was extracted in the ether layer on a roller mixer for half an hour. The ether phase was removed and concentrated to 100 ul. 2 ul aliquots were injected onto the GLC. Quantitation was by peak height ratios of phenelzine to phendimetrazine by reference to a standard curve of 1-10 ug/ml. Complete recovery of phenelzine was attained and the standard deviation was better than 2%. The identity of the

phenelzine acetonide peak was confirmed by reference to the retention times of standard material and by mass spectrometry.

It was hoped that this method could be used to detect plasma levels of phenelzine although it was not known whether or not therapeutic dosages of phenelzine would give levels above the detection limit of 0.5 µg/ml in all or any of our patients. Drug concentrations in urine are up to 100 times higher than those in plasma, the exact relationship depending on the extent of tubular reabsorption. Moreover it is possible to use much larger volumes of urine than can reasonably be obtained of plasma. For these reasons the detection of free phenelzine in urine was expected to be much simpler and we were hopeful of obtaining clear-cut results using urine.

The relationships between the amount of drug excreted in urine over a given period (e.g. 24 hours) and the concentration of the drug in the plasma is

$$Qu = Vu \times \int_0^t Cp.\, dt.$$

Where Vu is the renal clearance of the drug

$\int_0^t Cp.dt.$ is the area under the plasma concentration time curve for the period o-t (e.g. 0-24 hrs.)

and Qu is the quantity excreted in the time period considered.

Thus measuring Qu will give a relative measure of plasma concentration. It was intended to obtain this measurement

using 24 hr. urine collections but samples of plasma were also collected in the hope of obtaining direct measurements. To this end 30 mg. phenelzine was given at 8 a.m., 12.30 p.m. and 5 p.m. for 21 days. On the 4th and 14th days of the course 10 mls of blood was taken at 7.55 a.m. and the 8 a.m. dose of phenelzine given. The 12.30 p.m. and 5 p.m. doses were omitted on those days. Further samples of blood (10 mls taken into lithium/heparin tubes) were taken at 9 a.m., 11 a.m., 2 p.m., 5 p.m., 8 p.m. and 7.55 a.m. on the following day. The samples were centrifuged for 10 minutes immediately after collection. The plasma was then frozen at -20^{o}C until assay. The urine collection of Day 13 was used for phenelzine estimation and the patients were particularly closely supervised on that day in order that we might be sure of obtaining a complete collection.

OTHER CONSIDERATIONS

As in the first study patients who had received a course of MAOIs in the six months prior to the study were excluded and if possible all other drugs were stopped for a week prior to commencing the study. In this second study the patients were rather more severely depressed than those in the first study and in some hypnotics could not be withdrawn (for details see Appendix I). In this inpatient study the dietary and drug restrictions were less worrying as the patients were being treated under closely controlled conditions. A low tyramine diet was administered. They were advised

only to eat the foods provided and no drugs incompatible with phenelzine were given. Strict control over the actual ingestion of the tablets was maintained. They were given according to a timed schedule and counts of the tablets were made to see that this had indeed been carried out accurately. Dietary tryptophan influences urinary tryptamine levels (La Brosse et al, 1964). Constant tryptophan diets could not be provided in the wards used and in any case they are very repetitive and rather unpalatable. Plasma tryptophan levels have been shown not to vary in psychiatric patients on a standard ward diet (Coppen et al, 1965) and it was therefore felt that dietary tryptophan was not likely to influence results in this study. There is also a question that variations in urinary pH might influence urinary tryptamine levels. Previous authors have felt that keeping the patients on a uniform diet provided adequate control of this source of variability (Coppen et al, 1965) and as the patients in this study were maintained on a uniform ward diet it was felt that this aspect was probably controlled.

In summary the regime for the second study was as follows:

As outpatient - assessed for suitability for trial by Standardised Psychiatric Interview (Goldberg et al, 1970) and the neurotic/endogenous rating (Carney, Roth & Garside, 1965).

Following admission - Estimation of acetylator status (Price Evans, 1969).

Administration of Modified Goldberg Score.
Administration of side effects check list.
Twice daily ratings on visual analogue scale commenced and maintained until discharge.

Day 1 - 24 urine collections commenced and maintained for 24 days.
Phenelzine 30 mg. t.i.d. commenced.

Day 4 - 12.30 p.m. and 5 p.m. doses of phenelzine omitted. 7 blood samples taken.

Day 7 - Modified Goldberg Score administered.
Side Effects check list administered.

Day 14 - 12.30 p.m. and 5 p.m. doses of phenelzine omitted - 7 blood samples taken. Modified Goldberg Score administered. Side Effects check list administered.

Day 21 - Modified Goldberg Score administered.
Side Effects check list administered.
Phenelzine stopped.

Day 24 - Modified Goldberg Score administered.
Side Effects check list administered.

Day 24 + 4 weeks - Modified Goldberg Score administered.

Day 24 + 8 weeks - Modified Goldberg Score administered.

The results of the biochemical estimations including determination of acetylator status were retained by the biochemist until the study was completed.

RESULTS OF SECOND STUDY

Between 1.4.73 and 1.8.74 thirty patients who had neurotic depression according to the stated criteria agreed to enter the study. The number of patients collected was much smaller than that of the first study because many of the patients who were otherwise suitable were not prepared to come into hospital for four weeks. The patients in the study are therefore a somewhat selected sample of the neurotically depressed patients attending the clinic but the nature of the study made this unavoidable. None of the patients defaulted from the course of treatment. Details of the patients' case histories and the results in the individual cases are in appendices I and II. These patients were rather more severely ill than the outpatients in the first study. The mean overall severity score (modified Goldberg) before treatment was begun was 18.4 for the fast acetylators and 20.3 for the slow. The corresponding figures for the first study were 14.8 for the fast acetylators and 15.0 for the slow.

Determination of acetylator phenotype was carried out by sulphadimidine loading as described by Evans (1969). Attempts were made to use the simple method described by Schroder (1972) for estimating the level of sulphadimidine. This method depends upon a colour change. Schroder states that in some samples this is difficult to detect. This was our experience and the method described in Evans (1969) paper was used. In

10 of the patients' serum samples were used to confirm the results. In no case did this change the grouping. The results of the acetylator phenotyping are seen in Figure 10. In those patients in whom urine testing gave results between 65% and 69% sulphadimidine acetylated, the testing was repeated with serum at a later date and in all cases the result was within the range for fast acetylators.

Blood samples were collected for phenelzine estimation as described. During the study it became apparent that the serum levels of phenelzine achieved were too low for consistent reliable detection and that only levels in the urine would be obtained. The original protocol with omission of two phenelzine dosages on Days four and fourteen and the carrying out of seven venepunctures on each of these days was however followed so that the treatment procedures would be the same in all of the patients.

Continuous 24 hour urine collections were carried out throughout the study and urinary tryptamine levels were estimated on samples from Days 1, 3, 13 and a pool of Days 20, 21 and 22. 2 fast acetylators and 1 slow acetylator gave incomplete collections for Day 1. As this was intended as a basal estimation this result was omitted. 4 fast acetylators and 3 slow acetylators gave incomplete collections for Day 3. If the collection for Day 2 was complete this was substituted and this was the case in 1 fast and 2 slow acetylators. Where there was

also doubt about the collection for Day 2 a pool of Days 5-8 were substituted. The collections for the other days were all thought to be complete. Where the collection for Day 3 had been substituted by that of Day 2 or a pool of Days 5-8, collections from Day 12 or a pool of Days 15-18 were substituted for that of Day 13 for purposes of tryptamine estimation.

Estimations of free phenelzine were made on the urine collections for Day 13. These were satisfactory in 27 cases. In the case of 2 fast acetylators and 1 slow acetylator the results were regarded by the biochemist as being falsely low and these have been omitted from the calculation of the results.

In calculating the results a comparison is being made between the findings in the 13 slow acetylators and the 17 fast acetylators. Comparisons were made by Students 't' test (unpaired).

Firstly, the overall severity scores (modified Goldberg) prior to treatment, after one week's treatment, after two weeks' treatment, after three weeks' treatment and on the 24th day (3 days after treatment was stopped) were compared. (Table 23; Figure 11). The differences between the initial score and the scores after 1 week, 2 weeks, 3 weeks and 3½ weeks (24 days) were then compared (Table 24; Figure 12). The visual analogue scale cannot be used as an absolute figure as the point indicated by the patient is arbitrary. The results using the VAS were calculated as follows.

The morning ratings on the anxiety, tension and depression lines were added together to make a single score. Average scores for each week were calculated and rate of change measured using the index week score (score of 2nd, 3rd or 4th week) as a percentage of the first week score. Comparisons between fast and slow acetylators using this measurement are seen in Table 25; Figure 13).

In the initial study it was felt that the method of determining the side effects was unsatisfactory as many of the patients achieved higher scores before starting the drug than they did while on the full dosage. It was determined in the second study to find which symptoms did in fact show a tendency to increase while the patients were on the drug (Tables 26 and 27). The side effects which showed a tendency to increase were quite consistent between the two groups although not entirely so. Those which increased were

INSOMNIA	CONSTIPATION
TREMOR	FAINTS/DIZZINESS
ATAXIA	MICTURITION DIFFICULTY
SWEATING	BLURRED VISION

The side effects were calculated in terms of these plus any other new symptoms spontaneously reported by the patients. Comparisons between the side effects at the different weeks of the study are shown in Table 28 and Figure 14.

Excretion of tryptamine in µg/24 hours was compared for Day 1, Day 3 (replaced by other days in the cases indicated in Appendix I) and a pool of Days 20, 21 and 22. Comparisons between these results in fast and slow acetylators are shown in Table 29 and Figure 15. The differences between the tryptamine excretion on Day 1 and that on Day 3, Day 13 and the pool of Days 20-22, were then compared and the results are shown in Table 30 and Figure 16.

The excretion of free phenelzine in µg/24 hours for Day 13 was compared between the two groups. On this day particular efforts were made to obtain certainly complete collections and the patients were observed constantly. There can be confidence that the collections for this day were complete. The results are shown in Table 31 and Figure 17.

The patients who were not removed from the study at the end of the 24 days were followed up for 8 weeks and were rated on the modified Goldberg score at 4 weeks and 8 weeks after completion of the treatment period. Comparisons of these ratings are shown in Table 32 and Figure 18.

The relationships between these variables in the individual cases are illustrated in Appendix 2. The relationships between the mean values of the fast and slow acetylators regarding these variables are illustrated in Figures 19-25.

DISCUSSION

These studies were designed to test the hypothesis that the effects of phenelzine are dependent upon acetylator status, the drug being broken down by acetylation, a mechanism for which there is genetic polymorphism. It was predicted that, if the hypothesis were true:

1. The antidepressant effect of the drug would be greater in slow acetylators than in fast.
2. The difference between the efficacy of phenelzine and placebo would be greater in slow acetylators than the same difference in fast.
3. The side effects of phenelzine would be greater in slow acetylators than in fast.
4. Slow acetylators would achieve a greater degree of inhibition of monoamine oxidase than would fast acetylators.
5. Slow acetylators would achieve higher levels of free phenelzine than would fast acetylators.

In the first study predictions (1), (2), and (3) were examined. A consistent trend whereby the antidepressant effect of phenelzine was greater in slow acetylators than in fast was shown and in those patients who were on active drug during the first three-week period this difference was statistically significant (Table 13). For fast acetylators phenelzine was not significantly more effective than placebo as an antidepressant while

for slow acetylators it was more effective to a highly significant degree (Tables 15 and 16). With regard to side effects no significant differences and no consistent trends were demonstrated. These results are in keeping with the hypothesis but other possible explanations for the results must be considered: With regard to the first result, namely that the depression of slow acetylators improved to a more marked extent than did that of the fast, it could be postulated that the difference in improvement rates occurred for reasons unconnected with the administration of phenelzine. Spontaneous improvement rates in depressive illness are high (Klerman & Cole, 1965) and in many of these patients reactive factors were important. It is possible that there were more patients among the slow acetylators than the fast in whom such factors played a large part. Moreover it is possible that depressive illnesses in slow acetylators have an intrinsically better prognosis than those in fast. Acetylator status is genetically determined (Evans, Manley & McKusick, 1960). In at least some depressive illnesses genetic factors are important (Winokur et al, 1971). Monoamine oxidase activity, which, if the monoamine theory of affective disorders is correct, is relevant for depressive illnesses, has been shown to be under genetic control (Nies et al, 1973). It is possible that these factors are interdependent and that for genetic reasons the prognosis of depressive illness is better in slow acetylators than it is in fast. If

either of these factors were important the slow acetylators would be expected to have improved more than the fast acetylators while they were on placebo as well as while they were on active drug. This did not happen (Tables 10, 11 and 12). With regard to the result, that for fast acetylators phenelzine was not significantly more effective as an antidepressant than placebo but that for slow acetylators phenelzine was more effective to a highly significant degree, one could suggest that the difference was due to the fact that fast acetylators respond better to placebo than do slow acetylators. Indeed this suggestion has been put forward (Carr, 1974) but it is not reasonable. Not only were there no significant differences established between fast and slow acetylators with regard to placebo response but there was not even a consistent trend (Tables 10, 11 and 12). One would not have expected such a difference to be shown. It has been demonstrated that it is difficult to support the concept that placebo reactors, or non-reactors, exist as a distinct entity (Wolf et al, 1957). These authors showed that intra-individual response to placebo varies as much as inter-individual response. This evidence is against the idea that placebo response could relate to a genetically determined characteristic.

Any explanation for these results has to account for the fact that while on phenelzine slow acetylators improve more than fast but while on placebo this is not the case. There is an explanation other than our

hypothesis which fits these criteria. It has been suggested that 5-hydroxytryptamine and other naturally occurring amines are subject to polymorphic acetylation. Oxidative deamination to 5-hydroxyindol-3-ylacetic acid was the only known biotransformation of 5-hydroxytryptamine until investigations in animals of the metabolism of the ^{14}C - labelled compound were carried out (McIsaac and Page, 1959). It was demonstrated that 35-83% of the labelled dose was metabolised by oxidative deamination and 5-25% by N-acetylation. In experiments using material from animals which had been pretreated with monoamine oxidase inhibitors it was shown that a wide variety of normally occurring amines, including 5-hydroxytryptamine, tryptamine and to a lesser extent noradrenaline, is acetylated by mammalian tissues (Weissbach, Redfield and Axelrod, 1961). If the acetylation to which these amines are subject were polymorphic one would expect that among patients in whom the activity in monoamine oxidase was blocked because they were on MAOIs slow acetylators would metabolise the amines more slowly than fast. If it is accepted that depression is associated with a deficiency of these amines polymorphic acetylation of the amines could explain why the slow acetylators on phenelzine achieved a greater antidepressant response than the fast acetylators even if phenelzine were not subject to polymorphic acetylation. The nature of the acetylation to which 5-hydroxytryptamine is subject in human liver was examined in 1969 (White, Jenne and Evans

1969). Their results showed that the capacity to acetylate 5-hydroxytryptamine did not correlate with the capacity of the same livers to acetylate isoniazid and a sulphonamide. They concluded from this that 5-hydroxytryptamine is not a substrate for the polymorphic enzyme N-acetyl transferase and that it might be acetylated by a different enzyme. If this is so the above explanation for my results is unlikely to be tenable but conflicting findings were produced by Schloot et al (1969) who concluded that 5-hydroxytryptamine was likely to be a natural substrate for the polymorphic enzyme N-acetyl transferase. This question therefore remains open.

The results regarding the side effects neither support nor conflict with the hypothesis. It was always realised that the presence of side effects would be difficult to assess. In making this assessment one is entirely dependent upon the patient's subjective complaints of the symptoms and these may depend upon his personality and the degree of persisting depression as much as upon the actual severity of the drug-induced effect. These factors, particularly the possibility that those patients who remained most depressed would be likely to have least tolerance for somatic symptoms, may have blurred existing differences but there is no doubt that these were not demonstrated by this study. The results of this first study are relevant to the hypothesis only if the patients all took their medication or if the

extent to which they failed to take it did not vary between the two groups. While it is known that they all took at least some of their medication, because phenelzine could be detected in their urine, there is no means of being certain that they took their tablets exactly as directed. There can be certainty about the patients' ingestion of the tablets in the prescribed dosage in the second study. In this study the numbers of patients are much smaller and there is no placebo control. The results could be distorted if the groups differed markedly in personal characteristics such as environment, previous personality, etc. Detailed accounts of the patients and their depressive illnesses are therefore given in Appendix I. These factors are difficult to quantify but it may be seen that there were no marked differences between the groups.

The second study examines predictions (1), (3), (4) and (5). Prediction (1) was confirmed. The antidepressant effect as measured by the modified Goldberg score and the visual analogue scale was significantly greater in slow acetylators than in fast. (Tables 23, 24 and 25: Figures 11, 12 and 13). The increased antidepressant effect in slow acetylators was lasting. At follow-up at 4 and 8 weeks after completion of the course slow acetylators continued to show a significantly lower score on the modified Goldberg score (Table 31 and Figure 17). These results only refer to patients who continued in the study. In 6 fast acetylators and 1 slow acetylator

the outcome of the course of phenelzine was so unsatisfactory that they were removed from the study on the 24th day (details in Appendix I). One would expect that had these patients been included in the follow-up studies the difference between fast and slow acetylators would have tended to be increased rather than lessened. As in the first study no statistically significant differences were shown regarding side effects. A trend whereby slow acetylators tended to develop more side effects than fast as the study progressed was demonstrated (Table 28 and Figure 14). The side effects were assessed in terms of a score derived from those symptoms which showed a tendency to increase while the patients were on the drug. The symptoms in this category were fairly consistent throughout all of the groups in the first and second studies (Tables 17, 18, 19, 20, 26 and 27) although in the first study the patients complained of headaches, fatigue and apathy while those in the second study did not. The difference with regard to fatigue and apathy is probably explained by the fact that the patients in the first study were outpatients attempting to cope with their normal activities whereas those in the second study were inpatients with no duties or current responsibilities.

The results regarding urinary tryptamine excretion differed between the two groups in that the slow acetylators excreted more tryptamine on Day 13 than did the fast and in that the difference between the

excretion on Day 1 and that on Day 13 was greater for slow acetylators than for fast (Table 29 and Figure 15 and Table 30 and Figure 16). The tryptamine excretion of the patients on Day 1 was below the normal range of 36-120 ug/day described by Sjoerdsma et al (1959). This compares with the finding of Coppen et al (1965) that excretion of tryptamine is low in depressed patients. It was known that some of the collections for Day 3 were incomplete and collections for other days were therefore substituted (for details see Appendix I). Where substitutions were made for Day 3 substitutions were also made for Day 13 so that in all cases the third sample for tryptamine estimation was taken 10 days after the second. It does not seem likely that this variation in the collection day has influenced the results. The mean tryptamine excretion of the total group is very little different from that of those patients whose collection was in fact made on the stated day (Table 33). The results shown in Tables 29 and 30 and Figures 15 & 16 indicate that slow acetylators achieve significantly greater inhibition of monoamine oxidase than do fast at Day 13 but that this difference is lost by Days 20-22 when the results for the two groups are almost the same. This suggests that inhibition of monoamine oxidase as a result of phenelzine administration occurs more slowly in fast acetylators than in slow acetylators. The significant difference in monoamine oxidase inhibition between the two groups precedes the significant difference in

antidepressant response and the possibility is suggested that if the phenelzine had been continued in the fast acetylators for some time after they had achieved the same degree of monoamine oxidase inhibition as the slows a greater antidepressant response might have been seen. Phenelzine levels were assessed on urine collections from Day 13. Great care was taken to obtain complete collections on that day. Slow acetylators excreted significantly more free phenelzine than did fast (Table 31 and Figure 17).

Of the five predictions set out at the beginning of the study, (1), (2), (4) and (5) were correct. Significant differences were established in the predicted direction in every case. Prediction (3) concerning the side effects was neither confirmed nor refuted. It has already been mentioned that polymorphic acetylation of 5-hydroxytryptamine could explain the results of the first study so that these cannot be held necessarily to mean that phenelzine is subject to polymorphic acetylation. Polymorphic acetylation of 5-hydroxytryptamine could not explain the difference between fast and slow acetylators with regard to phenelzine levels and inhibition of monoamine oxidase. If the relevant monoamines are polymorphically acetylated the difference in antidepressant response between fast and slow acetylators would be enhanced but it does appear that the explanation for the results of these two studies is that the hypothesis set out at the beginning is correct, that is to say that the monoamine oxidase

inhibitor drug phenelzine is metabolised by polymorphic acetylation and its effects are dependent upon acetylator status.

The relationships between the means of variables are seen in Figures 19-25 and between the variables in the individual cases in Appendix II. In the majority of cases the assessment of the mental state on the modified Goldberg score correlates well with the patients' self-rating on the VAS although this is not always the case. There appears to be some relationship between the antidepressant response and the side effects score. It appears that the patients who are least depressed have fewest side effects (Figure 23). From this figure it may be seen that the mean modified Goldberg score of the 16 patients scoring 5 or less on the side effects score is 2 (SD. 3.79) while that of the 14 patients scoring 6 or more on the side effects score is 6 (SD. 4.29) ($p < 0.01$). This confirms our suspicion that persisting depression is associated with an increased tendency to complain of side effects and it is possible that this may have masked a tendency for phenelzine to provoke an excess of side effects in slow acetylators.

A clear relationship between phenelzine level and antidepressant effect was not demonstrable (Figure 21). On the basis of the fact that slow acetylators have a greater antidepressant response than fast and of the fact that slow acetylators achieve higher levels of

phenelzine one might have expected higher levels of phenelzine to be associated with a greater antidepressant response. There is no definite tendency in this direction. To some extent this can be explained by the fact that some of the patients would have responded well to the drug if it had been a placebo. A placebo response of 35.2 $\pm$ 2.2% of cases was shown in a large variety of conditions by Beecher (1955). Previous studies of the treatment of depressive illness of neurotic type have shown even higher placebo responses (Greenblatt, Grosser and Wechsler, 1964). This could explain the association between low phenelzine levels and considerable antidepressant response which occurred in several cases but it cannot explain the association between high phenelzine level and very limited antidepressant response which occurred in 2 cases. One fast and one slow acetylator achieved relatively high levels of phenelzine but their antidepressant response was so limited that they were removed from the study at day 24 and given alternative treatment (see Appendix I). It therefore appears that high phenelzine levels do not necessarily lead to a marked antidepressant effect. There is some tendency for tryptamine level Day 13 to relate to antidepressant response (Figure 19). In this figure the differences in modified Goldberg score may be seen to range from 4 to 23. The mean tryptamine level of those patients in whom the difference in modified Goldberg score is between 4 and 13, is 68.3 (SD. 24) and the mean tryptamine level

of the patients in whom the difference in modified Goldberg score is between 14 and 23 is 92.1 (SD. 54.8) (p N.S.). There are however some cases in which a relatively high tryptamine excretion is associated with a relatively poor antidepressant response. There appears to be little relationship between monoamine oxidase inhibition as measured by urinary tryptamine excretion and excretion of free phenelzine. Some patients achieved high urinary tryptamine levels with relatively low phenelzine levels and some, despite high phenelzine levels, continued to show low excretions of tryptamine. This tends to suggest that the sensitivity of monoamine oxidase to inhibition by MAOIs is not constant throughout the population. There is no clear tendency for the presence of side effects to relate either to phenelzine excretion or tryptamine excretion (Figures 24 and 25).

IN CONCLUSION

These studies were conducted with a view to examining the hypothesis that the monoamine oxidase inhibitor drug, phenelzine, is metabolised by polymorphic acetylation and that therefore the results of its administration, including level of drug achieved, antidepressant effect, side effects and inhibition of mono amine oxidase, would depend upon the acetylator phenotype of the subjects. To this end two studies were conducted to examine the effects of phenelzine and relate them to acetylator status in a total of one hundred and two neurotically depressed patients. It was predicted that if the

hypothesis were true.

1) Slow acetylators would derive a greater antidepressant response than would fast.

2) The difference between response to phenelzine and to placebo would be greater in slow acetylators than in fast.

3) Side effects would be greater in slow acetylators than in fast.

4) Monoamine oxidase inhibition would be greater in slow acetylators than in fast.

5) Higher phenelzine levels would be obtained in slow acetylators than in fast.

Significant differences in the expected direction were demonstrated regarding all predictions save that about side effects concerning which the results were certainly not contradictory to the hypothesis. The hypothesis can therefore be said to have been shown to be correct. The demonstration that the effects of phenelzine are dependent upon acetylator status is of some practical importance. For fast acetylators phenelzine is not significantly more effective than placebo. Prior determination of acetylator status could prevent the giving of this moderately toxic drug to patients it is unlikely to help. At present MAOIs are not drugs of first choice in the treatment of depressive illness. Tricyclic antidepressants have been shown to be more effective when given to an unselected population (Clinical Psychiatry Committee, 1965) and they do not

necessitate dietary restrictions. The comparative efficacy of tricyclic and MAOI antidepressants in slow acetylators is unknown and it may be that in these patients MAOIs might be effective enough to justify a more widespread use than has hitherto been the case.

The results are also of theoretical importance. As previously mentioned the uncertain antidepressant efficacy of MAOIs casts doubt upon the monoamine theory of the affective disorders for which the evidence is less than entirely convincing. The present findings offer an explanation for the variability of the results of previous studies - namely that the populations have not been controlled for acetylator status - a factor which is highly relevant to the effects of the drug.

These studies show that phenelzine, a drug which is capable of increasing levels of monoamine in the brain, is an effective antidepressant in cases in whom it is not metabolised too quickly. The finding of increased earlier inhibition in slow acetylators and the relationship shown between tryptamine excretion and antidepressant response suggest that phenelzine does act by inhibiting monoamine oxidase. These findings give evidence to support the monoamine theory of depressive illness and strengthen the idea that these disabling disorders have a biological cause which is at least potentially reversible.

SUMMARY

The monoamine theory of depressive illness postulates that depression is associated with a deficiency of monoamine transmitter at synaptic sites in the brain. The evidence for this is in two sections. Some is based on pharmacological studies and some on more direct studies of monoamines and their metabolites. Different workers have tended to find rather conflicting results in the direct studies of monoamines. The pharmacological evidence concerns the fact that both main groups of antidepressants, the tricyclics and the monoamine oxidase inhibitors have properties which enable them to increase the amount of monoamine available at synapses. That these drugs elevate mood by increasing the amount of monoamine at synapses and not by means of some other property is not established. The evidence that tricyclics are effective antidepressants is convincing. It would be technically impossible to demonstrate that in depressed patients these drugs act as antidepressants by means of increasing the amount of monoamine at synaptic sites. The ability of MAOIs to increase the amount of monoamine available at synaptic sites depends upon their property of inhibiting monoamine oxidase and it is possible by various means to assess the degree of inhibition of monoamine oxidase in depressed patients. That the antidepressant efficacy of MAOIs is related to the degree of inhibition of monoamine oxidase that they produce is not established and indeed the evidence that they are effective antidepressants is less than

convincing. The results of different workers are very variable. It appears that some patients respond and some do not and it has not been possible to differentiate these groups on clinical grounds. Several MAOIs are hydrazines. Other hydrazine derivatives have been shown to be metabolised by acetylation, a mechanism for which there is genetic polymorphism. The clinical effects of these drugs have been shown to relate to acetylator status. The studies discussed here were undertaken to examine the hypothesis that phenelzine, an MAOI which is a hydrazine derivative, is metabolised by acetylation and that the effects of this drug are dependent upon the acetylator status of the patient. It was predicted that if the hypothesis were true:

1) The antidepressant effect of the drug would be greater in slow acetylators than in fast.
2) The difference between the efficacy of phenelzine and placebo would be greater in slow acetylators than in fast.
3) The side effects of phenelzine would be greater in slow acetylators than in fast.
4) Slow acetylators would achieve a greater degree of inhibition of monoamine oxidase than would fast acetylators.
5) Slow acetylators would achieve higher levels of free phenelzine than would fast acetylators.

Two studies were carried out to examine this hypothesis. The first was a double-blind crossover trial of phenelzine /placebo in 72 neurotically depressed outpatients. The active drug was given for 3 weeks, the dosage being 15 mg.

t.i.d. in the first week and 30 mg. t.i.d. in the subsequent 2 weeks. In this study phenelzine was shown to be significantly more effective as an antidepressant in slow acetylators than in fast. It was demonstrated that for fast acetylators phenelzine is not significantly more effective than placebo but that for slow acetylators it is more effective to a highly significant degree. No significant differences regarding side effects were established between the two groups. The second study concerned 30 neurotically depressed inpatients, all of whom were treated with phenelzine 30 mg. t.i.d. for 3 weeks. In this study phenelzine was again shown to be significantly more effective as an antidepressant in slow acetylators than in fast. Slow acetylators achieved significantly greater levels of inhibition of monoamine oxidase than did fast and slow acetylators excreted significantly more free phenelzine than did fast. Again no significant differences were established between the two groups with regard to side effects.

All of the predictions except that about side effects were shown to be correct and the hypothesis may be said to be confirmed. It is held that it has been established that phenelzine is metabolised by polymorphic acetylation and that the clinical effects of the drug depend upon the acetylator status of the patient. It may reasonably be suggested that neglect of this factor is responsible for the variable results of previous trials of this and similar drugs. These

studies have established that in patients who do not metabolise them too quickly, monoamine oxidase inhibitors are effective antidepressants and that to some extent their antidepressant efficacy is related to inhibition of monoamine oxidase. These findings are consistent with the theory that depression is associated with a deficiency of monoamines at relevant sites.

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STATEMENT CONCERNING AMOUNT OF COLLABORATIVE WORK INVOLVED IN THIS STUDY.

The idea of studying the relationship between response to phenelzine and acetylator status was my own. I designed the first study without help. Dr. W. Marsh assisted me in selecting patients for this study and in carrying out the repeated assessments of the patients' mental states. The biochemical work involved in this study was carried out by Dr. E.B. Hendry, Western Infirmary, Glasgow and Dr. W. Tilstone, Department of Pharmaceutical Chemistry, Strathclyde University. I calculated the results of the first study and wrote the paper in which they were published. I designed the second study without help. All of the clinical work, including the psychiatric ratings and the collection of the urine and blood samples was done by me. I did none of the biochemical estimations, having no expertise in this field. I calculated the results in the second study and the discussion of them and of relevant published studies is entirely my own work.

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TABLE I

Studies of Nialamide in which the following criteria - a) use of control group; b) random assignment of patients to treatment groups; c) double blind design - are met.

AUTHORS	No. of cases	Type of patient	Source of sample	Dose of drug	Duration of treatment	Result
INGLIS CAIRD & SLOANE (1961)	26	11 with manic/ depressive psychosis (depressed type) 15 with psychoneurotic depressive reaction	Inpatients consecutively admitted depressed patients who were not overtly suicidal or too agitated to cooperate	50 mg. t.i.d.	21 days	No significant difference in efficacy between placebo and active drug
SHAFFER et al (1962)	58	alcoholics	Inpatients consecutive alcoholic admissions co-operative and physically fit	100 mg. b.d.	30 days	No significant difference in efficacy between placebo and active drug
RICKELS et al (1963)	22	depressed neurotics	Outpatients selected from clinic population on basis of being those to whom staff would normally give antidepressant medication	100 mg. b.d. for 1 week followed by 100 mg./day for 3 weeks	8 weeks (4 wks drug 4 wks placebo)	No significant difference in efficacy between placebo and active drug.

TABLE 2.

Studies of Isocarboxazid in which the following criteria - a) use of control group; b) random assignment of patients to treatment groups; c) double blind design - are met.

AUTHORS	No. of cases	Type of patient	Source of sample	Dose of drug	Duration of treatment	Result
JOSHI (1961)	53	"Primary" depressions mixed neurotic and endogenous + depression secondary to chronic psychiatric disorder	New inpatients + Selected depressed chronic patients	10 mg. t.i.d.	3 months	Active drug significantly more effective than placebo
OVERALL, HOLLISTER, POKORNY, CASEY & KATZ (1962)	113	1) Neurotic depressive reaction 2) Psychotic depressive reaction 3) M/D reaction, depressed type. 4) Involutional reaction depressed type 5) Schizophrenic reaction. schizo-affective depressed.	Inpatients not otherwise specified	Isocarboxazid 5 mg - 6 caps /day for 2 weeks	12 weeks	No significant differences between groups
ROTHMAN, GRAYSON & FERGUSON (1962)	64	Schizophrenic schizoaffective psychoneurosis Depression Personality Disorder	Acute inpatients not otherwise specified	40 mg./day reducing to 20 mg. on improvement	10 weeks	Isocarboxazid not significantly more effective than placebo

contd./

TABLE 2 (contd.)

AUTHORS	No. of cases	Type of Patient	Source of sample	Dose of drug	Duration of treatment	Result
GREENBLATT, GROSSER & WECHSLER (1964)	281	Psychoneurotics manic depressives involutionals schizophrenic reactions schizoaffective type character disorders with depression	Inpatients not otherwise specified	Isocarboxazid 40 or 50 mg./ day	8 weeks	Isocarboxazid not significantly more effective than placebo
KURLAND, DESTOUNIS, SHAFFER & PINTO (1967)	145	Patients with target symptom of depression regardless of diagnosis who had sufficient depression to be an appropriate candidate for anti-depressants	Newly admitted inpatients to 1) a large state hospital 2) a small research ward	Isocarboxazid 40 mg./day for week followed by 30 mg/day for 2 weeks.	3 weeks	State hospital isocarboxazid not significantly more effective Research ward isocarboxazid significantly more effective.

TABLE 3.

Studies of Phenelzine which meet the following criteria - a) use of a control group; b) random assignment of patients to treatment groups; c) double blind design; d) declared dosage.

AUTHORS	No. of cases	Type of patient	Source of sample	Dose of drug	Duration of treatment	Result
HUTCHISON, SMEDBERG (1960)	34	Endogenous depressives	Inpatients not otherwise specified	15 mg. t.i.d.	4 weeks	phenelzine not significantly more effective than placebo
REES & DAVIES (1961)	20	Mixed endogenous and neurotic depressions	Inpatients successive admissions	30 mg. t.i.d.	3 weeks	Phenelzine significantly more effective than placebo.
HARE, DOMINIAN & SHARPE (1962)	43	Primary depressive illness (mixed neurotic and endogenous)	39 day patients 4 inpatients	30 mg. b.d.	2 weeks	Phenelzine not significantly more effective than placebo.
GREENBLATT, GROSSER & WECHSLER (1964)	281*	Psychoneurotics manic/depressives involutionals schizophrenic reactions schizo-affective type character disorders with depression	Inpatients not otherwise specified	60 or 75 mg./day	8 weeks	Phenelzine not significantly more effective than placebo.

*281 in trial totally c E.C.T., imipramine & isocarboxazid group included as well as phenelzine & placebo.

contd./

TABLE 3 (contd)

AUTHORS	No. of cases	Type of patient	Source of sample	Dose of drug	Duration of treatment	Result
CLINICAL PSYCHIATRY COMMITTEE of MEDICAL RESEARCH COUNCIL	122	Mixed all aged between 40-69	Inpatients not otherwise specified	15 mg. t.i.d.	4 weeks	Phenelzine not significantly more effective than placebo
LASCELLES (1966)	40	Patients presenting with facial pain with depressive symptoms.	Outpatients	15 mg. t.i.d.	4 weeks	Phenelzine significantly more effective than placebo
ROBINSON NIES, RAVARIS LAMBORN (1973)	60	"Atypical" depressions	Outpatients	60 mg./ day	6 weeks	Phenelzine significantly more effective than placebo
TYRER CANDY & KELLY	32	Phobics	Outpatients	15 mg. t.i.d.	8 weeks	Phenelzine significantly more effective than placebo
RASKIN SCHULTERBRANDT REAT, CROCK & ODLE (1974)	118*	Neurotic, psychotic, schizophrenic depressions	Newly admitted inpatients	15 mg. t.i.d.		Phenelzine not significantly more effective than placebo

*trial split between placebo, phenelzine & diazepam.

TABLE 4

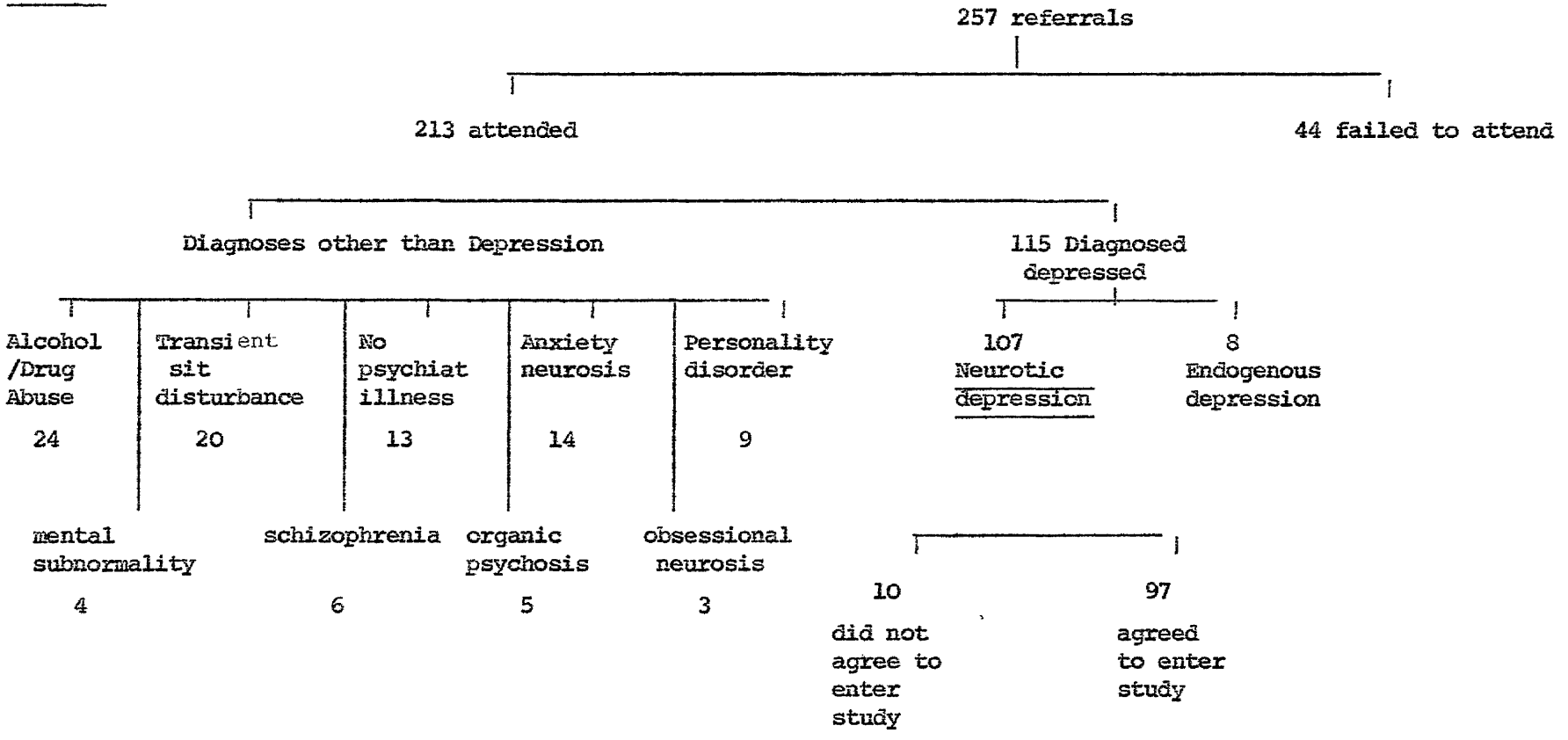
Studies of Tranylcypromine in which the following criteria - a) use of control group; b) random assignment of patients to treatment group; c) double blind design - are met.

AUTHORS	No. of cases	Type of patient	Source of sample	Dose of drug	Duration of treatment	Result
BARTHOLOMEW (1962)	64	18 with endogenous depression 12 with involutional depression 34 with reactive depression	Consecutively referred depressed patients regarded as suitable for outpatient trial	30 mg. - 60 mg./ day	6 weeks	Tranylcypromine significantly more effective than placebo
GOTTFRIES (1963)	50	11 endogenously depressed 39 neurotically depressed	Inpatients not otherwise	15 mg. - 30 mg./ day	15 days	Tranylcypromine not significantly more effective than placebo
KHANNA et al (1963)	30	Depressed not otherwise specified	Inpatients not otherwise specified	30 mg./	2 weeks	Tranylcypromine significantly more effective than placebo

TABLE 5

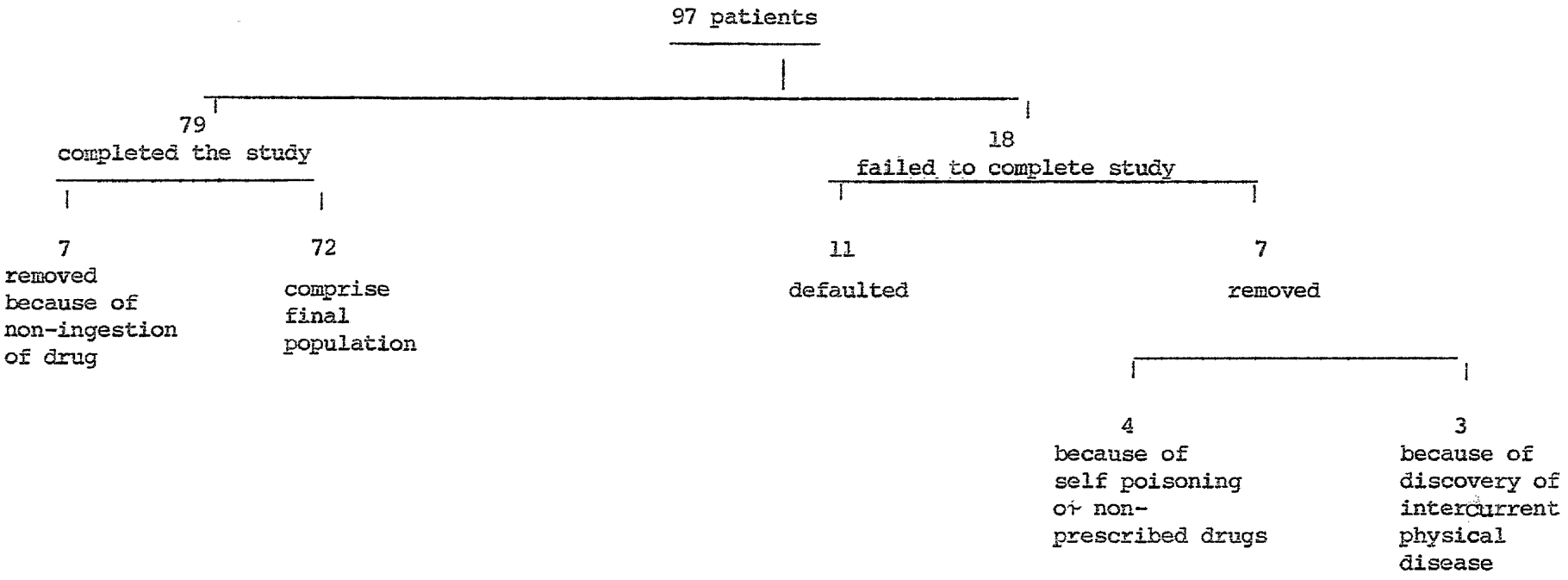
Body Weight (Kg)	Dose Sulphadimidine (mg)
〈51	500
51 to 83	750
〉83	1000

TABLE 6



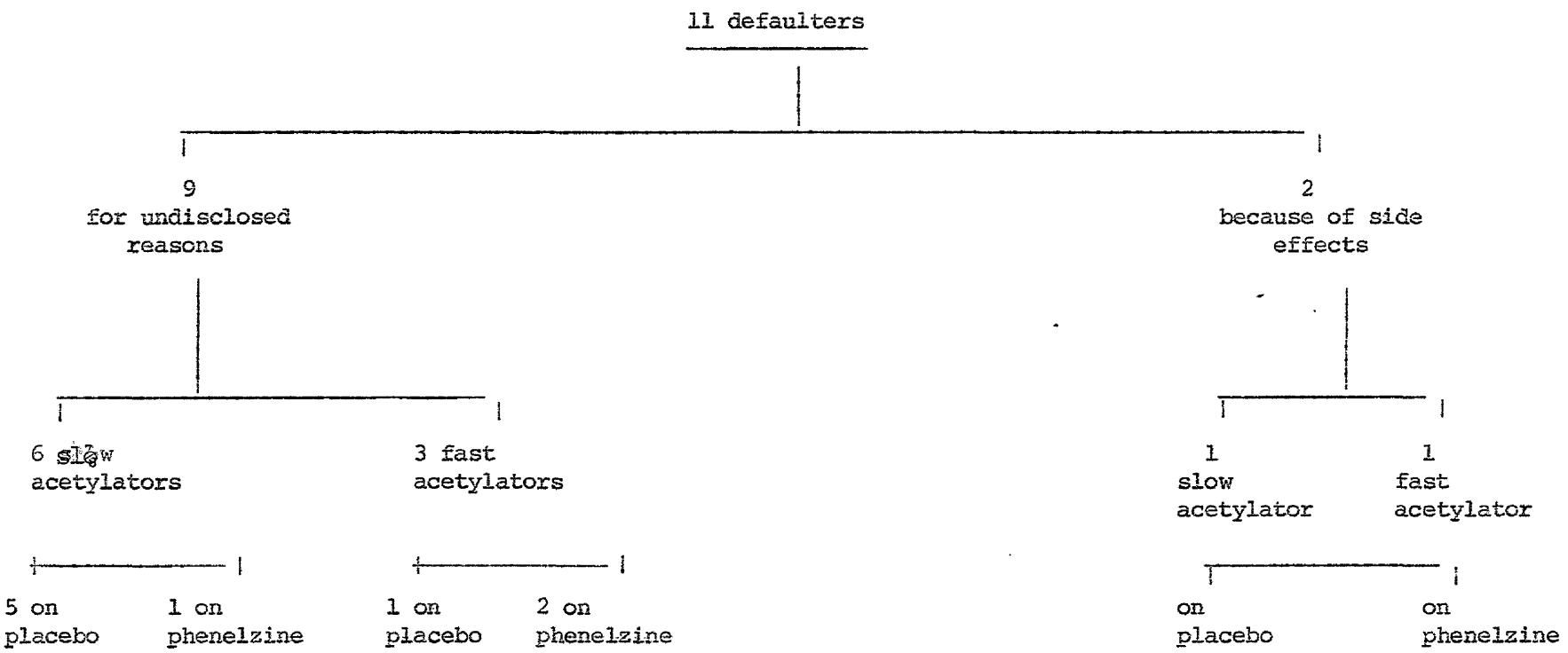
OUTCOME of ALL PATIENTS REFERRED WITH DEPRESSION DURING PERIOD OF STUDY.

TABLE 7



PROGRESS of 97 PATIENTS WHO COMMENCED THE STUDY

TABLE 8



DETAILS OF DEFAULTERS

TABLE 9

COMPARISONS of STARTING SCORES (Week 0 Scores)

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Fast Acetylators Placebo 1st (1) v. Slow Acetylators Placebo 1st (2)	23	23	14.0	15.5	3.6	4.5	1.30	44	N.S.
Fast Acetylators Placebo 1st (1) v. Slow Acetylators Drug 1st (2)	23	16	14.0	14.3	3.6	5.1	0.21	37	N.S.
Fast Acetylators Placebo 1st (1) v. Fast Acetylators Drug 1st (2)	23	10	14.0	16.9	3.6	4.2	2.03	31	N.S.
Fast Acetylators Drug 1st (1) v. Slow Acetylators Placebo 1st (2)	10	23	16.9	15.5	4.2	4.5	0.82	31	N.S.

contd./

TABLE 9 (contd.)

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Fast Acetylators Drug 1st (1) v. Slow Acetylators Drug 1st (2)	10	16	16.9	14.3	4.2	5.1	1.37	24	N.S.
Slow Acetylators Drug 1st (1) v. Slow Acetylators Placebo 1st (2)	16	23	14.3	15.5	4.2	4.5	0.82	37	N.S.
total sample of fast (1) total sample of slow (2)	33	39	14.2	14.0	4.6	5.4	0.22	70	N.S.

TABLE 10

Score Week 3 fast acetylators placebo			Score Week 3 slow acetylators placebo		
N	=	23	N	=	3
M	=	5.83	M	=	8.39
SD_1	=	4.43	SD_2	=	5.79

t = 1.17 (non significant)

TABLE 11

Week 3 - Week 6 (difference) fast acetylators placebo			Week 3 - Week 6 (difference) slow acetylators placebo		
N	=	10	N	=	16
M	=	0.60	M	=	1
SD	=	3.53	SD	=	2.96

t = 0.29 (non significant)

TABLE 12.

ACETYLATOR STATUS	MODIFIED GOLDBERG SCORE mean difference Wk 0 - Wk 3	MODIFIED GOLDBERG SCORE mean difference Wk 3 - Wk 6
Fasts (on placebo)	8.13	0.6
Slows (on placebo)	7.13	1.0

TABLE 13

Score Week 3 fast acetylators drug			Score Week 3 slow acetylators drug		
N	=	10	N	=	16
M	=	5.8	M	=	2.18
SD	=	4.55	SD	=	2.48

$t = 2.19$ $p < 0.05$ (2 tailed)
$p < 0.025$ (1 tailed)

In view of the fact that a prediction has been made the use of the one tailed test is permissible and this is used throughout the study with reference to comparisons about which a prediction has been made.

TABLE 14

Week 3 - Week 6 (difference) fast acetylators drug			Week 3 - Week 6 (difference) slow acetylators drug		
N	=	23	N	=	23
M	=	4.39	M	=	6.69
SD	=	4.78	SD	=	4.73

t = 1.61 (non-significant)

TABLE 15

Week 0 - Week 3 (difference) fast acetylators (placebo)			Week 0 - Week 3 (difference) fast acetylators (drug)		
N	=	23	N	=	10
M	=	8.13	M	=	11.30
SD	=	5.42	SD	=	6.40

t = 1.39 (non significant)

TABLE 16

Week 0 - Week 3 (difference) Slow acetylators (placebo)		Week 0 - Week 3 (difference) Slow acetylators (drug)	
N	= 23	N	= 16
M	= 7.13	M	= 12.06
SD	= 4.70	SD	= 5.10

$t = 3.03$

$p < 0.0025$ (1 tailed)

TABLE 17

INDIVIDUAL SIDE EFFECTS
FAST ACETYLATORS ACTIVE DRUG 1st

SYMPTOM	TOTAL SCORE WEEK 0	TOTAL SCORE WEEK 1	TOTAL SCORE WEEK 2	TOTAL SCORE WEEK 3	TENDENCY
Headaches	9	8	5	3	↓
Insomnia	7	4	5	7	↓ ↑*
Agitation	6	6	3	2	↓
Tremor	4	4	2	5	↓ ↑*
Seizures	0	0	0	0	
Ataxia	3	5	6	4	↑*
Choreiform movements	0	0	0	0	
Fatigue	10	13	11	9	↑*
Apathy	10	8	6	4	↓
Irritability	9	8	5	4	↓
Sadness	15	14	10	5	↓
Impotence	0	0	0	0	
Sweating	7	5	1	4	↓ ↑*
Nausea	7	6	6	5	↓
Constipation	3	4	4	9	↑*
Faint/Dizzy	1	4	5	10	↑*
Micturition difficulty	0	0	0	1	↑*
Blurred vision	0	1	3	2	↑*
Hyperpyrexia	1	1	1	1	
Hot flushes	3	3	3	3	
Palpitations	5	4	4	4	↓
Diarrhoea	4	4	4	0	↓
Rashes	1	0	0	0	↓
Jaundice	0	0	0	0	

TABLE 18

INDIVDUAL SIDE EFFECTS
FAST ACETYLATORS ACTIVE DRUG 2nd

SYMPTOM	TOTAL SCORE Week 0	TOTAL SCORE Week 4	TOTAL SCORE Week 5	TOTAL SCORE Week 6	TENDENCY
Headaches	20	12	13	12	↓ ↑ *
Insomnia	24	12	14	16	↓ ↑ *
Agitation	20	9	7	1	↓
Tremor	16	6	8	6	↓ ↑ *
Seizures	0	0	0	0	
Ataxia	10	5	15	13	↓ ↑ *
Choreiform movements	0	0	0	0	
Fatigue	25	11	20	11	↓ ↑ *
Apathy	22	3	8	4	↓ ↑ *
Irritability	26	5	5	1	↓
Sadness	32	8	8	4	↓
Impotence	0	0	0	0	
Sweating	16	9	8	9	↓ ↑ *
Nausea	8	8	8	1	↓
Constipation	6	2	5	6	↓ ↑ *
Faint/Dizzy	8	6	14	12	↓ ↑ *
Micturition difficulty	3	3	1	5	↓ ↑ *
Blurred vision	7	4	9	7	↓ ↑ *
Hyperpyrexia	3	3	3	3	
Palpitations	10	10	10	7	↓
Hot Flushes	12	12	9	8	↓
Diarrhoea	3	3	2	2	↓
Rashes	3	1	1	1	↓
Jaundice	0	0	0	0	

TABLE 19

INDIVIDUAL SIDE EFFECTS
SLOW ACETYLATORS ACTIVE DRUG 1st

SYMPTOM	TOTAL SCORE Week 0	TOTAL SCORE Week 1	TOTAL SCORE Week 2	TOTAL SCORE Week 3	TENDENCY
Headaches	9	8	6	7	↓ ↑ *
Insomnia	8	5	6	5	↓ ↑ *
Agitation	11	8	6	1	↓
Tremor	11	6	6	9	↓ ↑ *
Seizures	0	0	0	0	
Ataxia	5	4	12	4	↓ ↑ *
Choreiform movements	1	1	1	1	
Fatigue	18	15	17	9	↓ ↑ *
Apathy	16	13	7	5	↓
Irritability	15	11	3	2	↓
Sadness	23	15	8	3	↓
Impotence	0	0	0	0	
Sweating	13	11	7	7	↓
Nausea	5	5	3	2	↓
Constipation	3	4	9	7	↑ *
Faint/Dizzy	5	7	11	7	↑ *
Micturition difficulty	1	0	3	0	↓ ↑ *
Blurred vision	4	8	6	10	↑ *
Hyperpyrexia	1	1	1	1	
Palpitations	7	4	4	4	↓
Hot Flushes	10	9	6	4	↓
Diarrhoea	1	1	1	0	↓
Rashes	1	1	1	1	
Jaundice	0	0	0	0	

TABLE 20

INDIVIDUAL SIDE EFFECTS
SLOW ACETYLATORS ACTIVE DRUG 2nd

SYMPTOM	TOTAL SCORE Week 0	TOTAL SCORE Week 4	TOTAL SCORE Week 5	TOTAL SCORE Week 6	TENDENCY
Headaches	18	10	14	13	* ↓ ↑
Insomnia	23	11	12	12	* ↓ ↑
Agitation	22	9	7	4	↓
Tremor	11	8	8	10	* ↓ ↑
Seizures	0	0	0	0	
Ataxia	6	4	20	10	↓ ↑
Choreiform movements	0	0	0	0	
Fatigue	27	12	16	12	* ↓ ↑
Apathy	26	6	10	10	* ↓ ↑
Irritability	28	12	8	5	↓
Sadness	36	12	10	5	↓
Impotence	2	0	0	0	↓
Sweating	14	11	13	13	↓ ↑ *
Nausea	12	10	10	10	↓
Constipation	9	3	6	9	↓ ↑ *
Faint/Dizzy	9	9	18	17	↑ *
Micturition difficulty	1	0	3	7	↓ ↑ *
Blurred vision	8	2	14	10	↓ ↑ *
Hyperpyrexia	2	2	2	2	
Palpitations	10	4	3	2	↓
Hot Flushes	11	7	7	7	↓
Diarrhoea	7	3	3	3	↓
Rashes	4	2	1	1	↓
Jaundice	0	0	0	0	

TABLE 21

SIDE EFFECTS - 11 SYMPTOM SCORE - PATIENTS ON ACTIVE MEDICATION 1st
FAST v. SLOW ACETYLATORS

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Week 0 score Fast Acetylators (1) Slow Acetylators (2)	10	16	5.1	5.9	3.0	2.8	0.6	24	N.S.
Week 1 score Fast Acetylators (1) Slow Acetylators (2)	10	16	5.6	5.1	3.8	3.1	0.39	24	N.S.
Week 2 score Fast Acetylators (1) Slow Acetylators (2)	10	16	4.9	5.5	2.3	3.5	0.48	24	N.S.
Week 3 score Fast Acetylators (1) Slow Acetylators (2)	10	16	5.7	4.4	3.9	4.2	0.79	24	N.S.

TABLE 22

SIDE EFFECTS - 11 SYMPTOM SCORE - PATIENTS ON ACTIVE MEDICATION 2nd
FAST v. SLOW ACETYLATORS

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Week 0 score Fast Acetylators (1) Slow Acetylators (2)	23	23	6.8	6.5	2.6	3.0	0.4	44	N.S.
Week 4 score Fast Acetylators (1) Slow Acetylators (2)	23	23	3.6	3.6	2.9	3.0	0.0	44	N.S.
Week 5 score Fast Acetylators (1) Slow Acetylators (2)	23	23	5.6	5.9	3.4	4.7	0.25	44	N.S.
Week 6 score Fast Acetylators (1) Slow Acetylators (2)	23	23	4.4	5.3	4.0	5.8	0.56	44	N.S.

TABLE 23

COMPARISONS OF MODIFIED GOLDBERG OVERALL SEVERITY RATINGS

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Overall Severity Wk 0 Fast acetylators (1) v. Overall Severity Wk 0 Slow Acetylators (2)	17	13	18.35	20.3	3.3	3.1	1.6	28	N.S.
Overall Severity Wk 1 Fast Acetylators (1) v. Overall Severity Wk 1 Slow Acetylators (2)	17	13	11.7	11.3	4.3	6.0	0.17	28	N.S.
Overall Severity Wk 2 Fast Acetylators (1) v. Overall Severity Wk 2 Slow Acetylators (2)	17	13	6.6	6.6	4.7	4.7	0.01	28	N.S.
Overall Severity Wk 3 Fast Acetylators (1) v. Overall Severity Wk 3 Slow Acetylators (2)	17	13	5.0	2.45	4.93	3.3	1.6	28	N.S.
Overall Severity Wk 3½ Fast Acetylators (1) v. Overall Severity Wk 3½ Slow Acetylators (2)	17	13	5.3	2.6	4.5	3.6	1.75	28	$p < 0.05$ 1 tailed

TABLE 24

COMPARISON of DIFFERENCES IN MODIFIED GOLDBERG SCORE BETWEEN INITIAL and SUBSEQUENT SCORES

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Difference Wk 0 - Wk 1 Fast Acetylators (1) Difference Wk 0 - Wk 1 Slow Acetylators (2)	17	13	6.0	8.5	4.1	5.6	1.43	28	N.S.
Difference Wk 0 - Wk 2 Fast Acetylators (1) Difference Wk 0 - Wk 2 Slow Acetylators (2)	17	13	11.7	13.6	5.75	5.1	0.95	28	N.S.
Difference Wk 0 - Wk 3 Fast Acetylators (1) Difference Wk 0 - Wk 3 Slow Acetylators (2)	17	13	13.35	17.8	5.25	4.4	2.48	28	$p < 0.01$ 1 tailed
Difference Wk 0 - Wk 3½ Fast Acetylators (1) Difference Wk 0 - Wk 3½ Slow Acetylators	13	13	13.05	17.7	5.2	4.6	2.51	28	$p < 0.01$ 1 tailed

TABLE 25

COMPARISON of VAS INDEX WEEK AVERAGE SCORE AS A PERCENTAGE OF INITIAL WEEK AVERAGE SCORE

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Vas 2nd wk as % of 1st wk Fast Acetylators (1) v. Vas 2nd wk as % of 1st wk Slow Acetylators (2)	17	13	82.6	61.2	34.3	30.8	1.76	28	$p < 0.05$ 1 tailed
Vas 3rd wk as % of 1st wk Fast Acetylators (1) v. Vas 3rd wk as % of 1st wk Slow Acetylators (2)	17	13	59.05	48.9	50.5	32.4	0.63	28	N.S.
Vas 4th Wk as % of 1st wk Fast Acetylators (1) v. Vas 4th Wk as % of 1st wk Slow Acetylators (2)	17	13	70.2	40.5	52.9	32.9	1.77	28	$p < 0.05$ 1 tailed

TABLE 26

SLOW ACETYLATORS

Weekly ratings of total individual symptoms on side effects score.

SYMPTOM	Wk 0	Wk 1	Wk 2	Wk 3	Wk 3½	Tendency
Headaches	21	10	10	10	7	↓
Insomnia	21	11	8	9	7	↓ ↑ *
Agitation	20	9	9	5	2	↓
Tremor	12	9	7	9	7	↓ ↑ *
Seizures	0	0	0	0	0	
Ataxia	4	12	13	12	6	↑ *
Choreiform movements	4	1	1	1		↓
Fatigue	27	22	18	11	8	↓
Apathy	27	19	9	5	4	↓
Irritability	26	14	5	2	1	↓
Sadness	28	17	6	3	3	↓
Impotence	0	0	0	0	0	
Sweating	14	5	5	9	8	↓ ↑ *
Nausea	12	5	5	2	0	↓
Constipation	12	12	17	18	12	↑ *
Faint/Dizzy	8	11	9	13	3	↑ *
Micturition difficulty	3	4	3	4	2	↑ *
Blurred vision	8	9	8	10	5	↑ *
Hyperpyrexia	0	0	0	0	0	
Palpitations	8	8	6	5	3	↓
Hot Flushes	6	4	3	3	3	↓
Diarrhoea	1	1	0	0	0	↓
Rashes	2	2	2	0	0	↓
Jaundice	0	0	0	0	0	

TABLE 27

FAST ACETYLATORS

Weekly ratings of total individual symptoms on side effects score.

SYMPTOM	Wk 0	Wk 1	Wk 2	Wk 3	Wk 3½	Tendency
Headaches	23	6	5	2	0	↓
Insomnia	22	12	11	9	11	↓ ↑ *
Agitation	15	8	6	4	4	↓
Tremor	12	6	4	4	4	↓
Seizures	0	0	0	0	0	
Ataxia	8	13	12	12	8	↑ *
Choreiform movements	0	0	0	0	0	
Fatigue	28	21	17	16	12	↓
Apathy	22	19	11	8	7	↓
Irritability	20	13	7	3	3	↓
Sadness	31	22	11	5	6	↓
Impotence	0	0	0	0	0	
Sweating	24	9	8	12	8	↓ ↑*
Nausea	11	9	4	1	0	↓
Constipation	5	2	9	9	6	↑*
Faint/Dizzy	10	16	13	12	6	*
Micturition difficulty	0	1	1	5	1	↑ *
Blurred vision	6	8	10	3	1	*
Hyperpyrexia	0	0	0	0	0	
Palpitations	10	8	5	4	1	↓
Hot Flushes	10	5	4	4	1	↓
Diarrhoea	3	2	0	0	0	↓
Rashes	2	0	0	0	0	↓
Jaundice	0	0	0	0	0	

TABLE 28

COMPARISONS of SIDE EFFECTS SCORES

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Side Effects Wk 0 Fast Acetylators (1) v. Side Effects Wk 0 Slow Acetylators (2)	17	13	5.8	5.7	2.7	2.9	0.12	28	N.S.
Side Effects Wk 1 Fast Acetylators (1) v. Side Effects Wk 1 Slow Acetylators (2)	17	13	4.8	5.0	2.6	2.7	0.18	28	N.S.
Side Effects Wk 2 Fast Acetylators (1) v. Side Effects Wk 2 Slow Acetylators (2)	17	13	4.8	5.5	2.2	3.3	0.70	28	N.S.
Side Effects Wk 3 Fast Acetylators (1) v. Side Effects Wk 3 Slow Acetylators (2)	17	13	4.5	5.9	2.5	2.7	1.4	28	N.S.
Side Effects Wk 3½ Fast Acetylators (1) v. Side Effects Wk 3½ Slow Acetylators (2)	17	13	3.1	3.4	1.9	2.3	0.37	28	N.S.

TABLE 29

COMPARISONS of TRYPTAMINE EXCRETIONS (µg/24 hrs.)

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Tryptamine Day 1 Fast Acetylators (1) Tryptamine Day 1 Slow Acetylators (2)	15	12	18	14	21	5	0.7	25	N.S.
Tryptamine Day 3 Fast Acetylators (1) Tryptamine Day 3 Slow Acetylators (2)	17	13	55.5	60.5	22.25	43	0.4	28	N.S.
Tryptamine Day 13 Fast Acetylators (1) Tryptamine Day 13 Slow Acetylators (2)	17	13	69.9	99.5	25.5	61.1	1.88	28	$p < 0.05$ 1 tailed
Tryptamine Days 20,21,22 Fast Acetylators (1) Tryptamine Days 20,21,22 Slow Acetylators (2)	17	13	105	101	55.3	36.3	0.25	28	N.S.

TABLE 30

COMPARISON OF DIFFERENCES IN TRYPTAMINE EXCRETION (µg/24 hrs.) BETWEEN INITIAL AND SUBSEQUENT SCORES

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Difference Day 1 - Day 3 Fast Acetylators (1) Difference Day 1 - Day 3 Slow Acetylators (2)	15	12	44	46	37.1	43.8	0.12	25	N.S.
Difference Day 1 - Day 13 Fast Acetylators (1) Difference Day 1 - Day 13 Slow Acetylators (2)	15	12	50	87	37.9	60.9	1.94	25	$p < 0.05$ 1 tailed
Difference Day 1 - Day 20-22 (pool) Fast Acetylators (1) Difference Day 1 - Day 20-22 (pool) Slow Acetylators (2)	15	12	85	88	61.4	36.6	0.14	25	N.S.

TABLE 31

COMPARISON OF LEVELS OF FREE PHENELZINE

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Excretion of free phenelzine Day 13 Fast Acetylators (1) Excretion of free phenelzine Day 13 Slow Acetylators (2)	15	12	698.6	1575.3	483	1183	2.70	25	$p < 0.01$ 1 tailed

TABLE 32

COMPARISON OF FOLLOW UP SCORES (MODIFIED GOLDBERG SCORES)

COMPARISON	N_1	N_2	M_1	M_2	SD_1	SD_2	t	df	significance
Score Week 3½ + 4 Fast Acetylators (1) Score Week 3½ + 4 Slow Acetylators (2)	11	12	4	1.4	3.1	2.0	2.33	21	$p < 0.025$ 1 tailed
Score Week 3½ + 8 Fast Acetylators (1) Score Week 3½ + 8 Slow Acetylators (2)	11	11	4.5	1.7	2.2	3.2	2.06	20	$p < 0.05$ 1 tailed

TABLE 33

URINARY TRYPTAMINE EXCRETIONS OF TOTAL SAMPLE AS COMPARED WITH THOSE ON WHOM COLLECTIONS WERE ACTUALLY MADE ON THAT DAY.

GROUP STUDIED	MEAN TRYPTAMINE EXCRETION µg/24 hrs.
Slow Acetylators. Day 3 patients whose collection was made on that day.	59.7
Slow Acetylators. Day 3 total sample	60.4
Slow Acetylators. Day 13 patients whose collection was made on that day	103.9
Slow Acetylators. Day 13 total sample	99.5
Fast Acetylators. Day 3 patients whose collection was made on that day	60.4
Fast Acetylators. Day 3 total sample	60.8
Fast Acetylators. Day 13 patients whose collection was made on that day	70.5
Fast Acetylators. Day 13 total sample	69.9

Figure 1

Symptom Areas - Standardised Psychiatric Interview (Goldberg, 1970)

SOMATIC SYMPTOMS

FATIGUE

SLEEP DISTURBANCE

IRRITABILITY

LACK OF CONCENTRATION

DEPRESSION

ANXIETY and WORRY

PHOBIAS

OBSESSIONS/COMPULSIONS

DEPERSONALISATION

Figure 2

Manifest Abnormalities: Standardised Psychiatric Interview (Goldberg, 1970)

SLOW LACKING SPONTANEITY

SUSPICIOUS DEFENSIVE

HISTRIONIC

DEPRESSED

ANXIOUS/TENSE

ELATED/EUPHORIC

FLATTENED/INCONGRUOUS

DELUSIONS: THOUGHT DISORDER: MISINTERPRETATIONS

HALLUCINATIONS

INTELLECTUAL IMPAIRMENT

EXCESSIVE CONCERN WITH BODILY FUNCTIONS

DEPRESSIVE THOUGHT CONTENT

Figure 3

SIDE EFFECTS CHECK LIST

HEADACHES

INSOMNIA

AGITATION

TREMOR

SEIZURES

ATAXIA

CHOREIFORM MOVEMENTS

FATIGUE

APATHY

IRRITABILITY

SADNESS

IMPOTENCE

SWEATING

NAUSEA

CONSTIPATION

FAINTS/DIZZINESS

MICTURITION DIFFICULTY

BLURRED VISION

HYPERPYREXIA

PALPITATIONS

HOT FLUSHES

DIARRHOEA

RASHES

JAUNDICE

OTHER (i.e. any complaint not mentioned volunteered by patient)

FIGURE 4

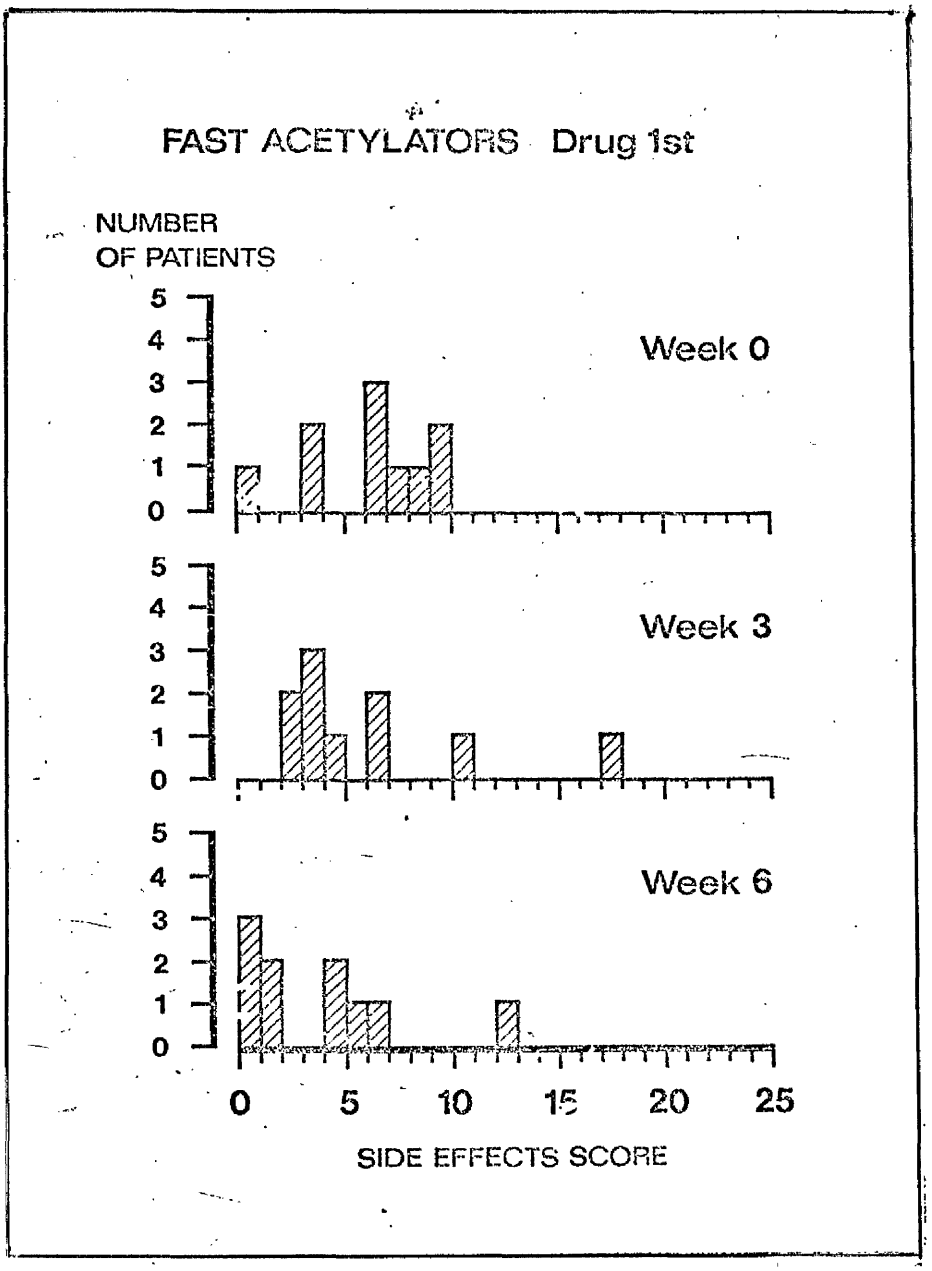

FAST ACETYLATORS Drug 1st
NUMBER
OF PATIENTS
Week 0
Week 3
Week 6
0
1
2
3
4
5
0
5
10
15
20
25
SIDE EFFECTS SCORE

FIGURE 5

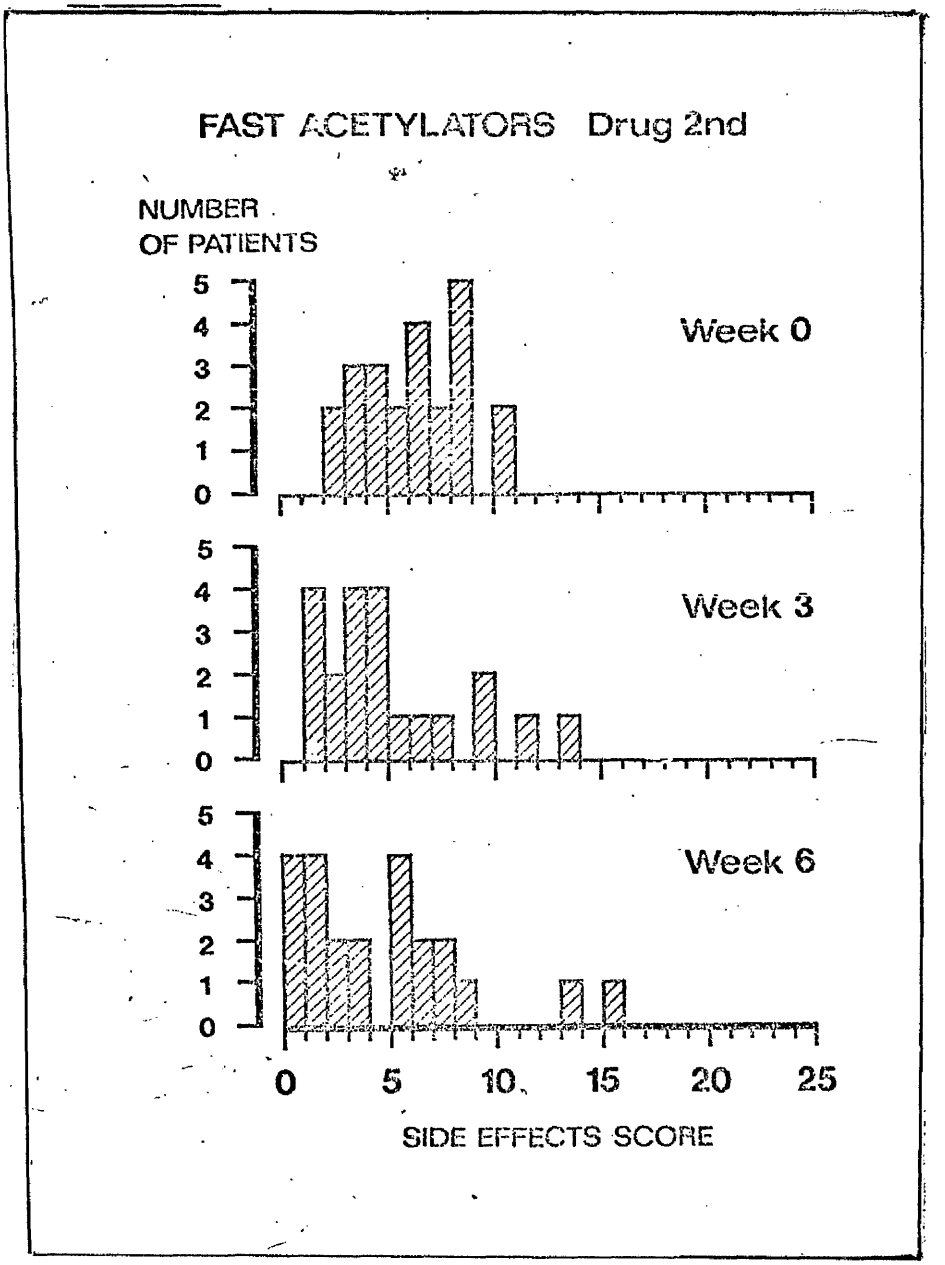

FAST ACETYLATORS Drug 2nd
NUMBER OF PATIENTS
Week 0
Week 3
Week 6
0
1
2
3
4
5
0
5
10
15
20
25
SIDE EFFECTS SCORE

FIGURE 6

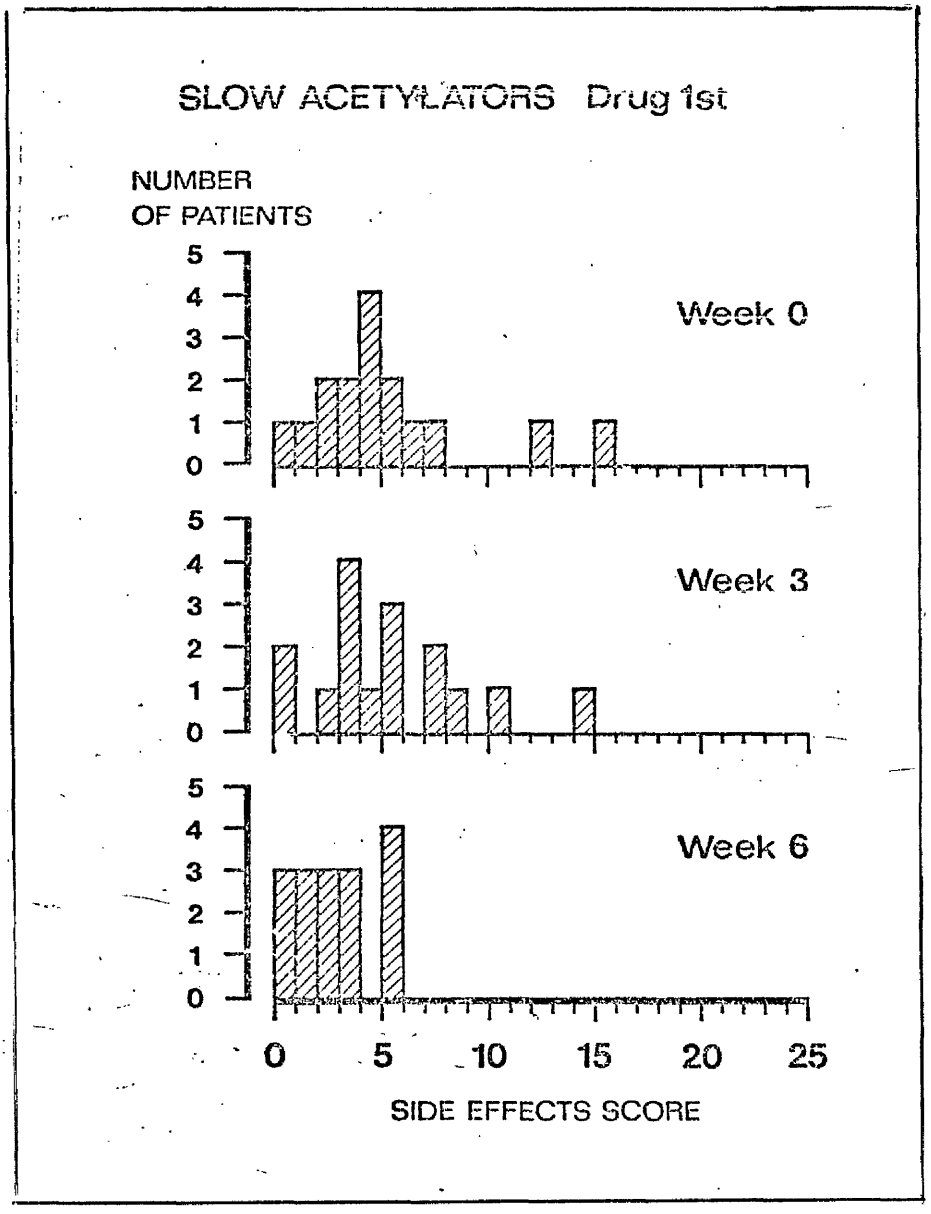

SLOW ACETYLATORS Drug 1st
NUMBER
OF PATIENTS
Week 0
Week 3
Week 6
0
1
2
3
4
5
0
5
10
15
20
25
SIDE EFFECTS SCORE

FIGURE 7

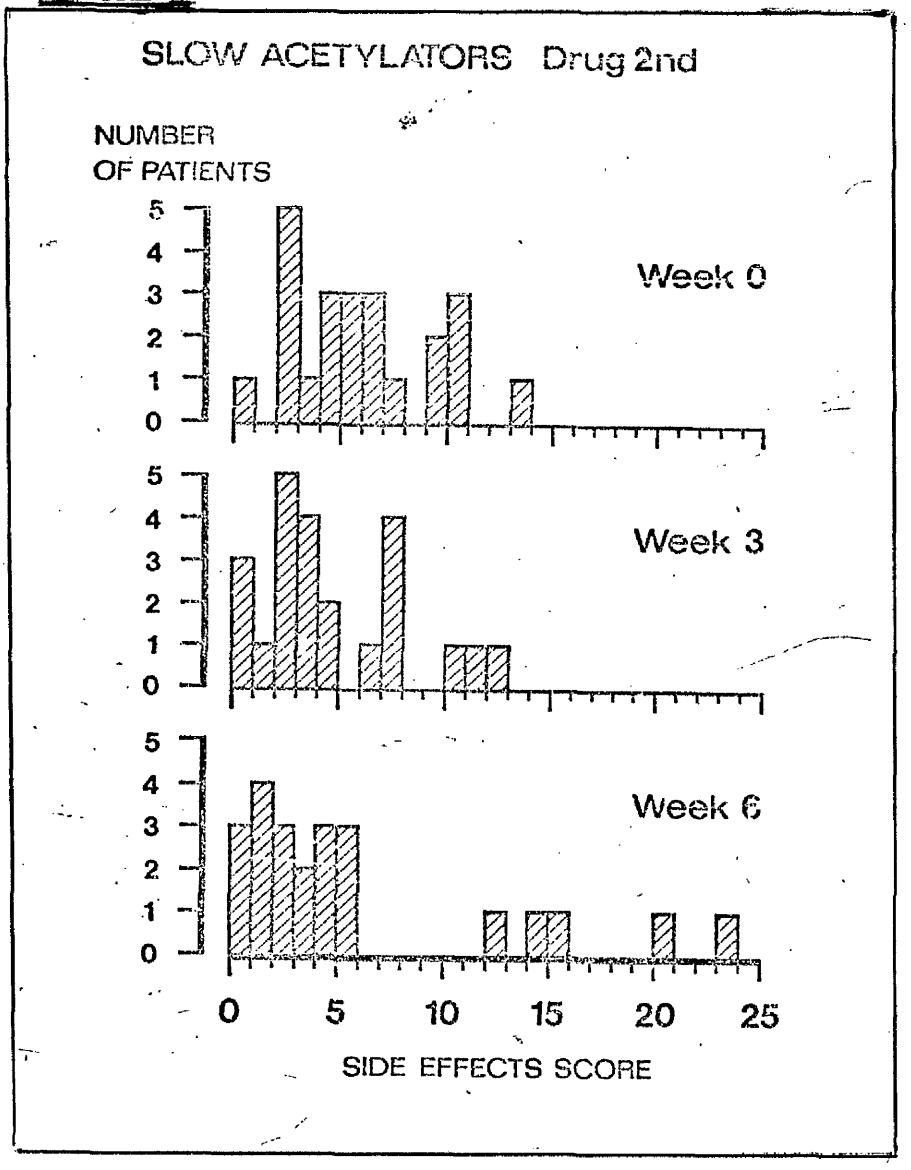

SLOW ACETYLATORS Drug 2nd
NUMBER
OF PATIENTS
Week 0
Week 3
Week 6
0
1
2
3
4
5
0
5
10
15
20
25
SIDE EFFECTS SCORE

FIGURE 8

Side Effects - Patients on active medication first
Slow acetylators vs. fast (mean scores)

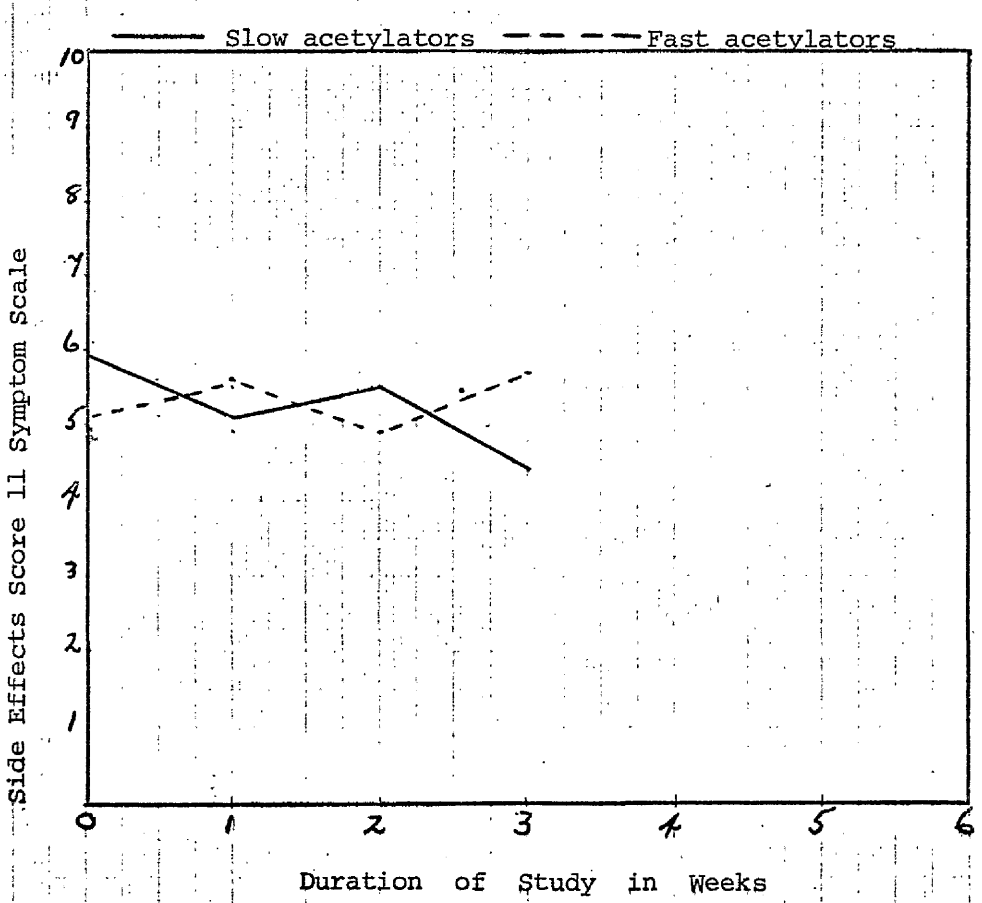


FIGURE 9

Side Effects - Patients on active medication second
Slow acetylators vs. fast (mean scores)

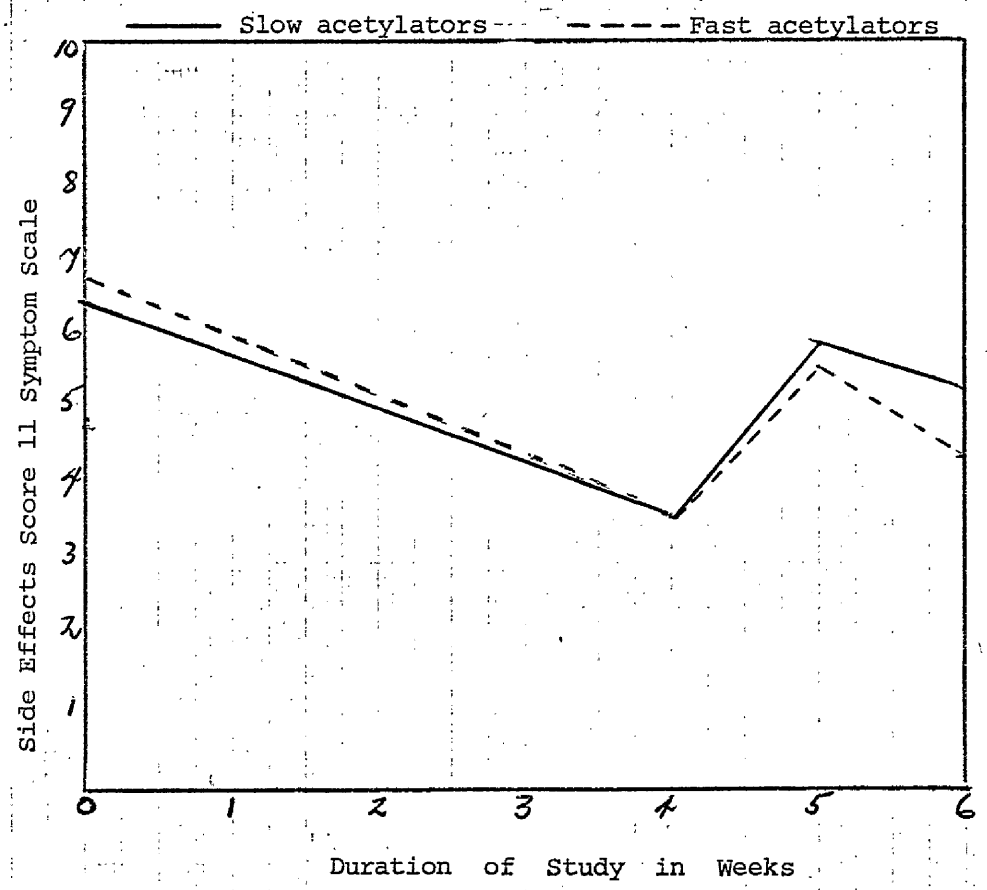


FIGURE 10

Acetylation Phenotype determined by
Sulphadimidine loading (Evans, 1969)

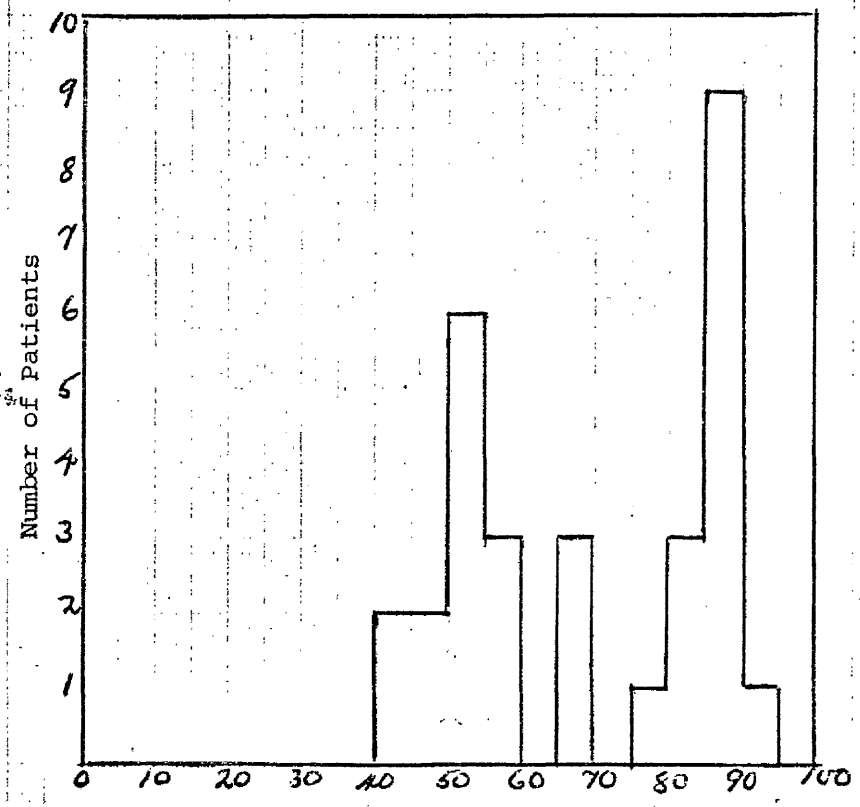


FIGURE 11

Modified Goldberg Scores (Means
Slow acetylators vs. Fast acetylators

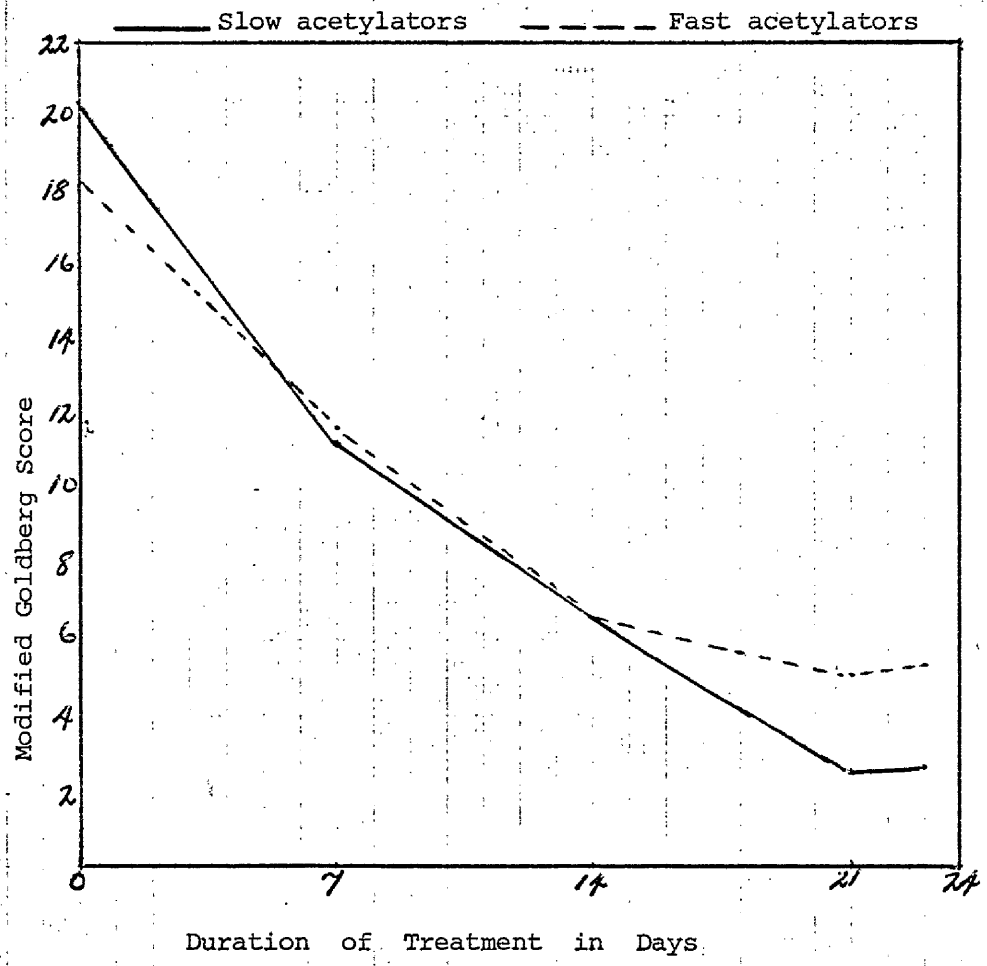


FIGURE 12

Difference between initial & subsequent Modified Goldberg Score
Slow acetylators vs. Fast acetylators (Mean Scores)

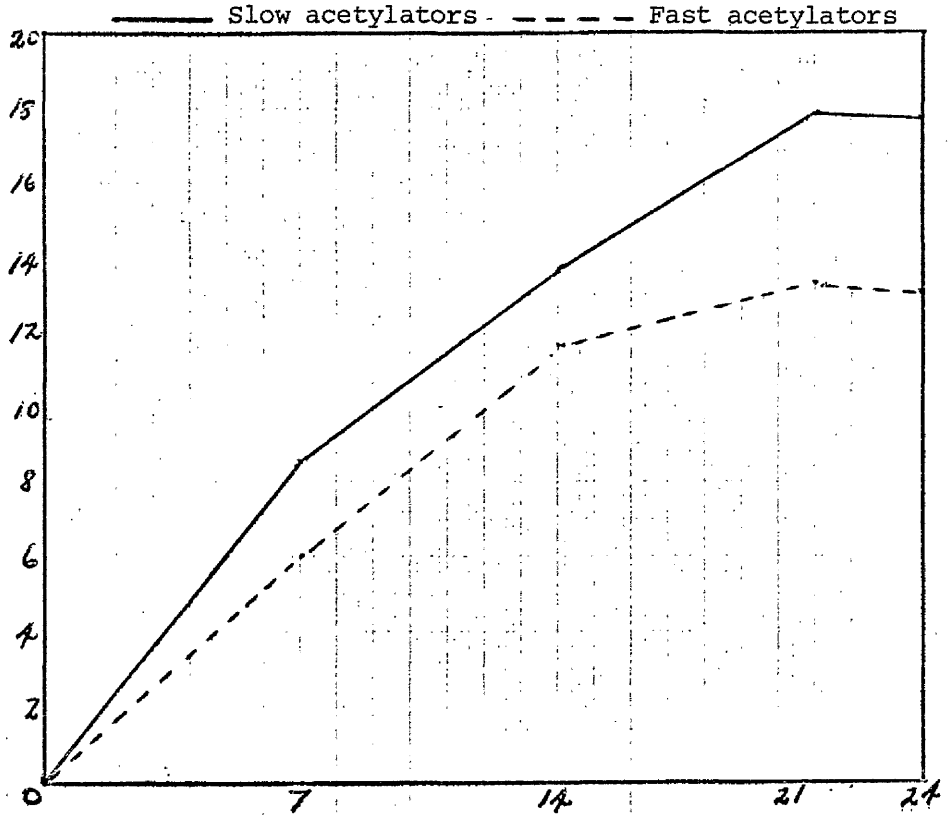


FIGURE 13

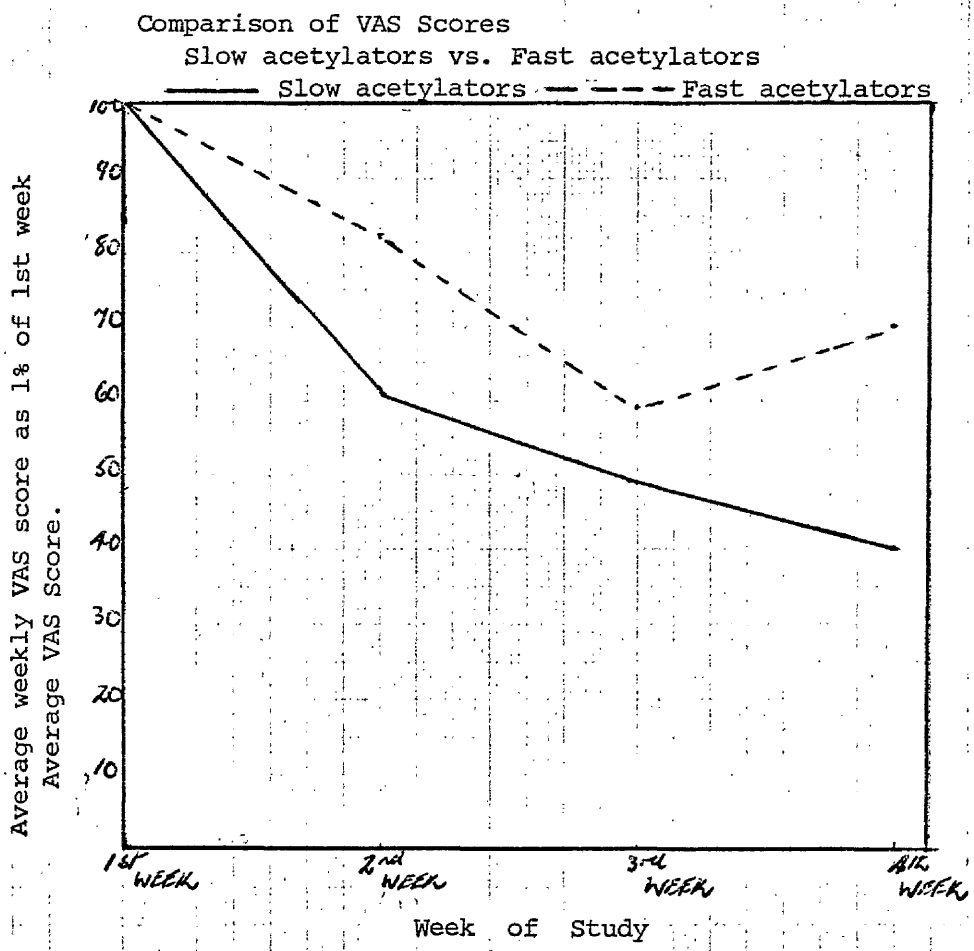

Comparison of VAS Scores
Slow acetylators vs. Fast acetylators
Slow acetylators
Fast acetylators
Average weekly VAS score as 1% of 1st week Average VAS Score.
100
90
80
70
60
50
40
30
20
10
1ST WEEK
2ND WEEK
3RD WEEK
4TH WEEK
Week of Study

FIGURE 14

Comparison of Side Effects (Mean Scores)
Slow acetylators vs. Fast acetylators.

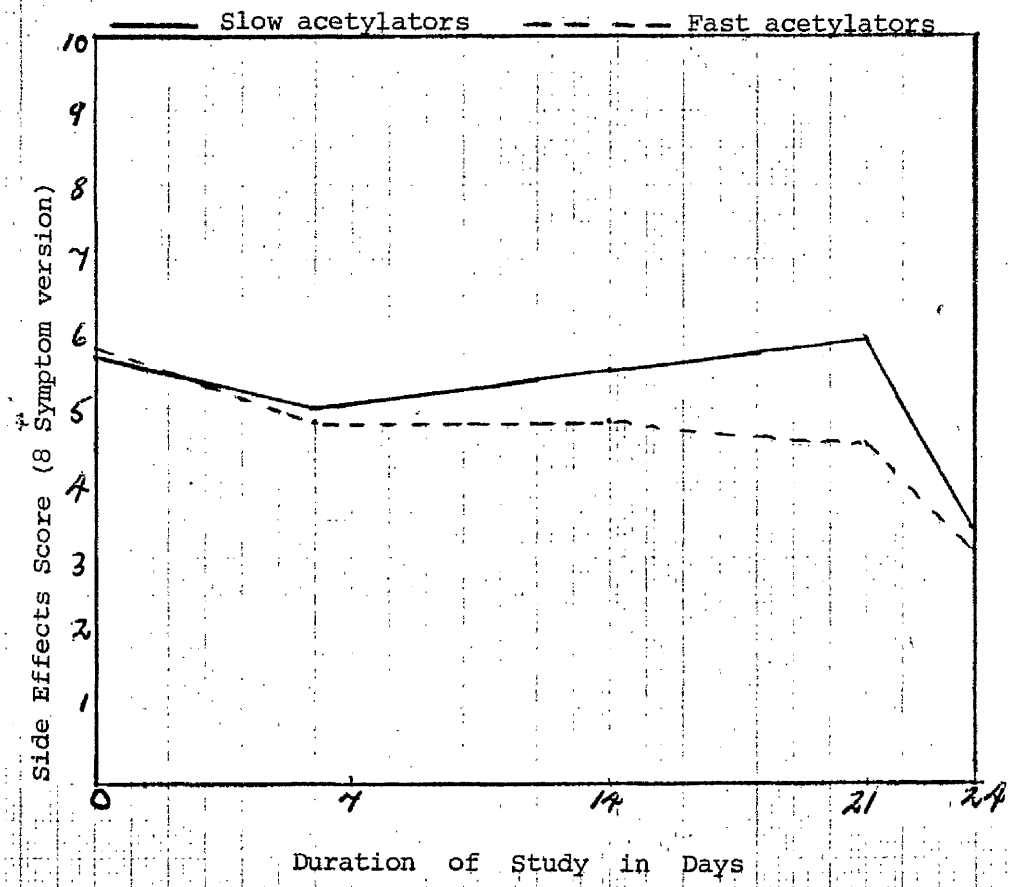


FIGURE 15

Comparison of Urinary Tryptamine Levels (Mean Scores)
Slow acetylators vs. Fast acetylators.

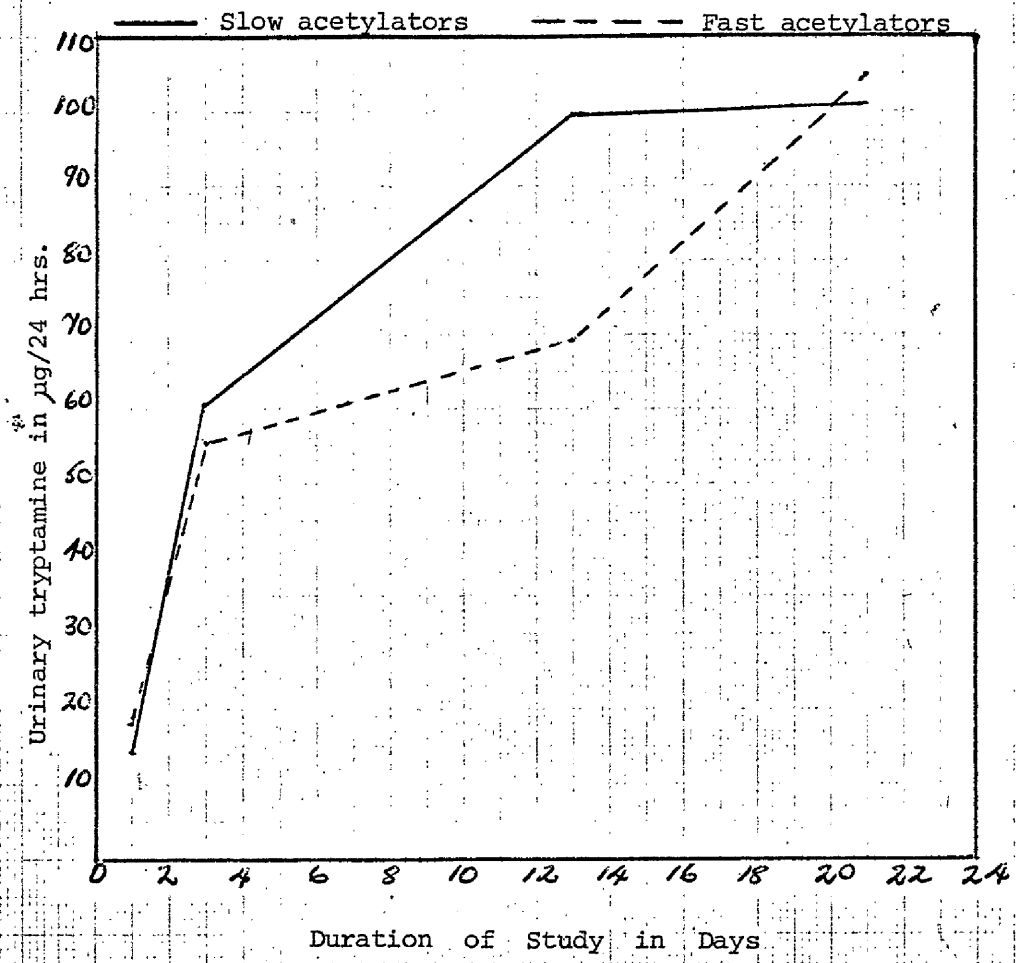


FIGURE 16

Comparison of difference between initial and subsequent tryptamine excretions (µg/24 hrs). Mean Scores
Slow acetylators vs. Fast acetylators.

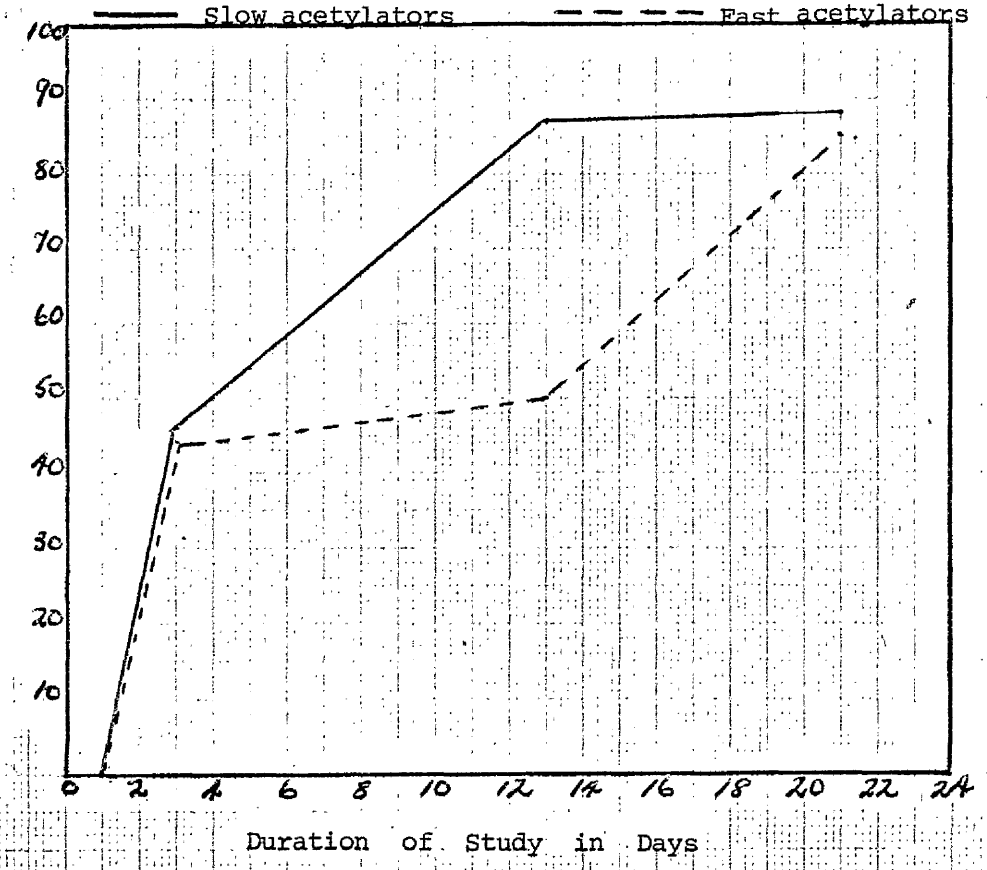


FIGURE 17

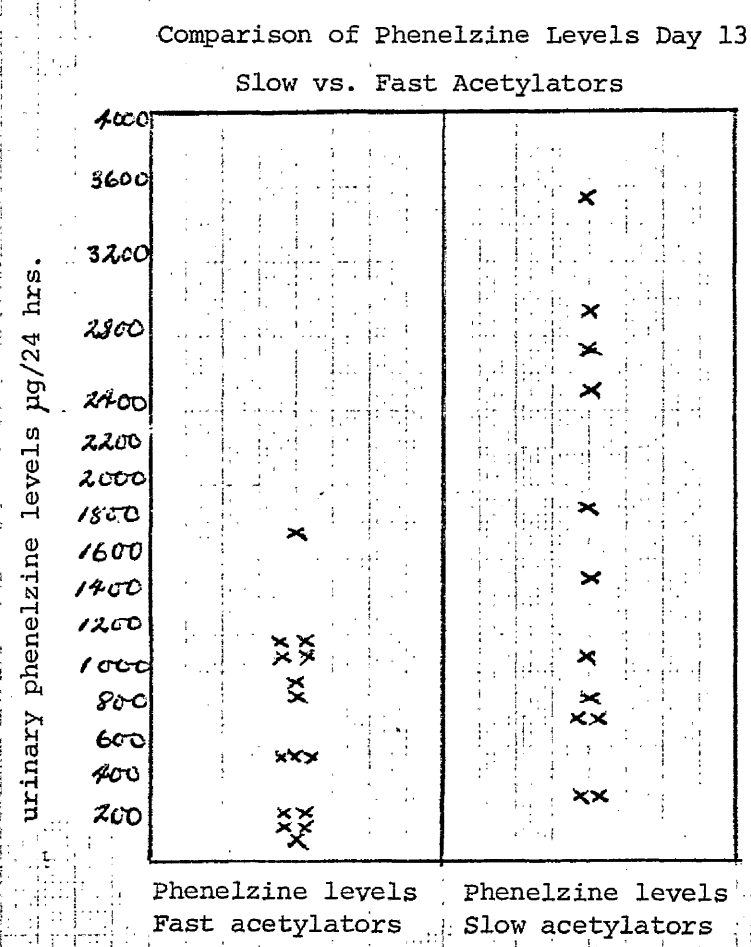
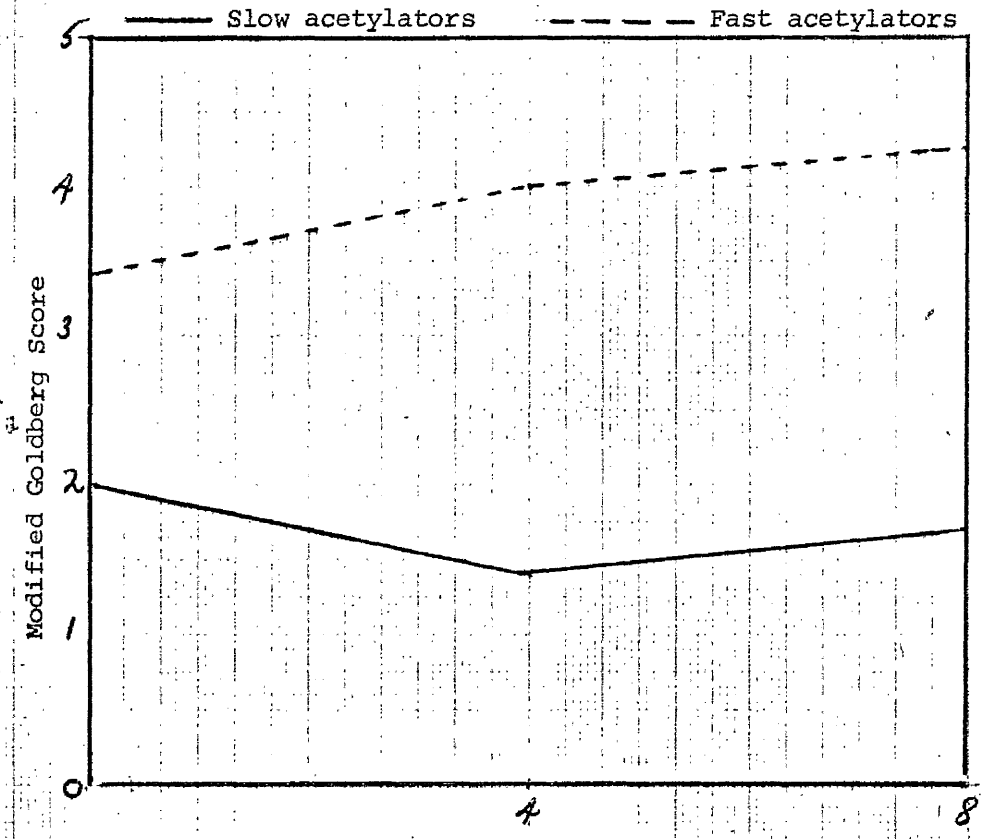

Comparison of Phenelzine Levels Day 13
Slow vs. Fast Acetylators
urinary phenelzine levels µg/24 hrs.
4000
3600
3200
2800
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
Phenelzine levels
Fast acetylators
Phenelzine levels
Slow acetylators

FIGURE 18

Comparison of Finishing & Follow-up Scores
(Cases followed-up only included)

Slow acetylators vs. Fast acetylators (Mean Scores)



Time in weeks since 24th day of Study.

FIGURE 19

Relationship between difference between initial and final scores (Modified Goldberg) and urinary tryptamine excretion Day 13.

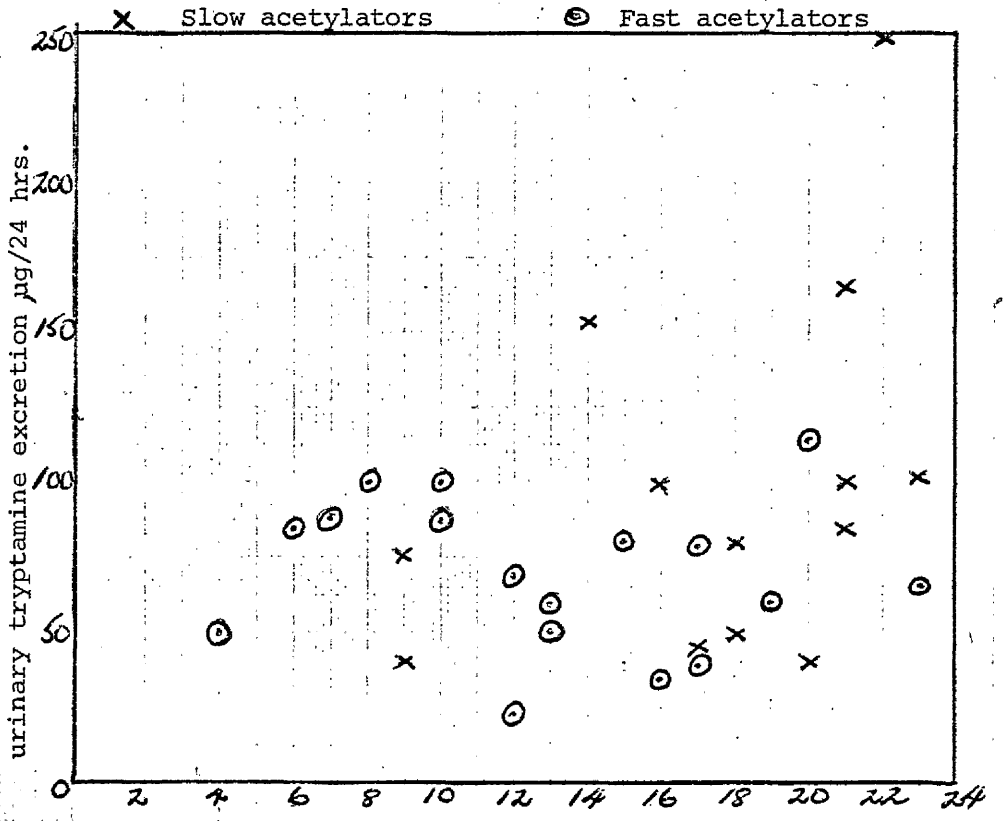


FIGURE 20

Relationship between difference between initial and final scores (Modified Goldberg) and urinary tryptamine levels Days 20, 21, 22.

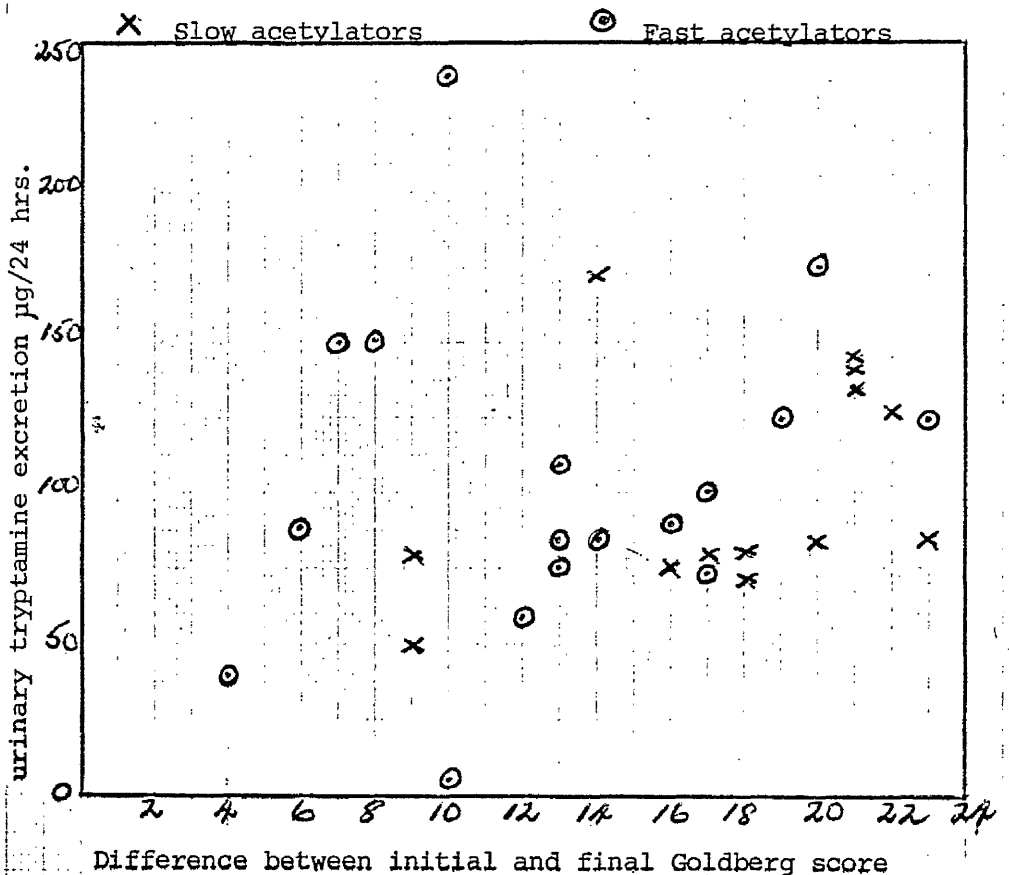


FIGURE 21

Relationship between phenelzine and difference between initial and final modified Goldberg scores.

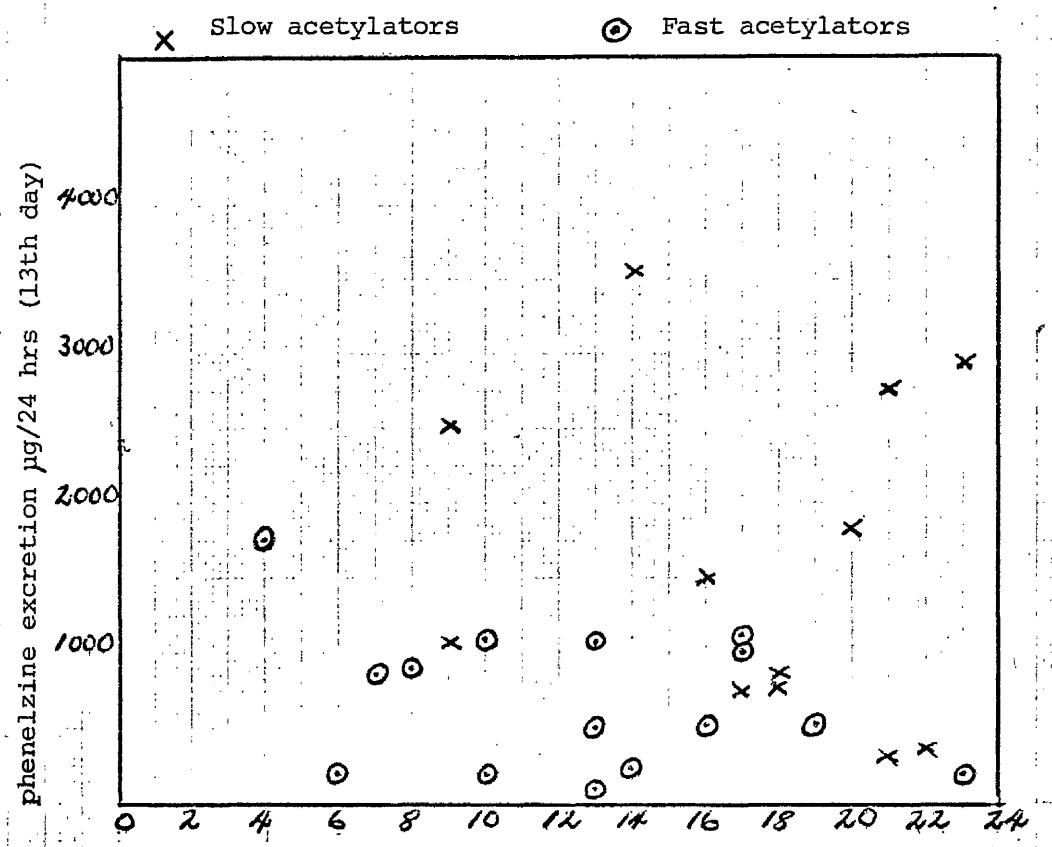


FIGURE 22

Relationship between phenelzine excretion and tryptamine excretion. Day 13.

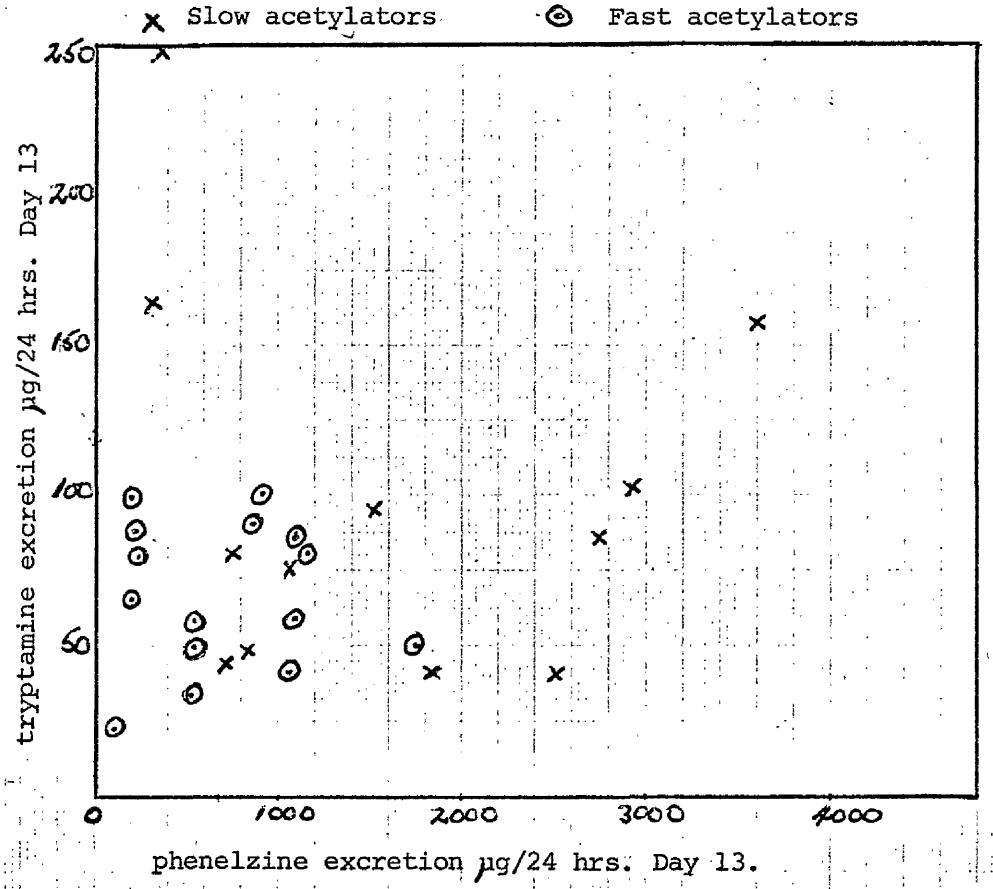


FIGURE 23

Relationship between Side Effects Week 3
and Modified Goldberg Score Week 3

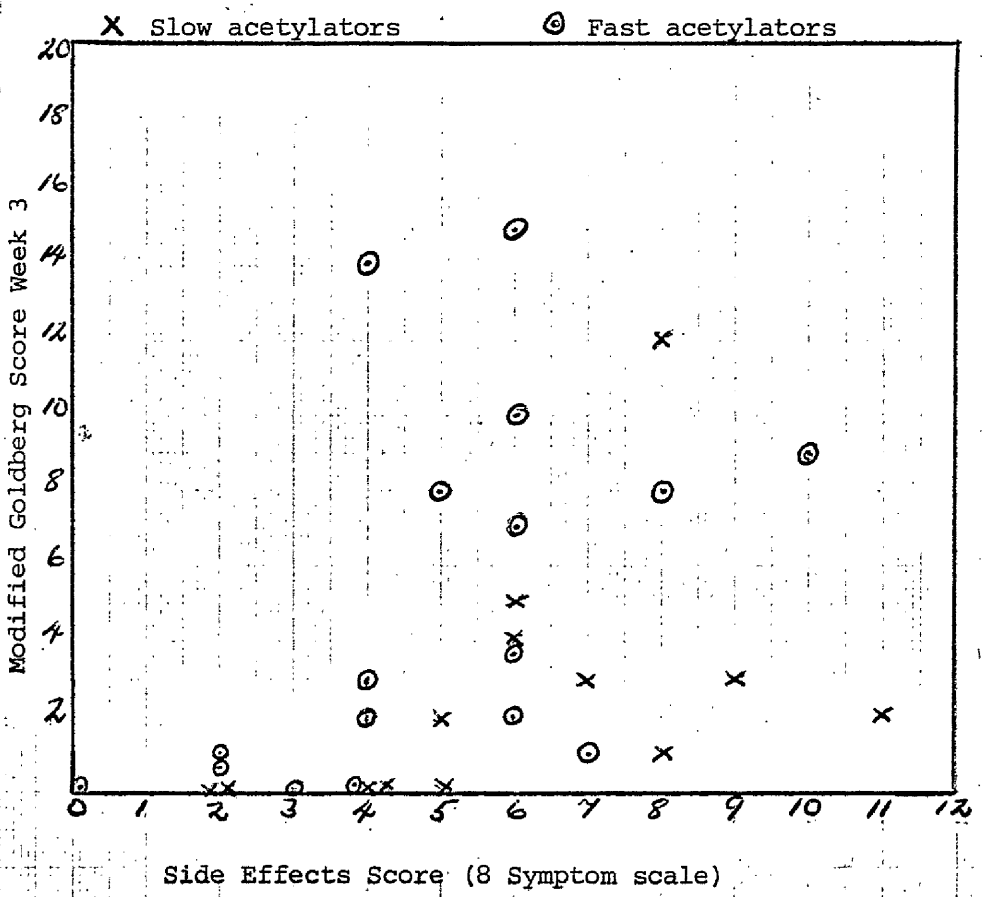


FIGURE 24

Relationship between Side Effects Week 3 and phenelzine excretion Day 13

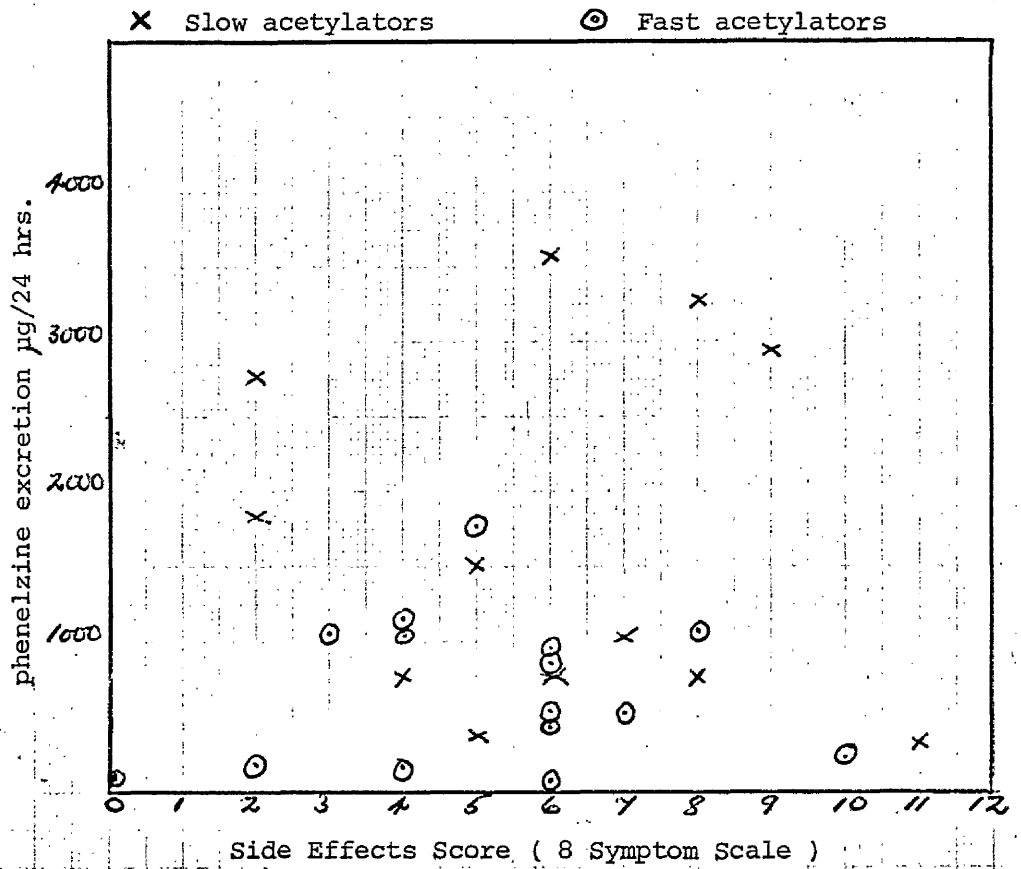
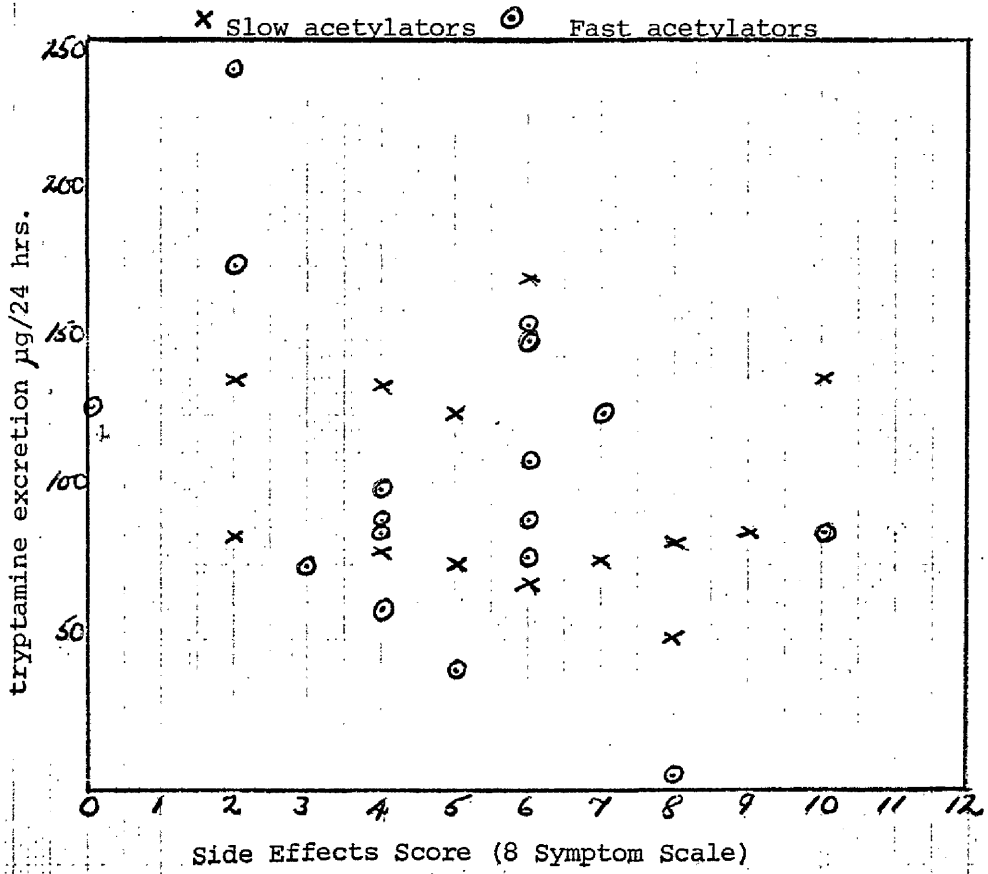


FIGURE 25

Relationship between Side Effects Week 3 and tryptamine excretion Days 20, 21, 22.



APPENDIX I

NAME	AGE	ACETYLATOR STATUS
Mrs. S.H.	35	Fast

OCCUPATION

Housewife

PRESENTING COMPLAINT

The patient complained of a "feeling that things she had done were never right". She was unable to cope with her responsibilities, could not enjoy herself and wept all the time.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms had developed 2-3 years before she was referred. There was no precipitant at that time but she had definitely deteriorated since the birth of her infant son 11 months prior to her attendance at the clinic. She had a constant feeling that something unpleasant was going to happen. She was not coping with her housework. She felt tired all the time and was distressed that she did not have the energy to play with her baby in the way that she felt she should. Her sleep was very poor - she repeatedly got up to make sure that the baby had not died in his cot. She was very irritable and difficult with her husband and her daughter. Her concentration was extremely poor and she could neither knit nor read nor sew. She could not make meals or shop efficiently. She was consistently in low spirits and wept a great deal. Her view of the future was uncertain rather than hopeless and she was not contemplating suicide as she felt she owed it to her husband and family to try to recover. She was never free from anxiety although she realised that her worries were trivial. She had become apprehensive about being alone in the house and about going out by herself. She had become preoccupied with the idea that people did not want her and were shunning her. She realised that this

idea was baseless but could not get it out of her mind. She also thought a good deal about the behaviour of her first husband and blamed him for the way that she felt. Self-blame was not a feature of her illness. Her appetite was unimpaired and she had not lost weight.

PAST PSYCHIATRIC HISTORY.

Nil.

PAST MEDICAL HISTORY

Dyspepsia of unknown cause 16 years previously.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was born and brought up in Glasgow, the younger of two daughters of a blacksmith, who died when the patient was seven years of age. Her own childhood was rather deprived as her mother had to work long hours in an unskilled occupation to support her daughters after the death of her husband. As a child the patient was regarded as nervous and highly-strung and was afraid of the dark. She attended a Junior Secondary School and left at 15 years of age. She quite enjoyed school and did fairly well. She worked in a tobacco factory until she was married, for the first time, at the age of 19 years. Her first husband was a violent man and a heavy drinker. The marriage was never a success and ended in divorce after six years. After the birth of her daughter in the second year of her first marriage the patient worked full-time as an instructress in an electronics factory and she had continued in this employment until after she was married for the second time in 1969. Her second husband was an engineer, 3 years older than herself,

who had not been previously married. This marriage was described as very happy and they had one son, aged eleven months. Mrs. K had this child as a duty to her husband rather than because she wanted a second child and was sterilised after he was born. They had no financial difficulties. They lived in the Corporation flat she and her daughter had occupied before the second marriage. This accommodation was cramped and in a poor district and the family was anxious to move away. The patient had always been over-anxious and had always been inclined to feel that people were against her. She had enjoyed her work in the factory and very much missed the company of the other women there. She did not like being home all day with her child.

DRUGS PRIOR TO ATTENDANCE

During the past year she had had

"Prothiaden" 1 capsule t.i.d.
Chlordiazepoxide 10 mg. t.i.d.
Diazepan 5 mg. t.i.d.

None of these had produced any benefit and when she attended the clinic she had stopped taking all of them.

She smoked 10 cigarettes per day. She did not drink.

AT INTERVIEW

She presented as depressed and tense. She was somewhat guarded in what she said. Otherwise there was no abnormality in her mental state.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (3).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	2	1	1	1		
Anxiety	4	4	2	2	3	2		
Phobias	2	2	2	2	1	1		
Obsessions	2	2	1	1	2	0		
Depressed	3	3	2	1	2	1		
Anxious	3	3	2	2	2	2		
Overall severity	23	23	15	12	15	10		

The patient's response was always limited and she deteriorated further after the cessation of the drug. She was therefore removed from the study and treated with E.C.T. and tricyclics. She improved but at best was tense, oversensitive and had a poor stress tolerance.

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	0	1	2	2	2
tremor	0	1	1	1	1
ataxia	1	1	1	1	0
sweating	1	1	2	1	1
constipation	0	0	0	0	0
faints/dizziness	1	1	0	1	0
micturition difficulty	0	0	0	0	0
blurred vision	1	1	0	0	0
Other	0	0	0	0	0
Total	4	6	6	6	4

NAME	AGE	ACETYLATOR STATUS
Mrs. M.B.	32	Fast

PRESENTING COMPLAINT

The patient said that for two years she had not been the bright, cheerful person that she had been formerly and that eight weeks previously she had suddenly developed the idea that she was going to die and had since been unable to stop crying.

HISTORY OF PRESENTING COMPLAINT

This lady's acute symptoms were superimposed on a more long-standing state of vague despondency. There was no obvious precipitant. Her main symptom was a fear that she had cancer and was about to die. She realised that this preoccupation was unreasonable. She felt tired all the time and the simplest task was an effort. She was spending a great deal of the day in bed for this reason. Her sleep was not impaired. She was irritable and quarrelled with her husband for no reason. She kept weeping and could not control this. She did not feel hopeless and had no suicidal ideas. Guilt was not a marked feature although she was aware that she had neglected her responsibilities since she had become ill. She felt constantly anxious about trivia and in addition to her fears about her own health, she was afraid that her children would die and kept going into their rooms at night to make sure that they were breathing. She had become unable to go out alone because of her fears of death and had ceased doing her own shopping entirely. She had lost a stone in weight in six weeks and her appetite was very poor.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was born and brought up in Glasgow, the eldest of four children of an engraver. Her parents were alive and well. Their home life was happy and the patient was an outgoing, friendly child. She attended Senior Secondary school and did well but insisted, against advice, on leaving at fifteen because all her friends were leaving. She became an office worker and worked successfully in this capacity until her marriage at 22 years of age to a computer operator of the same age. The marriage was said to be happy. She had two daughters aged 6 and 2 years. The elder daughter was apprehensive and nervous and was unsettled at school. The patient described herself as always having been "nervous, jumpy and inclined to over-react" but she had never previously felt consistently depressed. She had numerous friends and led a fairly full social life.

DRUGS PRIOR TO ATTENDANCE

Diazepam 5 mg. q.i.d. for two weeks followed by chlordiazepoxide 10 mg. q.i.d. for two weeks followed by phenobarbitone 60 mg. t.i.d. All without effect.

She smoked 10 cigarettes per day.

She drank spirits occasionally at social occasions.

AT INTERVIEW

She was rather tearful and despondent but her anxiety was a much more marked feature. She was very restless and constantly sought reassurance regarding her fears of malignancy. Otherwise her mental state

was normal.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of her initial assessment her score on the neurotic/endogenous rating was (4).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	2	2	1	0	0	0	0	0
Anxiety	4	4	3	0	0	0	0	1
Phobias	4	3	2	2	1	1	1	1
Obsessions	1	1	0	0	0	0	0	0
Depressed	2	2	1	0	0	0	0	0
Anxious	4	3	2	0	0	0	0	1
Overall severity	23	20	12	2	1	1	1	4

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	1	0	0	0
tremor	0	0	0	0	0
ataxia	0	1	0	0	0
sweating	2	0	0	1	0
constipation	0	0	0	0	0
faints/dizziness	2	2	0	2	1
micturition difficulty	0	0	0	0	0
blurred vision	1	0	1	0	0
Other	0	0	Dry mouth 1	Dry mouth 1	0
Total	7	4	2	4	1

Days 2 and 12 substituted for Days 3 and 13 for tryptamine assessment.

NAME	AGE	ACETYLATOR STATUS
Mr. J. McK.	33	Fast

OCCUPATION

Shipwright

PRESENTING COMPLAINT

The patient's symptoms had been steadily worsening over 2-2½ years. He complained of a constant feeling of despondency, of a fear that "something dreadful" was going to happen and of a preoccupation with ideas of personal unworthiness.

HISTORY OF PRESENTING COMPLAINT

Two events appeared to have precipitated this patient's symptoms. In 1971 he knocked down a child while driving his car. The child was not seriously injured but the patient was very upset by this incident. Shortly afterwards he knocked his head against a plank while at work. He was not injured but he felt that this piece of carelessness showed that he was no longer competent at his job. From that time he became increasingly despondent and anxious. At the time of his presentation he had been off work because of his symptoms for about a year. He was in financial difficulties because he had refused to draw State benefits, feeling that he did not deserve them. He complained a good deal about headaches which he thought might indicate that he had had a brain tumour. He felt tired and physically weak. His sleep was broken but this was a life-long trait which had been no worse since he had become ill. He felt low in spirits all the time and wept a good deal. His attitude towards the future was despondent but he had no suicidal ideas. He blamed himself for his condition and felt very guilty about injuring the child in the accident and about failing to support his family. He constantly felt anxious and any stress, however slight,

caused him to feel panic stricken. He had begun to avoid social situations in case any argument might break out as he felt that this was something with which he could not cope. For this reason he could not go out into the street in case he met anyone he knew, had to get off buses unless they were almost empty and went out and paced the streets in the evening if relatives called. His appetite was poor and he had lost 1 stone in weight in a year.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was born and brought up in Glasgow, the second of four children of a lorry driver. He had no neurotic traits in childhood. He attended an R.C. Junior Secondary school where he was an average scholar. He left at 15 years of age to be apprenticed as a shipwright. Until ceasing work because of his symptoms he had been employed by Upper Clyde Shipbuilders as a shipwright for ten years. He was married at 20 years of age to a girl of his own age. They had four children. The marriage was described as happy. They had a good deal of financial difficulty because of the patient's rather long illness and because of his objections to drawing sickness or unemployment benefit. He was not normally particularly anxious but all his adult life he had been very shy. He had no friends and made no attempt to make any. He had normally been in the habit of attending a few social functions in the company of his wife but since becoming ill had ceased

to do so.

DRUGS PRIOR TO ATTENDANCE

Diazepam 5 mg. t.i.d.

He smoked 20 cigarettes per day and drank alcohol occasionally.

AT INTERVIEW

He was very tense and he was depressed. He talked freely about his symptoms showing no psychomotor retardation. He was reluctant to speak much of the road traffic accident about which he felt guilty. His guilty ideas did not amount to delusions and his belief that it was wrong to claim State benefits was of long-standing and was evidently shared by some other members of his family. There was no other abnormality in his mental state.

Physically he was entirely well.

During the course of phenelzine he was on no other drugs.

At the time of the initial assessment his score on the neurotic/endogenous rating was (4).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	1	1	0	0	1	0
Anxiety	4	4	2	2	1	1	2	2
Phobias	4	4	2	0	0	1	1	2
Obsessions	1	1	1	0	0	0	0	0
Depressed	3	3	2	1	0	0	1	0
Anxious	3	3	2	1	0	1	1	1
Overall severity	24	24	14	7	1	4	8	6

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	1	0	0	0	0
tremor	2	1	0	0	0
ataxia	1	1	0	1	1
sweating	2	2	1	1	1
constipation	1	1	2	0	0
faints/dizziness	1	1	1	0	0
micturition difficulty	0	0	0	0	0
blurred vision	0	1	1	0	0
Other	0	0	0	0	0
Total	8	7	5	2	2

NAME	AGE	ACETYLATOR STATUS
Mrs. M.C.	42	Fast

OCCUPATION

Housewife

PRESENTING COMPLAINT

The patient's symptoms began suddenly in 1971. She suffered a spontaneous, incomplete abortion followed a few days later by a haemorrhage which took place in a city store and caused her to lose consciousness. After this incident she felt tired, lethargic, low-spirited and apprehensive about going into public places. She brooded a good deal about the loss of this child and after a further spontaneous abortion in 1972 her symptoms deteriorated further. At the time of her presentation she complained of a constant preoccupation with sad thoughts. She thought a good deal about the possibility that she might have malignant disease and about her inadequacies as a housewife and mother. She was tired and lacking in energy and interest. Her sleep was fitful, she was easily irritated and her concentration had become poor. Her mood was depressed but her attitude to the future was not hopeless and she was certainly not suicidal. She said that she had a lifelong tendency to worry to excess, although she had a remarkably philosophical attitude towards the family's chronic financial difficulties. Her principal anxieties centred around the probable fate of her family if, as she feared, she was suffering from malignant disease. Her anxieties about going into public places had extended to a fear of being left alone and at the time of her presentation she was to some extent reluctant for her husband to obtain work. Her appetite was poor but she had not lost weight.

PAST PSYCHIATRIC HISTORY

None.

PAST MEDICAL HISTORY

Chronic dyspepsia of unknown aetiology.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

None.

PERSONAL HISTORY

The patient was born and brought up in Glasgow. She was the only daughter of a labourer who was not in regular employment. She had 2 brothers, one older and one younger than herself. Their home life was described as happy although they were undoubtedly economically deprived. She had no neurotic traits in childhood. She attended a Junior Secondary school where she was an average pupil. She enjoyed school and had many friends. She left school at 15 and thereafter worked in various factories until she was aged 19, when she gave up work because she was illegitimately pregnant. She had hoped to marry the father of her child but he deserted her when he learned of the pregnancy. The child was brought up by the patient and her mother in the patient's parental home. After this daughter was born the patient only worked for short periods in part-time employment. She married when she was 31 years of age, her husband being a single man of the same age. The patient's daughter was thereafter largely brought up by her grandmother. The marriage was described as successful, although the patient's husband was chronically unemployed. There were three sons of the marriage, aged 10, 8 and 5 years and the patient had had spontaneous abortions in 1967, 1971, 1972. She and her husband both wanted more children. The patient's mother died in 1970 and this was a considerable loss to the patient as she had always been dependent on her mother. She stated that she was always inclined to worry to excess and to cope poorly with adverse circumstances. In the past she had turned to her mother when in any difficulty. Although as a

girl she was outgoing and sociable after the birth of her daughter she became seclusive and shy because she was ashamed of being an unmarried mother. She had few social contacts and no interests apart from her family and home.

DRUGS PRIOR TO ATTENDANCE

Diazepam 5 mg. q.i.d. - this had no effect.
Doxepin 25 mg. t.i.d. for three months, finishing six weeks before her presentation.
Nitrazepam 10 mg. nocte.

The patient neither smoked nor drank.

AT INTERVIEW

She was mildly depressed and more severely anxious. She sought constant reassurance, particularly about her health. Her mental state was otherwise normal.

Physically she was entirely well.

During her course of phenelzine she continued to take nitrazepam 10 mg. nocte.

At the time of her initial assessment her score on the neurotic/endogenous rating was (1).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	2	1	1	2	2	2
Anxiety	2	2	2	2	1	2	2	2
Phobias	4	4	4	3	2	2	2	2
Obsessions	1	0	0	0	0	0	0	0
Depressed	2	2	2	1	1	1	0	1
Anxious	3	3	2	2	2	2	2	1
Overall severity	20	19	16	12	10	12	10	10

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	0	0	1	2
tremor	1	1	1	0	0
ataxia	1	1	1	1	1
sweating	1	1	0	0	1
constipation	0	0	1	1	0
faints/dizziness	1	1	1	1	1
micturition difficulty	0	0	0	1	0
blurred vision	1	1	1	1	1
Other	0	0	0	0	0
Total	7	5	5	6	6

NAME	AGE	ACETYLATOR STATUS
Miss A.B.	39	Fast

OCCUPATION

Waitress

PRESENTING COMPLAINT

She complained that she had not felt well for 2-3 years. She complained of a feeling of pressure on top of her head which she felt slowed her down mentally. She felt depressed and weepy and nervous and had not been able to work for two months.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms had been very much worse in the past eight weeks although they had been present to some extent for a considerable time before that. No precipitant was detected. On questioning she explained that she felt constantly tired, slept poorly, was inclined to be irritable with the family, concentrated very badly and had lost interest in everything, to such an extent that she could not be bothered to keep tidy, wash her hair, etc. She felt very low in spirits and wept a good deal. She was despondent about the future and would not have cared if she had died although she had no intention of harming herself. She worried a good deal about her own future, about the health of her aged parents and about the future of her illegitimate son. Her appetite remained constant and she had not lost weight.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was born and brought up in Glasgow, the youngest of three daughters. When she was a child her father was a regular serviceman but he was later employed as a joiner. Both parents survive, now being in their seventies. She attended a junior secondary school where she was an average pupil. She worked as a sales assistant in ladies gown shops for some years. When she was 23 her illegitimate son was born. The child's father was a negro and the fact of the patient being the unmarried mother of a child of mixed race caused a family upset which had never really settled. The patient regretted not having married her son's father and wished that she had not yielded to family pressure on this score. After the birth of her son the patient took up factory work, the child remaining in the family home being cared for by the patient's mother. In the five years prior to her attendance the patient had worked as a waitress. The patient lived with her son and her aged parents in a decaying part of the city where most of the population was elderly. There was a good deal of strife in the house, particularly between the patient and her father. Her social life was somewhat restricted although she did visit her married sisters a good deal at the weekends. She did not regard herself normally as being anxious in nature and said that she usually had no problems in coping with her difficulties.

DRUGS PRIOR TO ATTENDANCE

Diazepam 5 mg. t.i.d. off and on for three years.

She smoked 15 cigarettes per day and was in the habit of taking 1-2 measures of spirits on Saturdays only.

AT INTERVIEW

She appeared depressed and self-blame was a prominent feature of her thought content. She was also very tense and rather restless. There was no other abnormality in her mental state.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (3).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	1	0	0	0	1	2
Anxiety	3	3	2	1	0	0	1	1
Phobias	0	0	0	0	0	0	0	0
Obsessions	1	1	1	1	0	0	0	0
Depressed	3	2	2	1	0	0	1	2
Anxious	3	3	1	1	0	0	1	1
Overall severity	19	17	10	6	0	0	6	9

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	1	0	0	0
tremor	0	0	0	0	0
ataxia	0	1	1	0	0
sweating	2	1	1	1	1
constipation	1	0	0	0	0
faints/dizziness	0	1	1	0	0
micturition difficulty	0	0	0	0	0
blurred vision	0	0	0	0	0
Other	0	0	0	0	0
Total	5	4	3	1	1

Days 5-8 and Days 15-18 substituted for Day 3 and Day 13 for tryptamine assessment.

NAME	AGE	ACETYLATOR STATUS
Mr. G.H.	52	Fast

OCCUPATION

Dispatch Assistant

PRESENTING COMPLAINT

Patient had felt depressed, unable to cope, and totally lacking in interest since the death of his wife two years previously.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms were clearly precipitated by the death of his wife from carcinoma of the breast two years before he attended the clinic. His wife had had a mastectomy ten years before she died and had had repeated courses of various forms of treatment, including radiotherapy and further surgery, over the next few years but the patient did not appear ever to have realised that her illness was likely to have a fatal outcome. His symptoms had steadily deteriorated and three weeks before he attended he had given up work because of them. He felt apathetic and listless. He was intolerant of others and easily irritated. His concentration was so poor that he really could not attend to the simplest task and it was for this reason that he had given up his job, feeling that he could not do it properly because he could not concentrate. He felt depressed all the time and any reminder of his wife made him worse. He wept constantly. He felt "unwanted, hopeless and useless" and wanted to die although he would not have committed suicide. He felt that without his wife the future was meaningless. He had a lifelong tendency to worry but since her death he had worried constantly about the most trivial matters. He could not stop thinking about his wife. His appetite was not impaired and he had not lost weight.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY.

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was born and brought up in Glasgow. He was an only child. His mother chronically abused alcohol. His father was an unskilled man and often unemployed so that the family was frequently in financial difficulty, He performed poorly at school and left at 14. As a child he was anxious, shy and never had many friends. The patient always worked in unskilled jobs but was clearly a reliable worker, holding down jobs for many years. He worked for 22 years in the dispatch department of a firm until giving up his job three weeks before attending hospital. He was married for the first time in his early 20's. The marriage lasted for seven years until his wife ran off with another man. There was one son of this marriage but the patient had not seen him for many years. He divorced his wife for adultery and remarried in his early 30's. His wife was four years younger. There were 2 sons of this marriage, aged 17 and 15. Mrs. H. . had developed carcinoma of the breast ten years before her death but despite increasing ill-health had apparently coped very well with her home and family. The patient did not anticipate her death and was very shocked by it. He had never been well since. He had been shy and anxious all his life and had relied upon his wife's support in making the simplest decision. He had no hobbies or interests and had been accustomed to spending every evening at home in his wife's company.

DRUGS PRIOR TO ATTENDANCE

None.

The patient smoked 10 cigarettes per day. He did not drink at all.

AT INTERVIEW

He presented as a very tense, tearful, despondent man with limited assets of intelligence and personality. His mental state was otherwise normal.

Physically he was entirely well.

During his course of phenelzine he had no other drugs.

At the time of the initial assessment his score on the neurotic/endogenous rating was (1).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	4	3	2	0	0	0	0	1
Anxiety	4	4	1	0	1	1	1	1
Phobias	0	0	0	0	0	0	0	0
Obsessions	2	2	1	0	1	0	0	0
Depressed	3	3	1	0	1	1	1	1
Anxious	3	3	1	0	0	1	1	1
Overall severity	22	21	8	0	4	5	5	6

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	0	0	1	1	1
tremor	0	0	0	0	0
ataxia	0	0	1	1	0
sweating	1	1	1	1	1
constipation	0	0	0	0	0
faints/dizziness	0	0	1	1	0
micturition difficulty	0	0	0	1	0
blurred vision	0	0	1	1	0
Other	0	0	0	0	0
Total	1	1	5	6	2

NAME	AGE	ACETYLATOR STATUS
Mr. J.A.	29	Fast

OCCUPATION

Unemployed Fitter.

PRESENTING COMPLAINT

The patient had been preoccupied with ideas of personal failure and despondency about the future for eighteen months. For the last four months he had been very much worse and was depressed, worried and unable to concentrate at all.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms originally dated from Autumn, 1972. At that time he gave up a post as a sales clerk as he could not cope with it. This disappointed his family and caused the patient to feel that he was a failure. The later deterioration of his symptoms, four months before his presentation, appeared to be precipitated by the breaking off of his engagement to be married. In addition to his spontaneous complaints, questioning revealed that he slept poorly, wakened early, was irritable with his family and lacked confidence in all of his abilities. His depression was marked, he wept a good deal and could see no hope for the future. He had thought about suicide but had no real suicidal intent. He was preoccupied with self-depreciatory ideas. His concentration was poor and he had no interest in any of his former pursuits. He had a life-long tendency to be over-anxious but felt that this had become worse. He was avoiding social occasions but this was really because he wished to avoid admitting to acquaintances that he was unemployed and felt that they would be bound to discover this during conversation. His appetite was unimpaired and he had not lost weight.

PAST PSYCHIATRIC HISTORY

None.

PAST MEDICAL HISTORY

None.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

None.

PERSONAL HISTORY

Patient was born and brought up in Glasgow, the elder of 2 sons of a fitter. The family life was described as happy. The family was Church-going and had high ethical and moral standards. In particular they regarded as important to work hard and improve one's lot in life by one's own efforts. From early childhood the patient was shy and a poor mixer. He attended a Senior Secondary school and did well most of the time. When he was fifteen he failed some examinations, lost confidence in his ability to cope academically and left school. He was apprenticed as a pipe fitter. He served his five year apprenticeship and then continued for a further four years with the same firm. He was then declared redundant with 50 others because the firm was in financial difficulties. He had great difficulty in obtaining work and could not get a position as a pipe fitter. After some months of unemployment he took a job as a sales clerk. He always disliked this job and found it difficult. After two years he gave this up and obtained a job as a labourer, feeling he was fit for nothing else. He worked in this capacity for six months but gave it up in March, 1973, and when he presented had been unemployed for ten months. He and his family regarded this as disgraceful. The patient had always been shy of the opposite sex but he had met the girl who became his fiancee in 1971 at work. In November, 1973 she

broke off the engagement because he was unemployed. This upset the patient very much. The patient stated that he had always been shy, solitary, a worrier and afraid of failure. He had few friends. His only hobby was reading books about the Second World War.

DRUGS PRIOR TO ATTENDANCE

In the ten months before he attended the patient had had

amitriptyline 25 mg. t.i.d.
doxepin 25 mg. t.i.d.
diazepam 5 mg. q.i.d.

None of these had produced any improvement and in the three weeks before attending he had stopped taking all tablets.

He did not drink alcohol and smoked 10 cigarettes per day.

AT INTERVIEW

He presented as a very neat and extremely polite young man. He rather lacked spontaneity and seemed reluctant to discuss his difficulties. He was quite markedly depressed and initially seemed lacking in hope for the future but was brightened by the offer of treatment. Otherwise his mental state was normal.

He was physically entirely well.

During his course of phenelzine he had no other drugs.

At the time of the initial assessment his score on the neurotic/endogenous rating was (2).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	4	3	3	3	2	2		
Anxiety	3	2	2	2	1	1		
Phobias	1	1	1	1	0	0		
Obsessions	1	1	1	1	0	0		
Depressed	3	2	2	2	1	1		
Anxious	2	2	2	1	1	1		
Overall severity	19	15	15	13	7	7		

The patient deteriorated after the 24th day and was therefore removed from the study. He was placed in group psychotherapy and later treated with imipramine and chlorpromazine. His response was rather slow but he returned to what was thought to be his previous normal.

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	1	1	2	1	1
tremor	1	0	0	0	0
ataxia	0	1	1	1	0
sweating	0	0	0	2	0
constipation	0	0	0	1	1
faints/dizziness	0	1	1	1	1
micturition difficulty	0	0	0	0	0
blurred vision	0	0	0	0	0
Other	0	0	0	0	0
Total	2	3	4	6	3

NAME	AGE	ACETYLATOR STATUS
Mrs. J. McD.	44	Fast

OCCUPATION

Housewife/Supervisor in Biscuit Factory.

PRESENTING COMPLAINT

The patient complained that she felt she was getting into a muddle with everything, that she kept crying, that she sometimes just wanted to die and that she kept worrying.

HISTORY OF PRESENTING COMPLAINT

The onset of the patient's symptoms was indefinite but she thought it had been about five years previously. During this period her symptoms had been present intermittently but in the three months befor her attendance they had been very much worse and the patient attributed this to the fact that her father was terminally ill. During these three months she had not been at work and had not been going out because of her symptoms. She also complained of headaches, of profound lethargy, of marked insomnia and of irritability. She felt that her concentration had become so poor that she could not do anything properly. Her depression was constant and she cried every day. She felt hopeless about the future and had contemplated suicide. She felt that she was useless and thought that her lack of education had been a handicap to her husband. She had always been of an anxious disposition but since being ill had become much more so, to such an extent that she was never free from worry. She had become indecisive and brooded a good deal about her father's impending death.

PAST PSYCHIATRIC HISTORY

Until five years before her attendance she had had no symptoms suggestive of psychiatric disorder. In this five-year period she had attended her general practitioner on account of her symptoms of depression and anxiety and

had been treated with minor tranquillisers. She had had a brief admission to a psychiatric unit eight months before this attendance.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Father has senile dementia.

PERSONAL HISTORY

The patient was born and brought up in Glasgow, one of six children, 5 daughters and 1 son. Her father was chronically unemployed and her mother supported the family by working as a hawker. She attended Junior Secondary school intermittently as her mother frequently kept her off to attend to the house or to help her with her hawking business. She left school at 14 and became a factory worker. She was married at the age of 20 to a joiner of 23. The marriage was described as happy. They had two children, a son, now aged 23, who had tuberculous meningitis at the age of 7 and an orchidectomy for a testicular tumour when aged 17. Their daughter, aged 17, was well and gave no cause for concern. The patient's husband was in regular work and supported his family but the patient had returned to work ten years previously and had recently been promoted to supervisor. She had been to visit her sisters and father in the United States in the Summer of 1973 and felt that this had precipitated her deterioration as she had been very greatly distressed by seeing her father demented and ill and by the family quarrels which had taken place over who was to care for their father. When well the patient was very cheerful, gregarious and fond of social occasions. She was described as being extremely vivacious and talkative and the life and soul of the party. Normally she ran the home, coped with her job and had a full social life and helped her sister in the running of a stall at the local market. She was

always anxious however and tended to over react to stress.

DRUGS PRIOR TO ATTENDANCE

Chlordiazepoxide 10 mg. t.i.d.
Nitrazepam 10 mg. nocte.

She did not smoke but took the occasional social drink.

AT INTERVIEW

The patient had a flamboyant manner but there was no doubt that she was markedly depressed. She was agitated and restless and talked at great length and under pressure. Otherwise her mental state was normal.

Physically she was entirely well.

During her course of phenelzine she continued to take nitrazepam 10 mg. nocte.

At the time of her initial assessment her score on the neurotic/endogenous rating was (4).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	4	4	2	0	0	0	0	0
Anxiety	4	4	1	0	0	0	0	1
Phobias	0	0	0	0	0	0	0	0
Obsessions	1	1	1	0	0	0	0	0
Depressed	4	4	1	0	0	0	0	0
Anxious	3	3	2	0	0	0	0	0
Overall severity	23	23	10	0	0	0	0	1

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	2	0	0	0
tremor	1	1	0	0	0
ataxia	1	0	0	0	0
sweating	2	0	0	0	0
constipation	2	0	0	0	0
faints/dizziness	1	0	0	0	0
micturition difficulty	0	0	0	0	0
blurred vision	0	0	0	0	0
Other	0	0	0	0	0
Total	9	3	0	0	0

Days 5-8 and 15-18 substituted for Days 3 and 13 for tryptamine assessment.

NAME	AGE	ACETYLATOR STATUS
Miss M.M.	58	Fast

OCCUPATION

Retired clerkess

PRESENTING COMPLAINT

The patient complained that about three years previously she had begun to feel depressed. More recently she had felt increasingly lonely and more and more of a failure.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms clearly dated from the death, some three years previously, of her brother with whom she had lived. She had been depressed following this but with time this depression had deteriorated rather than improved. In the year prior to her attendance she had become very much worse. She had lost interest in all of her former pursuits and her concentration had become very poor. She had become preoccupied by the idea that she had failed her brother and perhaps caused his death. She felt very depressed and felt that she would be helped by weeping but could not weep. She thought that the future held nothing for her and that she would be better off dead but she had no suicidal intent. Her sleep was poor but no worse than it had been for many years. She worried a good deal about trivia as well as important issues but this was a lifelong habit. She had always been to some extent socially phobic and this had become rather worse. Her appetite had become very poor and she had lost 1½ stones in weight over the past year.

PAST PSYCHIATRIC HISTORY

Lifelong tendency to excessive anxiety and attended general practitioner for anxiety symptoms over a twenty

year period. She also had a long history of somatic symptoms of which the organic basis was ill-defined.

In 1967 her symptoms were so severe that she could not work and she attended a psychiatric unit for a year, receiving group psychotherapy. She did not go back to work after this but retired at 54 years of age on grounds of nervous illness.

PAST MEDICAL HISTORY

Appendicectomy 20 years ago.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was bron and brought up in Glasgow. Her father was a heavy drinker and left the family when the patient was about 5 years of age. Her mother died when she was about 10 years of age. She had one brother sixteen years older than herself and was largely brought up by him. She was an average pupil at school and left at 14 years of age to become a cashier in a tobacco factory. She was employed there for 40 years but ceased working altogether at the age of 54 because of her chronic anxiety symptoms. Neither she nor her brother ever married and she kept house for him until his death three years before her attendance. About eight years before his death he became hemiplegic as a result of a cerebro-vascular accident and was cared for by the patient. He was by no means a total invalid during this time but was not fit to work. By all accounts the patient looked after him devotedly and had no reason to reproach herself. She had few friends or interests. All her life she had been shy and seclusive, had fussed about details and had been inclined to be over-sensitive and easily hurt. She has always been self-conscious about eating in restaurants. Despite these traits she had been a reliable

and conscientious worker for years and normally maintained a high standard of housewifery, and entertaining among her limited circle of friends. She had entirely ceased to be able to carry out these activities.

DRUGS PRIOR TO ATTENDANCE

Diazepam 10 mg. q.i.d.)
Nitrazepam 10 mg. nocte) for three years.
She smoked 20 cigarettes per day and drank only on rare social occasions.

AT INTERVIEW

The patient was tearful and importunate. She was very garrulous. She was extremely indecisive and apprehensive. Her attitude towards the future was nihilistic and she could not be reassured about the cause of her brother's death and her own part in this. There were no other abnormalities in her mental state.

Physically she was entirely well.

During her course of phenelzine this lady continued to take nitrazepam 10 mg. nocte as she had done for many years. She had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (5).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	2	1	0	0	1	0	0
Anxiety	2	3	1	0	0	1	1	1
Phobias	1	1	0	0	1	0	0	0
Obsessions	1	1	1	1	0	0	0	0
Depressed	2	2	1	0	0	0	0	0
Anxious	3	3	1	1	1	1	1	1
Overall severity	17	17	7	3	3	4	3	3

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	1	1	0	0
tremor	2	0	0	1	1
ataxia	1	1	1	1	1
sweating	2	0	0	1	0
constipation	0	0	0	1	1
faints/dizziness	1	1	1	0	0
micturition difficulty	0	1	1	0	0
blurred vision	0	0	0	0	0
Other	0	0	0	0	0
Total	8	4	4	4	3

NAME	AGE	ACETYLATOR STATUS
Miss J.M.	28	Fast

OCCUPATION

Clerkess

PRESENTING COMPLAINT

Patient complained that for five months she had felt low-spirited and weepy. She was lacking in energy and during this time had not felt able to work.

HISTORY OF PRESENTING COMPLAINT

The above features had developed to some extent for months prior to the patient's giving up work and appeared to some extent to have been precipitated by the marriage of a female cousin who was really the only social contact of this isolated young woman. It was difficult to determine exactly when she last felt quite well. On direct questioning she said that in addition to the above symptoms, she had intermittent headaches, was irritable with her grandmother, felt anxious about trivia and felt apprehensive when out alone. She had become indecisive and brooded a good deal about the future with particular reference to how lonely she would be when her grandmother died. She brooded a good deal about her past failures. Although she was markedly lacking in hope for the future she had no suicidal ideation. Her appetite was unimpaired and she had not lost weight.

PAST HISTORY OF PSYCHIATRIC ILLNESS

Neurotic depressive illness treated with drugs on inpatient basis followed by a prolonged period of group psychotherapy.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Patient's mother was a chronic attender at the psychiatric department suffering from a multiplicity of neurotic symptoms.

PERSONAL HISTORY

The patient was born in Glasgow. She was the daughter of her mother's first marriage which was never successful. She was brought up from infancy by her maternal grandmother. Her mother remarried and her second husband adopted the patient but she continued to live with her grandmother. She had one half sister, 15 years younger than herself. She coped reasonably well at school but her social adjustment was poor from childhood and she had few close friends. She left school at 15 and had been employed as a filing clerkess. She had worked continuously for six years for the same firm until five months before this presentation, when she had stopped work because of her symptoms. She lived with her grandmother, aged 87. She had few interests or social contacts outwith her family.

DRUGS PRIOR TO ATTENDANCE

"Motival" 2 tablets per day for five months prior to attendance.
She smoked 10 cigarettes per day and drank only at social occasions.

AT INTERVIEW

She presented as anxious, apprehensive and indecisive and tearful. There was no other abnormality in her mental state.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (3).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 1
Depression	2	2	2	1	0	1	1
Anxiety	2	2	2	1	1	1	1
Phobias	2	2	2	2	1	0	2
Obsessions	1	2	2	1	0	0	1
Depressed	1	1	1	0	0	0	0
Anxious	2	2	2	0	0	0	2
Overall severity	13	14	14	5	2	2	9

In view of rapid relapse patient was removed from follow-up one week after completion of study.

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	0	1	0	0
tremor	1	1	0	0	0
ataxia	1	2	1	1	1
sweating	2	0	1	1	1
constipation	0	0	1	1	0
faints/dizziness	1	1	1	1	1
micturition difficulty	0	0	0	0	0
blurred vision	1	1	0	0	0
Other	0	0	0	0	0
Total	8	5	5	4	3

NAME	AGE	ACETYLATOR STATUS
Mrs. M.S.(1)	31	Fast

OCCUPATION

Housewife

PRESENTING COMPLAINT

The patient complained of tearfulness, restlessness and inability to cope with her domestic responsibilities. She was preoccupied with a multiplicity of vague somatic complaints which she feared indicated her impending death. She had become afraid of being in the house at night and would go out and pace the streets.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms were clearly precipitated by the death of her husband five months previously. Her husband had been known for years to have tuberculosis but was thought to be reasonably well and was able to go to work. He died one night of a severe haemoptysis. Mrs. S was with him in the house when he became ill but was unable to get help before her husband died about 15 minutes after he started bleeding. Three weeks before his death a gypsy had told the patient that her husband was going to a place where he would be far, far happier and that she would be going there too. The patient feared that the gypsy's prophecy had been fulfilled by her husband's death and she began to think that she was going to die and interpreted a variety of minor somatic complaints as evidence that this was so. She felt tired all the time and slept poorly. If she wakened through the night she would go out and walk the streets because she could not tolerate the memories of her husband's death. She felt that she was becoming impatient with her children and that her concentration and interest were failing. She constantly felt low-spirited and this feeling was worsened by circumstances which brought it home to her that she no longer had her husband to turn

to. She wept a good deal and felt as if she would never be happy again but she had no suicidal intent. She was becoming increasingly anxious and worried a good deal about trivia. She had a marked fear of being alone in her house and arranged for neighbours to come in during the day. She could not avoid thinking about her husband's death and going over the details of it in her mind. She was eating poorly and had lost a stone in weight since her husband's death.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY

"Back trouble" aged 16: 2 weeks hospitalisation.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was born and brought up in Glasgow, the youngest of four children of working class parents. Her home life as a child was happy but she was regarded by her mother as being "highly strung". No clear history of neurotic traits in childhood was obtained. She attended Junior Secondary school where she took domestic subjects. She left at 15 and worked for seven and a half years in the same box factory until her marriage at 23 to a man of 28 who was known to have drug-resistant tuberculosis. He remained relatively well until his death and worked regularly in unskilled jobs. There were three children of the marriage, aged 7, 6 and 2. The marriage was described as happy. The patient had no serious financial difficulties. She lived in a two-roomed flat without basic amenities in very old property. The patient was described as always having been of anxious personality and she had always been a dependent woman, relying on

her husband to make even minor decisions for her.

DRUGS PRIOR TO ATTENDANCE

Chlordiazepoxide 10 mg. t.i.d.

She smoked 20 cigarettes per day and drank on social occasions.

AT INTERVIEW

She was tense, agitated and depressed. Her manner was a little histrionic and she was rather importunate, constantly seeking reassurance and support. Her mental state was otherwise normal.

Physically she appeared entirely well. She was investigated intensively for tuberculosis before being placed in the study.

During her course of phenelzine she had no other drugs.

At the time of her initial assessment her score on the neurotic/endogenous rating was (3).

Three weeks after her discharge the patient attended the clinic complaining of back and pubic pain. This was found to be due to osteitis pubis of non-tuberculous aetiology. She required inpatient orthopaedic treatment for some time and follow-up was therefore not possible.

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	3	2	1	1		
Anxiety	3	3	2	2	1	1		
Phobias	3	3	3	1	1	1		
Obsessions	2	2	1	0	0	0		
Depressed	3	2	2	1	1	1		
Anxious	3	3	2	2	2	1		
Overall severity	23	21	17	11	9	7		

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	0	1	0	0	1
tremor	2	2	2	2	2
ataxia	1	2	1	1	0
sweating	2	1	1	2	2
constipation	2	2	2	2	2
faints/dizziness	2	2	2	2	0
micturition difficulty	0	0	0	0	0
blurred vision	1	1	1	1	0
Other	0	0	0	0	0
Total	10	11	9	10	7

NAME	AGE	ACETYLATOR STATUS
Mrs. M.G.	36	Fast

OCCUPATION

Housewife.

PRESENTING COMPLAINT

The patient complained of depression, irritability and loss of interest.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms had been present for 2 years and appeared to have been precipitated by her having a hysterectomy for menorrhagia. In addition to the above symptoms she complained of headaches, of anergia and of severe sleep disturbance. Her concentration had deteriorated so that she was burning meals, spoiling material when dressmaking, etc. Her depression was severe and constant. She wept a good deal, felt hopeless about the future and thought about suicide. She had in fact attempted suicide by self-poisoning one year and three months before being seen but said at the time of attendance that she had no suicidal intent as she felt she must go on living to care for her children. She had always been inclined to be overanxious but she had lately become preoccupied with worries about her children to an extent that she realised was totally unreasonable. She had become afraid to go out. This was because she feared that she would "make a fool of herself" if people spoke to her. She had become indecisive even about trivial matters. Her appetite had become poor and she had lost 2 stones in weight in 2 years.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY

Appendicectomy as a girl.
Hysterectomy for menorrhagia.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS.

Nil.

PERSONAL HISTORY

The patient was born and brought up in a poor area of Glasgow. She was the youngest of 13 children of an unskilled man. Only 6 of the children now survive. Their childhood was happy although they lived in very overcrowded circumstances and were economically deprived. Despite her circumstances she did well at primary school and was granted a place in the top stream at the Convent of Our Lady & St. Francis where she did well. She left at fifteen because she wanted to work to bring money into the house, her father having died by that time. She worked as a machinist until her marriage at 22 to a labourer of 24. The marriage was described as very happy and the patient and her husband appeared to have centred their lives around their family of 3 daughters, aged 13, 7 and 6 years, and 1 son, aged 11 years. The children were all well and gave no real cause for anxiety. They had no financial difficulties as the patient had always prided herself on being a good manager, doing all her own baking and making all of her own clothes and those of her three daughters. She had been quite pleased about having the hysterectomy as she had conscientious objections to contraception but did not really wish to have a very large family. She did not appear to have any guilt about this operation as there appeared to be no question in her mind that the operation might have been done for any reason other than medical necessity. Normally the patient was cheerful and very active. She and her husband belonged to social clubs connected with the

Church and the patient served on the committees of these. She was a keen knitter, dressmaker and baker and also decorated her own home. She had always been inclined to be overanxious.

DRUGS PRIOR TO ATTENDANCE

Amitriptyline 25 mg. t.i.d. had been prescribed for months but she did not take it regularly.

When she attended she was having "Doxepin" 25 mg. q.i.d. without effect.

She was prescribed Nitrazepam 10 mg. nocte but did not take it regularly.

She smoked 10 cigarettes per day.

She did not drink.

AT INTERVIEW

She presented as very depressed with guilt and loss of hope for the future being prominent features. To a lesser degree she was agitated and tense. Her mental state was otherwise normal.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of her initial assessment her score on the neurotic endogenous rating was (3).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	4	3	3	3	3	3		
Anxiety	3	2	1	0	0	0		
Phobias	2	2	2	2	2	2		
Obsessions	1	1	1	1	1	1		
Depressed	4	3	3	3	3	3		
Anxious	3	3	2	1	1	1		
Overall severity	24	20	17	14	14	14		

In view of her persisting significant depression this lady was removed from the trial on the 24th day and given a course of 10 ECT to which she made a partial response.

She was discharged and treated with imipramine 50 mg. q.i.d. After 3 months on this she was well.

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	2	1	1	1
tremor	0	0	0	0	0
ataxia	0	1	1	1	1
sweating	2	0	0	0	0
constipation	0	0	1	1	1
faints/dizziness	2	2	1	1	0
micturition difficulty	0	0	0	0	0
blurred vision	0	1	1	0	0
Other	0	0	0	0	0
Total	6	6	5	4	3

NAME	AGE	ACETYLATOR STATUS
Mr. J.F.	33	Fast

OCCUPATION

Electrician

PRESENTING COMPLAINT

He complained of feeling depressed all the time, of loss of interest and of lack of confidence.

HISTORY OF PRESENTING COMPLAINT

His symptoms had been present for three years and had grown steadily worse during this time so that for the 8 months prior to attending he had been unable to work. He could describe no precipitant. In addition to his spontaneous complaints, on direct questioning he admitted to frequent headaches, to tiredness and lethargy and to indecision. He was not irritable, he slept well and did not feel any more anxious than usual. His appetite was unimpaired and he had not lost weight. His depression was always present and was worsened by contact with other people. He was lacking in hope for the future and had thought about committing suicide. He blamed himself for his illness.

PAST PSYCHIATRIC HISTORY

None until 3 years before this attendance. During this 3 years he had attended several psychiatrists and had been given various treatments including E.C.T. He had evidently derived no benefit.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

A sister had had a brief period of outpatient psychiatric attendance. There was no clear description

of her illness.

PERSONAL HISTORY

The patient was born and brought up in Kilmarnock, the second of four children of an office timekeeper. His childhood was described as happy. He had no neurotic traits and got on well with his parents and siblings. He attended Senior Secondary school but left at 15. He was apprenticed as an electrician and completed his five-year apprenticeship. He thereafter worked on a contracting basis and travelled a good deal, both around Britain and abroad. He was unmarried and had no close friends of either sex. He had always been quiet, shy and lacking in confidence. After he became too unwell to work he went to live in his parents' home and was greatly distressed by his father's sudden death four months prior to his attendance at the clinic. There was no doubt that his symptoms had long antedated this.

DRUGS PRIOR TO ATTENDANCE

Over the three years of his illness he had had a variety of minor tranquillisers and tricyclic anti-depressants. None of these had helped him. When he attended he was having Doxepin 25 mg. t.i.d. without benefit.

He smoked 20 cigarettes per day and spent about £3/week on alcohol.

AT INTERVIEW

He was taciturn and withdrawn. He was undoubtedly depressed but only very mildly anxious. Otherwise his mental state was normal.

Physically the patient was entirely well.

During his course of phenelzine he had no other drugs.

At the time of the initial assessment his score on the neurotic/endogenous rating was (3).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	1	1	0	1	1	1
Anxiety	1	1	2	1	1	0	1	1
Phobias	0	0	0	0	0	0	0	0
Obsessions	1	1	1	1	0	0	0	0
Depressed	3	3	1	1	0	1	1	1
Anxious	1	1	1	1	0	0	0	0
Overall severity	13	13	8	7	1	3	4	4

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	0	0	0	0	1
tremor	0	0	0	0	0
ataxia	0	0	0	0	0
sweating	1	0	0	1	1
constipation	1	0	1	0	0
faints/dizziness	0	1	1	1	0
micturition difficulty	0	0	0	0	0
blurred vision	1	1	1	0	0
Other	0	0	Breathless 1	0	0
Total	3	2	4	2	2

Days 5-8 and 15-18 substituted for Days 3 and 13 for tryptamine assessment.

NAME	AGE	ACETYLATOR STATUS
Mrs. A.J.	57	Fast

OCCUPATION

School cleaner

PRESENTING COMPLAINT

The patient stated that she had not felt well for a year but that she had deteriorated rapidly in the past three months. She complained of a feeling of pressure on her head and a choking feeling. She felt depressed and just wanted "to lie and lie" rather than do anything. She felt as if she was shaking all the time. Because of these symptoms she had been off work for four months.

HISTORY OF PRESENTING COMPLAINT

There was no definite precipitant for her condition. For a year she had felt constantly tired and lacked interest in things. She had felt vaguely physically unwell during this time and in the last three months had had a frequent choking feeling which she was afraid was a sign of malignant disease. She had been thoroughly investigated from the physical point of view and had been told that she was well. She realised that it was ridiculous to continue to be preoccupied with a fear of malignancy but nonetheless brooded about this frequently. She was sleeping badly, wakening early after a restless night. She was very irritable and constantly picked quarrels with her daughter. She constantly felt low-spirited and wept a good deal. She felt despondent about the future and had wished for death although she had no intention of committing suicide. She had no guilty ideas and indeed tended to be extrapunitive. She worried a good deal about her children. This was a lifelong tendency but she could no longer put her worries to the back of her mind. She had become apprehensive about being alone in the

house in case she died and her daughter had therefore come to live with her. She was preoccupied with fears of cancer and with thoughts of her dead husband and how she longed to be with him. Her appetite was poor and she had lost a stone in weight in four months.

PAST PSYCHIATRIC HISTORY

None.

PAST MEDICAL HISTORY

She had had surgery for a prolapsed lumbar disc some years previously.

Dyspepsia ?due to peptic ulceration 20 years ago.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

None.

PERSONAL HISTORY

The patient was born and brought up in Glasgow, the fifth of eight children of a butcher. The family was poor but their home life was happy. She was at various schools as the family moved about a good deal. She left school at 13 years of age to keep house because of her mother's failing health. Her mother died when she was fifteen and she continued to care for the rest of the family until she was married at the age of 20 to a labourer of 23. Her marriage was described as extremely happy and the patient continued at the time of her presentation in 1973 to grieve for her husband who had died of a myocardial infarction in 1967. There were two children of the marriage, a son and a daughter, both married, the son living in London and the daughter in Glasgow. The patient worried a good deal about the financial circumstances of both her children, particularly the daughter who was inclined to get into debt as a result of hire purchase commitments. This was very contrary to the

patient's teaching as she was entirely opposed to credit and took a pride in the fact that she had always managed to run a comfortable home on the modest wages provided by her father and her husband without being in debt on any occasion. She was very concerned about her daughter's foolishness over money and it was possible that her illness could have been precipitated by this to some extent, although this was by no means clear. Since her husband's death she had worked as a school cleaner and when well enjoyed the work. She normally visited a fairly wide circle of friends and in the company of other widows attended Church functions. She had no financial worries. She had always been a hardworking, rather obsessional woman who set high standards for herself and her family. She had relied a good deal on the company and support of her husband and being a reserved woman found it difficult to confide her worries to anyone at all after his death.

DRUGS PRIOR TO ATTENDANCE

In the year before she attended the patient had been treated with prochlorperazine ("Stemetil") 5 mg. t.i.d; clorazepate ("Tranxene") 15 mg. t.i.d. and nitrazepam ("Mogadon") 10 mg. nocte. None of these had produced any improvement.

The patient neither smoked nor drank.

AT INTERVIEW

She was depressed, tense and lacked spontaneity. Otherwise her mental state was normal.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (5).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	4	3	3	1	1	1		
Anxiety	3	2	2	1	1	1	Patient given	
Phobias	2	1	1	1	0	1	E.C.T. at this	
Obsessions	1	0	0	0	0	0	point.	
Depressed	3	3	2	1	1	2		
Anxious	3	2	2	2	2	2		
Overall severity	22	16	14	9	8	12		

In view of her failure to respond the patient was removed from the study at Day 24 and given 8 E.C.T. This produced a significant improvement but she was not asymptomatic.

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	1	0	1	1	1
tremor	1	0	0	0	0
ataxia	0	0	0	0	0
sweating	0	0	0	1	0
constipation	0	0	1	1	1
faints/dizziness	0	1	0	0	0
micturition difficulty	0	0	0	1	0
blurred vision	0	0	1	1	0
Other	0	0	0	0	0
Total	2	1	3	5	2

NAME	AGE	ACETYLATOR STATUS
Mrs. M.S.(2)	28	Fast

OCCUPATION

Housewife

PRESENTING COMPLAINT

The patient complained that despite the fact that she had no reason at all to be unhappy she had been depressed since the birth of her baby one year previously.

HISTORY OF PRESENTING COMPLAINT

The patient complained that during her second pregnancy she had felt tired and irritable but had attributed this to her condition. Since the birth of her baby these symptoms had worsened and she had begun to suffer from constant headaches, and to feel miserable most of the time. She wept a good deal and felt apprehensive about her ability to cope in the future but her attitude was by no means one of hopelessness and she certainly had no suicidal ideas. She worried a good deal over trivia but this was a life-long tendency. Her interest in her children had declined and she felt that she neglected them and was unreasonably irritable with them. She could no longer concentrate on television, reading or knitting and she felt too apathetic to go out socially with her husband. Her appetite was good and she had not lost weight.

PAST HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS.

Nil.

PERSONAL HISTORY

The patient was born and brought up in Glasgow. Her father, a retired lorry driver, was 70 and her mother was 69. The patient was very much the younger of their two children, her only sister being 20 years older than herself. The patient had no neurotic traits in childhood and she described her home life as happy. She attended a Junior Secondary school and left at 15 years of age to become a clerkess. She worked in this capacity until her marriage at 24. She was pregnant on marriage. She had always felt very guilty about this and her parents were very upset about it. Her husband was one year older than herself and in regular employment as a joiner. He worked very long hours in order to obtain extra money and this caused difficulties between the patient and her husband as she felt that too much of the responsibility for the children rested on her. She had two daughters, aged 4 years and 1 year. Both were well but the patient found it difficult to control the behaviour of the elder girl. They had no serious financial difficulties. The patient has always been inclined to worry excessively about small matters but she was normally cheerful, optimistic and sociable. Since her marriage her social life has been very restricted and she was lonely in her home as she lived in a district where there were few other young women.

DRUGS PRIOR TO ATTENDANCE

Amitriptyline 50 mg. t.i.d. for one year without effect. Oral contraceptives since the birth of her second daughter and for 2 years after the birth of the first child. Nitrazepam 10 mg. nocte for one year.

She smoked 10 cigarettes per day but did not drink alcohol.

AT INTERVIEW

The patient was rather taciturn. She appeared depressed although she tried to control this. Anxiety

was present but it was not gross. Her mental state was otherwise normal.

Physically she was entirely well.

During her course of phenelzine she continued to take nitrazepam 10 mg. nocte but her oral contraceptives were stopped and she was given no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (4).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	2	3	2	0	0	0	1	1
Anxiety	2	2	2	0	0	0	1	1
Phobias	0	0	0	0	0	0	0	0
Obsessions	0	0	0	0	0	0	0	0
Depressed	3	2	1	0	0	0	0	1
Anxious	2	3	3	1	1	1	1	1
Overall severity	14	15	12	2	2	2	4	6

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	0	0	0	0
tremor	1	1	1	1	1
ataxia	0	1	1	1	0
sweating	2	0	0	0	0
constipation	0	1	2	2	1
faints/dizziness	1	1	1	1	1
micturition difficulty	0	0	0	1	0
blurred vision	0	1	1	0	0
Other	0	0	0	0	0
Total	6	5	6	6	3

NAME	AGE	ACETYLATOR STATUS
Miss M.W.	57	Fast

OCCUPATION

Sales Assistant in Dress Shop.

PRESENTING COMPLAINT

Patient complained of a "feeling of unreality and confusion". She could not concentrate on what she was saying, did not want to speak to people and was avoiding serving at work. She could not do her housework and could not sit still, but did not want to go out of the house. She felt as if she was waiting for something dreadful to happen. For six weeks her symptoms had been so bad that she could not work.

HISTORY OF PRESENTING COMPLAINT

The above features had developed gradually about one year prior to her attendance and had steadily worsened since. There was no detectable precipitant. On direct questioning she admitted also to having headaches, fatigue and insomnia. She had constant depression of mood and said that she had had fleeting thoughts of suicide. She had been anxious and of a worrying disposition all her life but these features had been worse lately. She had always been to some extent socially phobic and this too had become more severe. Her appetite was not impaired and she had not lost weight.

PAST PSYCHIATRIC HISTORY

1952 - operation for fibroids: depressed and anxious thereafter, treated by G.P. with barbiturates.

1960 - during mother's terminal illness required treatment with barbiturates.

1971 - symptoms of depression and anxiety: attended psychiatric outpatient clinic, treated with anxiolytics - never quite well since.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was born in Cambuslang and had lived there all her life. Her father was a crane driver and died in 1965 of heart failure. Her mother died in 1960, having been ill for some years as a result of diabetes and coronary artery disease. The patient is the 4th of 5 children and the only daughter. At the time of her illness she had lost touch with two of her brothers but visited one regularly and was in close contact with her orphaned niece, the daughter of her dead brother. She had attended a Junior Secondary school, leaving at 14. She worked in shops for a number of years but later worked in light engineering factories, being employed by one firm for 19 years until she became unwell in 1971. She had then been unemployed for some time but had been employed as a sales assistant for one year prior to her attendance. She had never married and lived alone. She had few close friends and few interests.

DRUGS PRIOR TO ATTENDANCE

Six weeks prior to attendance had had amitriptyline 25 mg. b.d. for ten days only with no effect.

Diazepam 5 mg. b.d. had been prescribed but she had not taken it regularly.

Haloperidol 1.5 mg. b.d. - currently prescribed.

Nitrazepam 5 mg. nocte occasionally in the past year.

She smoked 40 cigarettes per day but did not drink alcohol.

AT INTERVIEW

Her depressed mood was obvious and she was clearly anxious. There was no other abnormality in her mental

state.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (3).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	4	2	2	0	0	0	0	0
Anxiety	2	3	1	0	0	0	1	0
Phobias	2	2	2	0	0	0	0	0
Obsessions	2	2	2	1	0	0	0	0
Depressed	3	2	2	0	0	0	0	0
Anxious	2	2	1	0	0	0	1	0
Overall severity	20	17	13	1	0	0	3	0

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	2	1	1	1
tremor	1	0	0	0	0
ataxia	1	1	2	1	1
sweating	2	2	2	1	1
constipation	0	0	0	0	0
faints/dizziness	1	2	2	0	0
micturition difficulty	0	0	0	0	0
blurred vision	1	0	1	1	0
Other	0	bubbling in arms 1	0	0	0
Total	8	8	8	4	4

NAME	AGE	ACETYLATOR STATUS
Mrs. M.M.(1)	25	Fast

OCCUPATION

Housewife

PRESENTING COMPLAINT

The patient complained of feeling "ill, tired and terribly low-spirited".

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms had developed 18 months previously when she went to Peru. Her husband had obtained a position as an accountant there and they went to Lima immediately after their marriage. The patient was lonely, missed her family and was distressed by the social conditions. She began to feel depressed. She cried constantly, was afraid all the time and felt useless. She attempted suicide and returned to Scotland where she had inpatient psychiatric care and was treated with diazepam and barbiturates. Her symptoms did not really improved but she returned to South America. Once there she deteriorated further and after a few months came back to Scotland, on this occasion remaining for several months. Her symptoms still failed to improve but she returned to Lima. She continued to be depressed and her husband decided that they would require to return to Scotland permanently. They did so and she attended the clinic shortly afterwards. When she presented she stated that despite feeling tired all the time she slept fairly well. Her appetite was poor and she had lost a stone in weight over 18 months. She was very easily irritated and rather intolerant. Her concentration was much impaired to such an extent that she could not read, knit or do housework. She felt depressed and her view of the future was despondent, although she denied suicidal ideas. She felt that she was a burden to her husband and that she

had destroyed his career prospects. She had a lifelong tendency to worry to excess but felt that this had become much worse. She felt very anxious if left alone in the house but this too was a lifelong tendency. She described clear-cut episodes of depersonalisation which had occurred 3-4 times per week over about the past year.

PAST PSYCHIATRIC HISTORY

None before this eighteen-month episode but she had seen a psychiatrist in Lima and had attended two other clinics in Scotland when she had come back temporarily.

PAST MEDICAL HISTORY

Intermittent low back pain of unknown aetiology.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

The patient was the child of rather elderly parents and had one brother 10 years older than herself. Her father was a clerk. She was described as highly-strung and nervous as a child. She was afraid of the dark and her fear of being left in the house alone extended back into childhood. She attended a Senior Secondary school but did not do particularly well and left at 15 to train as a shorthand typist. She thereafter worked in one office until she was married at the age of 23 to a chartered accountant one year older than herself. The patient's parents were enthusiastic about this marriage, feeling that their daughter was improving her social position, but it did appear that the patient had always had some doubt about it and shared few of her husband's cultural and intellectual interests. The sexual side of their marriage had never been successful but as neither partner had much interest in these matters this was not a great cause for dissension. They did quarrel over the patient's wish for children. Her husband did not share this wish and had doubts about whether they should ever have a family. The patient had always been timid, anxious and dependent on her mother.

Her main interests were in reading, sewing, knitting and the care of her personal appearance. She was a pretty woman and apparently when well spent much time upon her appearance but had neglected this since the beginning of her illness.

DRUGS PRIOR TO ATTENDANCE

In the eighteen months before attending the patient had had various tricyclic antidepressants and minor tranquillisers, all without beneficial effect. When she attended she was having "Doxepin" 25 mg. t.i.d., diazepam 5 mg. q.i.d. and amylobarbitone 200 mg. nocte.

She smoked 10 cigarettes per day and had the occasional social drink.

AT INTERVIEW

She presented as anxious and depressed. Her behaviour had an undoubted histrionic quality but she did demonstrate a consistently depressed mood. Otherwise her mental state was normal.

Physically she appeared entirely well.

At the end of her course of treatment she developed dysuria and urinary retention. She was found to have a urinary tract infection which was slow to respond to appropriate medication. An intravenous pyelogram revealed a congenital abnormality of the renal tract.

During the course of phenelzine she had nitrazepam 10 mg. nocte.

At the time of the initial assessment her score on the neurotic/endogenous rating was (4).

On the 21st day of the course of phenelzine the dosage was halved to 45 mg./day because of side effects.

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	1	1	1	0	0	0
Anxiety	3	2	1	1	1	1	0	0
Phobias	1	1	1	1	1	1	0	1
Obsessions	1	1	1	1	1	1	0	0
Depressed	3	3	1	1	1	1	0	0
Anxious	3	2	1	1	1	1	0	0
Overall severity	20	17	8	8	8	7	0	1

During the two-month follow-up the patient had minimal doses of minor tranquillisers and it was not thought that her improvement was due to medication.

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	1	1	2	1	1
tremor	1	0	1	1	1
ataxia	1	1	1	2	2
sweating	2	1	0	0	0
constipation	0	0	0	0	1
faints/dizziness	0	1	1	2	1
micturition difficulty	0	0	0	2	1
blurred vision	0	1	1	0	0
Other	0	clenching of teeth pulsating in neck 1_1	clenching of teeth pulsating in neck 1_1	0	0
Total	5	7	8	8	7

NAME	AGE	ACETYLATOR STATUS
Miss J. McQ.	45	Slow

OCCUPATION

Secretary

PRESENTING COMPLAINT

The patient had not been well for 4½ years. She complained of feeling low-spirited and tired. She was restless, could not concentrate, slept poorly and her appetite was poor. She was preoccupied by a multiplicity of vague somatic complaints which she believed were an indication that she had a serious physical disease.

HISTORY OF PRESENTING COMPLAINT

The patient had always been of an anxious disposition. She was described by her general practitioner as always having had a dependent and rather histrionic personality. She had however coped satisfactorily with life and had no complaints, either somatic or psychiatric, until 4½ years before she presented at the clinic. Two years before her presentation her mother had had a myocardial infarction and one year later she died. The patient's symptoms worsened considerably after these events but they were undoubtedly present at an earlier date. At the time of her presentation she was totally preoccupied with the idea that she was likely to have an incurable disease. She complained of a multiplicity of vague somatic symptoms. She was constantly tired and slept only with hypnotics. She was irritable with others but this was principally because she felt that they did not realise how seriously ill she was. Her concentration had become so poor that she could not work, read, sew or watch television. She felt very low-spirited and felt hopeless about the future but had no thoughts of suicide. She felt anxious and worried all the time.

Her anxieties mainly concerned her health but she also worried about trivia to a needless degree. She had become unable to go out alone because she feared that she would become seriously ill outside. Her appetite was poor but she had not lost weight.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was the only child of her parents. Her father died when she was three years of age. She was brought up by her mother and indulgent aunts. She led a somewhat sheltered life and was inclined to be much in the company of her mother. She had no neurotic traits in childhood. She had a successful career at Senior Secondary school which she left at 17 years of age. After one year's secretarial training she obtained a post as a secretary and had worked in this capacity until she became unwell. Her work record was good - she had held several responsible secretarial positions for a number of years. When she presented she had been off work for 10 months because of her symptoms. She had never married. Although much of her social life was confined to her family circle she did have numerous friends. Her principal outside interest was amateur dramatics.

DRUGS PRIOR TO ATTENDANCE

In the ten months prior to attending the patient had had

Phenelzine 15 mg. b.d. for 10 days only - stopped this of her own accord as she was frightened by the dietary restrictions.

Amitriptyline 25 mg. q.i.d. for months.

Chlordiazepoxide 10 mg. q.i.d. intermittently.

When she attended she was having Diazepam 5 mg. t.i.d. and Mandrax 2 tabs. nocte.

She smoked 40 cigarettes per day and drank alcohol only on rare social occasions.

AT INTERVIEW

The patient appeared extremely depressed. She wept a good deal and was entirely preoccupied with hypochondriacal fears and ideas of self-blame. She was extremely agitated, wringing her hands ceaselessly and constantly seeking reassurance. There was no other abnormality in her mental state.

Physically she was entirely well.

During her course of phenelzine she also took nitrazepam 10 mg. nocte as she was most reluctant to be without hypnotics having taken them for years. She had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (3).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	3	2	0	0	0	0
Anxiety	4	4	3	2	1	1	1	1
Phobias	2	2	2	2	1	1	0	0
Obsessions	0	0	0	0	0	0	0	0
Depressed	3	3	3	2	0	0	0	0
Anxious	4	4	3	2	0	0	0	0
Overall severity	23	23	20	14	2	2	1	1

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	0	0	0	0	0
tremor	1	0	0	1	0
ataxia	1	1	1	1	1
sweating	0	0	0	2	2
constipation	2	2	2	2	2
faints/dizziness	1	1	1	2	0
micturition difficulty	2	2	2	1	1
blurred vision	2	2	2	2	1
Other	0	0	0	0	0
Total	9	8	8	11	7

NAME	AGE	ACETYLATOR STATUS
Mrs. A. McG.	49	Slow

OCCUPATION

Domestic

PRESENTING COMPLAINT

The patient stated that she had been ill for four years but had been much worse in the eight weeks prior to her presentation. For four years she had lacked confidence and interest and had felt sad, nervous and tremulous all the time. For the last weight weeks she had been weeping all the time.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms originally developed in 1970 after her discovery that her mother was suffering from malignant disease. She had never felt really well since then but in the intervening period had nursed her mother at home until her death and had then had grave cause for concern over her daughter who was discovered, at the age of 21, to have malignant hypertension which caused her to have a termination of pregnancy on medical grounds. There was no apparent precipitant for the patient's sudden deterioration eight weeks before her presentation. On systematic questioning it was found that in addition to her spontaneous complaints she felt very tired and apathetic, she was irritable and impatient with her children, she could not concentrate to knit or read, she felt despondent and hopeless about the future, she worried about trivia and had irrational fears about going out and about being left alone. She constantly feared that she might die and had the idea that she might have a cerebrovascular accident. She brooded a good deal about the termination of her daughter's pregnancy and felt that she should not have allowed this to take place. For eight weeks she had

not been able to go to work because of her symptoms although in the many years that she had worked she had been absent very rarely except at the time of her mother's fatal illness. Her appetite was unimpaired and she had not lost weight.

PAST PSYCHIATRIC HISTORY

Nine years previously developed a depressive illness after her father's death. She was treated as an inpatient for three weeks and given tricyclic antidepressants which produced a complete response.

PAST MEDICAL HISTORY

Pelvic floor repair
Surgery to varicose veins.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

The patient was born and brought up in Beith. She was the only child of a bootmaker. Her home life was happy and she had no neurotic traits. She had many friends at the Junior Secondary school which she attended until she was fourteen years of age. On leaving school she worked as a shop assistant until her marriage at 20 years of age. This marriage was never a success as her husband was a heavy drinker and chronically work-shy. After four years she divorced her husband for cruelty. The patient always worked outwith her home and at the time of her presentation had worked for many years in the Admiralty as a domestic. She had two children, a son aged 26, about whom she was concerned as he was courting a girl whom she regarded as unsuitable, and a daughter aged 23 who had severe malignant hypertension and was not expected to survive for many years. This girl had been engaged to be married at the time of her pregnancy and the

discovery of her severe hypertension. When it was found that she was so hypertensive and would require a therapeutic abortion, her fiance, who was responsible for her pregnancy, broke off the engagement. These events were very distressing to the patient and she had the idea that if she had resisted the idea of termination more strongly her daughter would have been married and might have had a child. The patient had no serious financial worries or other social problems. When well she was a very friendly, outgoing, competent person who had had no difficulties in bringing up her children singlehanded and who led a full social life.

DRUGS PRIOR TO ATTENDANCE

In the 3½ years before attending the patient had been treated with a variety of tricyclic antidepressants and minor tranquillisers by her general practitioner and none of these had produced any improvement. She was on diazepam 5 mg. q.i.d. when she attended.

She smoked 15 cigarettes per day and drank only on rare social occasions.

AT INTERVIEW

She was very tense, wringing a handkerchief between her hands constantly and she was also depressed. Otherwise her mental state was normal.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (4).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	1	0	0	0	0	0
Anxiety	3	3	0	0	0	0	0	0
Phobias	4	4	4	3	0	0	0	0
Obsessions	2	2	0	0	0	0	0	0
Depressed	2	2	1	0	0	0	0	0
Anxious	3	3	1	0	0	0	0	0
Overall severity	22	22	9	3	0	0	0	0

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	1	2	0	0	0
tremor	0	0	2	0	0
ataxia	0	2	0	1	0
sweating	0	1	2	1	0
constipation	0	0	0	2	1
faints/dizziness	0	1	1	0	0
micturition difficulty	0	1	0	1	1
blurred vision	0	1	0	0	0
Other	0	0	0	0	0
Total	1	8	5	5	2

NAME	AGE	ACETYLATOR STATUS
Mrs. M.M.(2)	39	Slow

OCCUPATION

Housewife

PRESENTING COMPLAINT

Patient complained that three months previously she had suddenly developed a feeling of "weepiness and nervousness".

HISTORY OF PRESENTING COMPLAINT

The patient could give no precipitant for her complaints. She had begun to feel tired all the time although her sleep was not disturbed. She had become irritable and "difficult to live with". She had begun to feel miserable and tearful for no reason. She had few guilty ideas, she did not feel hopeless about the future and she was not suicidal. She brooded a good deal about her own inadequacies. She felt constantly anxious. She worried ceaselessly about trivia and although she realised that this was ridiculous she could not control it. She had become incapable of travelling, feeling that she would collapse if she went on a bus or train and she could no longer do her shopping because she felt afraid in the street alone. These features were of eight weeks duration, i.e. they had arisen four weeks after the original depressive feelings. She had become indecisive even upon trivial matters such as family menus. Her appetite was good and she had not lost weight.

PAST PSYCHIATRIC HISTORY

NIL.

PAST MEDICAL HISTORY

NIL.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

NIL.

PERSONAL HISTORY

The patient was born and brought up in Glasgow. She has one brother three years older than herself. Her father, who had worked in an unskilled capacity in a gas works, had died 10 years before her presentation. Her mother was alive and well. She attended a Junior Secondary school where she mainly took domestic subjects. She was a happy child, free of neurotic traits. She left school at 15, working in a tobacco factory until her marriage at 23, to a man the same age as herself. The marriage was described as happy. The patient depended a great deal on the support of her husband in most matters but this arrangement appeared to suit them both. They had three children, aged 11, 9 and 3, none of whom gave any cause for anxiety. The patient's husband had worked as a lorry driver but two years prior to her presentation had obtained his own taxi cab. He was happier in this situation and the family was financially more comfortable than it had been in the past. The patient had for years been concerned about the fact that the family lived in a rather rough neighbourhood but with their increased affluence they had begun to have a prospect of moving away to a better district. The patient was described as normally being sociable, friendly and cheerful, if somewhat over anxious. She and her husband were active members of an orange lodge and participated freely in the varied social functions connected with that organisation. Since becoming ill she had cut herself off from all social activities.

DRUGS PRIOR TO ATTENDANCE

Diazepam 5 mg. q.i.d., Nitrazepam 10 mg. nocte, both for three months.

She smoked 10 cigarettes per day and drank alcohol only when at social functions.

AT INTERVIEW

She was restless, tense and tearful. She endeavoured

to conceal both her depressed mood and her tension but these became increasingly obvious as the interview progressed. Otherwise her mental state was normal.

At routine physical examination a small breast lump was found. The patient denied that she had ever noticed this and has always continued to maintain that she knew nothing of this lump until this examination. An immediate excision biopsy was arranged and she was found to have a benign fibroadenoma. Her symptoms and mental state were in no way changed by this. She was continued on diazepam only for one month after her return from the surgical ward but she did not improve at all and was then placed in the phenelzine trial.

During her course of phenelzine she continued to take nitrazepam 10 mg. nocte.

At the time of her initial assessment her score on the neurotic/endogenous rating was (3).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	2	2	1	0	0	0	0	0
Anxiety	3	3	1	0	0	0	0	0
Phobias	3	3	2	1	0	0	0	0
Obsessions	1	1	0	0	0	0	0	0
Depressed	2	2	1	0	0	0	0	0
Anxious	2	2	1	0	0	0	0	0
Overall severity	17	17	8	1	0	0	0	0

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	0	0	0	1	0
tremor	1	1	1	1	1
ataxia	0	1	1	0	1
sweating	0	1	0	0	0
constipation	0	0	1	1	0
faints/dizziness	1	0	0	0	0
micturition difficulty	0	0	0	0	0
blurred vision	0	0	0	1	0
Other	0	0	0	0	0
Total	2	3	3	4	2

NAME	AGE	ACETYLATOR STATUS.
Mrs. M.F.	25	Slow

OCCUPATION

Housewife

PRESENTING COMPLAINT

The patient complained of a "sick, miserable feeling". She constantly felt as if something terrible was going to happen and also complained of a numbness at the back of her head and in her eyes.

HISTORY OF PRESENTING COMPLAINT

The patient had had a spontaneous abortion in November, 1973. This had been a disappointment to her but she had coped reasonably with this. Her neighbour had been confined in March, 1973, at the time of the patient's own expected date of delivery, and her symptoms dated from then. She was preoccupied with the idea that the feeling in her head might indicate that she had cancer. She felt tired all the time and for the four months since her neighbour's confinement she had been unable to do her housework. She was sleeping very poorly, having both early and late insomnia. Her concentration had declined and she was not able to attend to books, knitting, etc. She felt low-spirited most of the time and was worse if she saw a baby or if anyone made reference to infants. She wept uncontrollably every day. Although she felt lacking in hope for the future she had no suicidal thoughts. She had always been a tense, anxious person but she had begun to worry much more than usual. She had become preoccupied with a fear, which she recognised as irrational, that some harm would come to her husband if he was not with her and she had begun to telephone him at work to make sure that he was alright. She was afraid of being in the house alone and always arranged to have relatives or friends in when her husband

was out. She was able to go out shopping but felt apprehensive on public transport. She thought a good deal about her spontaneous abortion and went over and over the unpleasant details of it. She could not put these thoughts from her mind. Her appetite was unimpaired and she had not lost weight.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Both her mother and one sister had at times attended their general practitioner because of anxiety symptoms and another sister had been treated for depression by her general practitioner following a miscarriage.

PERSONAL HISTORY

The patient was born and brought up in Glasgow, the second of four children of a housepainter. She was regarded by her family as being shy and nervous from early childhood. The home life was happy. She attended Senior Secondary school and although she was doing quite well she left at 15, without obtaining a leaving certificate. She obtained a job as a wages clerkess and worked for three years with the same firm until her marriage at the age of 18 to a motor mechanic, two years older than herself. The marriage was happy and successful. They had two children, a daughter aged 5 and a son aged 4. Both the patient and her husband liked children and wanted to have a large family. She had been very disappointed about having the spontaneous abortion at 22 weeks in November, 1973. They had no financial difficulties and no real domestic problems. As a young girl the

patient had been anxious and shy but she had become socially more confident in adult life, and when well enjoyed a variety of leisure pursuits.

DRUGS PRIOR TO ATTENDANCE

Imipramine 25 mg. q.i.d. for 3 weeks - without effect.

Nitrazepam 10 mg. nocte since November, 1973.

She smoked 10 cigarettes per day and did not drink.

AT INTERVIEW

She was tearful, anxious and importunate. Her tension was obvious and her depression appeared marked with indecision and self-depreciatory ideas being prominent features. Otherwise her mental state was normal.

Physically she was entirely well.

During her course of phenelzine she continued to take nitrazepam 10 mg. nocte.

At the time of the initial assessment her score on the neurotic/endogenous rating was (1).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	0	0	0	0	0	0
Anxiety	3	3	0	0	0	0	0	1
Phobias	2	2	1	0	0	1	1	1
Obsessions	1	1	0	0	0	0	0	0
Depressed	3	3	0	0	0	0	0	0
Anxious	3	3	0	0	0	0	0	1
Overall severity	21	21	1	0	0	1	1	4

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	0	0	0	0
tremor	1	0	0	0	0
ataxia	0	0	0	1	0
sweating	2	0	0	0	0
constipation	2	2	0	1	1
faints/dizziness	1	1	0	0	0
micturition difficulty	1	0	0	0	0
blurred vision	0	0	0	0	0
Other	0	0	0	0	0
Total	9	3	0	2	1

Days 5-8 and 15-18 substituted for Days 3 and 13 for tryptamine assessment.

NAME	AGE	ACETYLATOR STATUS
Mrs. H. McD.	48	Slow

OCCUPATION

Housewife.

PRESENTING COMPLAINT

The patient stated that she felt depressed, irritable, nervy and jumpy. She felt that she would be greatly helped if she could cry but that she could not.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms arose after the death of her first husband four years before this attendance. Her husband had died of carcinoma of the kidney in 1970, after a year's painful illness during which the patient nursed him at home. After this she had felt "numb and empty" for two years. She then ceased to be devoid of feeling and felt profoundly depressed but could not cry. She brooded about her husband's death and about ways in which she had failed to help him. She felt tired and listless and had no interest in anything. Her sleep was poor and for the past four years she had never slept for more than 4-5 hours. She was irritable and quarrelsome. Her concentration had failed and she had given up her life-long interest of dressmaking. She felt that she was worrying all the time about trivia and about other people's worries. She stated that she had less real cause for worry than she had ever had and yet her mind could not be at peace. She had always had mild obsessional tendencies but these had become worse. She checked doors and gas taps three times and had to get dressed, do the housework, etc. in a set order of steps. If this was broken she had to go back to the beginning. Although these features were undoubtedly present they did not limit her life to any extent. She had given up work eight weeks previously because of her symptoms. Her appetite was maintained and she had not

lost weight.

PAST PSYCHIATRIC HISTORY

Patient had attended hospital and had inpatient treatment in 1972. This was of no lasting benefit to her. Before her husband's death she had no psychiatric symptoms.

PAST MEDICAL HISTORY

Many years previously one of her ears was injured in a road traffic accident and she had since been deaf.

When she was 18 she had pulmonary tuberculosis.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

None.

PERSONAL HISTORY

The patient was born and brought up in Glasgow. Her father was a plater in a shipyard. The patient was the sixth of seven children of whom three died in early adult life from tuberculosis. Her childhood was happy. She attended a Junior Secondary school and left at 14. She then became a clerkess and worked at this until her marriage, aged 23, to a shipwright, 2 years her senior. Their marriage was happy. Throughout her marriage she worked in a biscuit factory. They had no children. Her husband died of carcinoma of the kidney in 1970. The patient had known of the diagnosis for a year previously but kept it from her husband whom she nursed at home. Her symptoms dated from his death. She felt lonely and isolated as her social life had really depended on her husband. She could not take her mind off his death and blamed herself for her shortcomings. She remarried in December, 1973 and her depression had become worse two months before this. She continued to deteriorate after her remarriage although she was greatly attached to her second husband and had no cause for unhappiness. All her life she had found social

situations a strain. She was quiet, reserved and always to some extent obsessional.

DRUGS PRIOR TO ATTENDANCE

She had had various minor tranquillisers and tricyclic antidepressants over the four years of her illness, all without lasting benefit. When she was assessed for the study she was on no drugs.

She did not smoke and drank only very rarely.

AT INTERVIEW

She was obviously very tense, clenching and unclenching her hands and arranging articles along the table in front of her. Her deafness was quite severe but she could co-operate with the interview situation. She appeared depressed to a marked degree although she seemed to be attempting to minimise this. Otherwise her mental state was normal.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of her initial assessment her score on the neurotic/endogenous rating was (1).

MODIFIED GOLDBERG SCORE

	0 Not assessed before hospitalisation	0	1	2	3	3½	3½ + 4	3½ + 8
Depression		3	0	0	0	0	0	0
Anxiety		3	0	0	0	0	0	0
Phobias		0	0	0	0	0	0	0
Obsessions		2	1	1	0	0	0	0
Depressed		3	1	0	0	0	0	0
Anxious		3	1	0	0	0	0	0
Overall severity		20	5	1	0	0	0	0

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	0	0	0	0
tremor	0	0	0	0	0
ataxia	1	1	0	0	0
sweating	0	0	0	0	0
constipation	2	2	2	2	2
faints/dizziness	1	0	0	0	0
micturition difficulty	0	0	0	0	0
blurred vision	0	0	0	0	0
Other	0	0	0	0	0
Total	6	3	2	2	2

NAME	AGE	ACETYLATOR STATUS
Mrs. A. McI.	36	Slow

OCCUPATION

Clerkess

PRESENTING COMPLAINT

The patient complained that for 3-4 months she had felt that she was not doing anything properly. She had lost interest in everything, felt despondent about the future and was afraid to go out.

HISTORY OF PRESENTING COMPLAINT

The exact time of onset of the patient's symptoms was not clear as they developed gradually and were superimposed upon a chronically mildly anxious personality and a long-standing feeling of guilt about being divorced although a Catholic. Over the three months prior to her attendance her symptoms had become increasingly severe and had come to limit her activities to a serious extent. She felt tired all the time and her sleep had become poor. Her insomnia was early. Her concentration had become very poor so that she could not even concentrate on short articles in magazines. She felt sad most of the time and this depression appeared to be connected with thinking about her own inadequacies. She wept a good deal about this and at times felt hopeless about the future, although she had no suicidal thoughts. She worried a good deal principally about the health of her aging father and about the state of her marriage, but she did not feel that she was any more anxious about these matters than she would normally have been. She had developed a fear that she would collapse on public transport or in shops. This was of only six weeks duration at the time of her presentation, although her other symptoms had been present for longer. Previously shopping in large stores had been one of her main interests. She had become extremely indecisive about trivial as well as

major issues. Her appetite remained good and she had not lost weight. Her symptoms had developed shortly after she had discovered that her husband, who had lived abroad all their married life apart from a few short holidays, would be returning to live in Scotland permanently. Although she stated she was pleased about this certainly she had considerable ambivalence towards her husband and had no wish to have children or be a housewife.

PAST PSYCHIATRIC HISTORY

None.

PAST MEDICAL HISTORY.

Tuberculosis in childhood.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

None.

PERSONAL HISTORY

The patient was born in Glasgow but during most of her childhood lived with her grandparents in Ayr because of the War. She was an only child. Her father was a toolmaker. Her mother died of cirrhosis of the liver (non-alcoholic) when the patient was 18. The patient was a happy child, free of neurotic traits. She had a successful school career and hoped to train as a teacher but had to leave school at fifteen years of age because of her mother's failing health. On leaving school she worked for three years as a sales assistant, then taking up clerical work at which she had since successfully been employed. She was married for the first time at 20 but the marriage lasted only ten months, failing, by the patient's account, because of her husband's untruthfulness and chronic unemployment. She divorced him for desertion but always felt guilty about this as it was against her principles as a Catholic and meant that she was denied Communion. At

33 years of age she remarried her husband being a joiner, two years older than herself, who had not previously been married. During the marriage he had mainly worked abroad and the patient had therefore continued to live with her father. This arrangement was said to be agreeable to all three parties. There were no children of either marriage and the patient was not sure that she wanted any. She had always been "a bit of a worrier" but was normally an effective worker and a cheerful, energetic and sociable person.

DRUGS PRIOR TO ATTENDANCE

Amitriptyline 25 mg. t.i.d and 50 mg. nocte for six weeks until two weeks before her presentation - this had no effect. Nitrazepam 10 mg. nocte for five months.

She smoked 30 cigarettes per day and drank on social occasions.

AT INTERVIEW

The patient appeared definitely retarded. All of her responses were slow and she had little spontaneous conversation. She was depressed and tense. There were no other abnormalities in her mental state.

Physically she was entirely well.

During her course of phenelzine she continued to take nitrazepam 10 mg. nocte as she was reluctant to do without it.

At the time of her initial assessment her score on the neurotic/endogenous rating was (4).

On the 21st day of the course of phenelzine the dosage was halved to 45 mg/day because of side effects.

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression		3	2	1	1	1	1	1
Anxiety		2	1	0	0	0	0	0
Phobias		3	2	2	1	1	0	1
Obsessions		2	1	0	0	0	0	0
Depressed		3	2	1	1	1	1	1
Anxious		3	1	1	0	0	0	0
Overall severity		22	12	7	4	4	3	4

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	1	0	1	2
tremor	1	1	0	1	1
ataxia	0	1	1	1	0
sweating	1	0	0	0	1
constipation	0	0	0	0	0
faints/dizziness	0	1	1	1	1
micturition difficulty	0	0	0	1	0
blurred vision	1	0	0	1	1
Other	0	0	0	0	0
Total	5	4	2	6	6

NAME	AGE	ACETYLATOR STATUS
Mrs. M.D.	27	Slow

OCCUPATION

Housewife

PRESENTING COMPLAINT

This patient presented with a five month history of loss of interest, inability to cope with her domestic commitments, loss of confidence, fear of going out, fear of being left alone in the house, and a constant "sad empty feeling".

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms clearly dated from her removal from her home in the slums of central Glasgow to a house in a Local Authority housing scheme on the periphery. She had enjoyed the communal life of the city and found her new environment foreign and lonely. Relatives had come from Ireland to stay with her as it was felt by the family that company would help her but this had been of no avail and latterly she had drawn away from any company. In addition to her spontaneous complaints, on direct questioning she admitted that she brooded about the possibility that she might have malignant disease, that she felt tired all the time for no reason, that her sleep was fitful, that she was unreasonably irritable with her husband and children, that she could not concentrate on cooking, housework or knitting and that her feeling of depression was profound. She felt she she would be helped if she could cry but she could not. She felt that the future was hopeless. She felt that she had brought her illness upon herself by her own inadequacies. She was not contemplating suicide as such an act would be totally against her religious principles. She felt constantly anxious. She was mainly worried about money. Although the family was poor they were in no greater financial difficulties

than they had ever been and she had not previously been concerned about money. She had become afraid of being alone in the house, and of going out. She had always been a little apprehensive of being in large crowded stores but she had lately become unable to go into a small local shop. She described feeling detached from the rest of the world saying "I feel as if I am away on my own and that no-one else is there". This was a fleeting experience which she found distressing. Her appetite was not really impaired and she had lost no weight.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil.

PERSONAL HISTORY

This patient was born and brought up in an impoverished area of central Glasgow. She was the eldest child of an unemployed labourer of Irish extraction. She attended a Catholic Senior Secondary school and did well but because of the family circumstances left at 15 years of age and obtained work as a wages clerkess. As a child she was always regarded as being over anxious. She became panic stricken at examinations at school and had always been afraid to go in lifts. She was employed by one firm for six years until her marriage at the age of 21 to an Irish labourer. She had two daughters, aged 5 and 4. Although always of a somewhat anxious disposition, before she became unwell she was a competent housewife and mother and was described as being very cheerful and sociable. She and her husband normally went out a good deal to dances and socials connected

with the local R.C. Church and Irish Societies. Since the onset of her symptoms she had abandoned all of these activities.

DRUGS PRIOR TO ATTENDANCE

None.

The patient did not smoke or drink at all.

AT INTERVIEW

She was obviously markedly depressed and she was definitely retarded. Her anxiety was not marked. There was no other abnormality in her mental state.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of her initial assessment her score on the neurotic/endogenous rating was (4).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	4	4	4	1	0	0	0	0
Anxiety	3	3	3	1	0	0	0	0
Phobias	4	4	4	2	0	0	0	0
Obsessions	0	0	0	0	0	0	0	0
Depressed	3	3	3	1	0	0	0	0
Anxious	1	2	2	0	0	0	0	0
Overall severity	19	21	21	6	0	0	0	0

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	2	0	0	0
tremor	0	0	0	0	0
ataxia	0	0	0	1	0
sweating	0	0	0	0	0
constipation	0	0	2	2	0
faints/dizziness	0	0	0	1	0
micturition difficulty	0	0	0	0	0
blurred vision	0	0	0	0	0
Other	0	0	0	0	0
Total	2	2	2	4	0

NAME	AGE	ACETYLATOR STATUS
Mr. P.F.	55	Slow

OCCUPATION

Storeman

PRESENTING COMPLAINT

Patient complained of nervousness, tension, poor concentration and a feeling of inadequacy in all respects. He felt as if he might weep and frequently did.

HISTORY OF PRESENTING COMPLAINT

The patient initially described the above complaints as being of two months duration but they had been present to a lesser extent for some months prior to that. He became unwell in the setting of occupational difficulty. He had been employed for years in the business of a relative of his wife. This man had suffered a cerebrovascular accident and the business was being placed in his son's hands. The patient feared (correctly as later became evident) that the son would not continue to employ him. On questioning Mr. F stated that he was suffering from increasingly severe headaches and feared that these might indicate serious illness. He felt tired much of the time although he slept quite well. He was becoming increasingly irritable at home and had lost interest in his former leisure pursuits. He felt low-spirited and wanted to get away from people although he did not have any wish to die. He was worried all the time about his job and about his son who was in financial difficulty. He had always been inclined to worry to excess. He had felt so lacking in self-confidence that he had given up driving his car and he had begun to check his work to an undue extent. His appetite was poor and he had lost 1 stone in two months.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY

Nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Nil apart from wife.

PERSONAL HISTORY

The patient was born and brought up in Glasgow. His father worked in the shipyards and died in a drowning accident when the patient was 18 months old. The patient had two older sisters and one younger brother. His mother worked throughout his childhood in a variety of unskilled occupations. He was an average pupil at school, leaving at 14. He was apprenticed as an electrical engineer and during the War served in R.E.M.Y. After the War he worked in a variety of jobs, being 17 years with Beardmores until he was declared redundant. He then became employed as a storeman in the business of a relative of his wife, and at the time of his presentation this job was in jeopardy. He was married at the end of the War and had two children, both now married. Neither the patient nor his wife approved of the spouses of either of their children. Their own marriage was reasonably happy although Mrs. F. was something of a chronic gynaecological invalid and had had continuous psychiatric care for 12 years following the birth of her second child. This was said to be a neurotic illness. The patient was described as always being anxious, inclined to be indecisive and to have difficulty in asserting himself. He and his wife had tended to adopt the mannerisms and lifestyle of persons of higher socio-economic status than themselves. They had few friends and what social life they had was among relatives, principally those of Mrs. F.

DRUGS PRIOR TO ATTENDANCE

"Ponstan" 2 caps/day for headache.
Diazepam 2 mg. b.d.

He smoked 30 cigarettes per day and drank only at occasions such as weddings and New Year.

AT INTERVIEW

The patient was very tense and smoked incessantly. At times he wept and he appeared significantly depressed. There was no other abnormality in his mental state.

Physically he was entirely well.

During his course of phenelzine he had no other drugs.

At the time of the initial assessment his score on the neurotic/endogenous rating was (4).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	2	2	1	1	1	1	1	2
Anxiety	3	3	2	2	0	0	0	0
Phobias	2	1	1	1	0	1	0	0
Obsessions	2	2	2	2	0	0	0	0
Depressed	2	3	2	2	1	1	1	2
Anxious	3	3	2	2	1	1	2	2
Overall severity	19	20	14	14	5	6	7	10

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	1	1	1	1
tremor	1	1	1	1	1
ataxia	0	0	1	1	0
sweating	2	1	0	0	0
constipation	0	0	1	1	1
faints/dizziness	1	1	0	1	0
micturition difficulty	0	0	0	0	0
blurred vision	2	0	0	0	0
Other	2	2	2	1	0
Total	10	6	6	6	3

NAME	AGE.	ACETYLATOR STATUS
Mrs. C.G.	53	Slow

OCCUPATION

Housewife.

PRESENTING COMPLAINT

The patient complained of depression, panic attacks, poor concentration and poor sleep.

HISTORY OF PRESENTING COMPLAINT

The patient had always regarded herself as highly-strung but had coped well with life until four years previously. Her symptoms then began to develop and appeared to be precipitated by her younger daughter's departure from the parental home on marriage. In addition to her spontaneous complaints, on direct questioning she admitted that she worried about her health and feared that she might have malignant disease. She slept poorly, her insomnia being mainly early, was irritable and quarrelsome with her husband about nothing. She concentrated poorly and had ceased to watch television, knit or sew. She complained of being depressed but her mood was by no means always depressed, fluctuating a good deal, and for brief periods she could be reasonably cheerful. She did not feel hopeless about the future and certainly was not suicidal. She thought a good deal about her own inadequacies and past failures. She stated that she was never free from worry although had no real reason for anxiety. She had become afraid to be in the house alone, afraid to go out alone and afraid to travel by car. She had become hopelessly indecisive, so much so, that she could spend hours deciding what to wear or what to make for a meal. Her appetite was not impaired and she had not lost weight.

PAST PSYCHIATRIC HISTORY

27 years previously, when puerperal, she had been treated with E.C.T. as an outpatient. This had not helped her and she had defaulted from attendance.

PAST MEDICAL HISTORY

Repeated minor chest infections over many years. Hysterectomy six years ago for menorrhagia.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

None.

PERSONAL HISTORY

The patient was born and brought up in Glasgow. She was the sixth of nine children of whom five still survive. Her father had his own business and although he was a heavy drinker maintained a very comfortable home for the family during the patient's childhood. She attended a Senior Secondary school and did reasonably well but had to leave at 14 when her father went bankrupt. She obtained a job in a biscuit factory where she worked until her marriage at the age of 20 to a man her own age. The marriage had never been particularly happy. Her husband drank fairly heavily and had little sympathy with his wife's desire to improve their social position or her worries about her health. He worked for the Corporation Housing Department. There were two daughters of the marriage, aged 31 and 27. The elder lived in England and the younger in Ayrshire. The younger girl had a child, aged 2, and the patient was distressed by the fact that she felt that her son-in-law did not really welcome her in his home. They had no financial worries and, although the patient would have preferred to own her home, she had no real complaints about the rented house in which they lived. She had always been an anxious woman and had never made friends easily, largely because she was much concerned with social distinctions

and did not really wish to mix with her neighbours or others with whom she had much contact. She had normally coped well however and had led an active life, taking a great interest in her personal appearance and in the decoration of her home. She had ceased these activities when she presented at the clinic.

DRUGS PRIOR TO ATTENDANCE

Glutethimide ("Doriden") 750 mg. nocte for years.

Diazepam 5 mg. t.i.d. for one year.

Amitriptyline 25 mg. t.i.d. three months before attending.

She had no benefit from these treatments.

The patient neither smoked nor drank.

AT INTERVIEW

She was obviously very tense and her depression, although present, was a less marked feature. Her manner was rather histrionic. Otherwise her mental state was normal.

Physically she was entirely well.

During her course of phenelzine she also had nitrazepam 10 mg. nocte.

At the time of the initial assessment her score on the neurotic/endogenous rating was (2).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	2	3	2	0	0	1	0	0
Anxiety	4	4	1	1	0	1	0	0
Phobias	2	3	2	2	2	2	0	0
Obsessions	2	2	1	1	0	0	0	0
Depressed	2	2	1	0	0	0	0	0
Anxious	3	3	1	1	0	1	0	0
Overall severity	21	22	10	6	2	6	0	0

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	0	2	2	1
tremor	1	0	0	0	0
ataxia	0	0	1	0	1
sweating	2	0	0	0	0
constipation	1	2	2	2	2
faints/dizziness	0	0	0	0	1
micturition difficulty	0	0	0	0	1
blurred vision	0	1	1	1	1
Other	0	0	0	0	0
Total	6	3	6	5	7

Days 2 and 12 substituted for Days 3 and 13 for tryptamine assessment.

NAME	AGE	ACETYLATOR STATUS
Mrs. E.B.	39	Slow

OCCUPATION

Housewife

PRESENTING COMPLAINT

The patient complained that she felt miserable, tired and ill and that she could not sleep. She thought that these feelings were secondary to a "burning, gnawing discomfort" which she had in her face.

HISTORY OF PRESENTING COMPLAINT

This lady's symptoms had been present for about two years. She was not a clear historian but it appeared that during this period she had had a multiplicity of somatic symptoms, all of which had been investigated at some length without any organic cause being demonstrated. Associated with these somatic complaints had been constant irritability, despondency, loss of interest and anxiety. Her sleep was very poor in that on average she thought that she slept for 4 hours per night. Her concentration was failing and she had no interest in any of her former pursuits. Her depressed mood was constant and nothing made her happy. She wept a good deal most days but she did add that she had always been inclined to weep easily. She did not feel at all hopeful that things would improve but she had no suicidal ideas. Although she said that she worried a good deal she was by no means constantly anxious. It appeared that she was no more worried than was usual for her. Her appetite was good and she had not lost weight.

PAST PSYCHIATRIC HISTORY

Until two years before she attended the patient had never had any form of psychiatric treatment but during

this period she had attended several clinics and had been treated with various minor tranquillisers and tricyclic antidepressants without benefit.

PAST MEDICAL HISTORY

No serious illnesses and no operations but she apparently had a long-standing tendency to complain about minor somatic symptoms.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

Patient's mother had had a course of E.C.T. as an inpatient.

Her sister had had depressive illnesses for which she had had inpatient treatment but was given drug therapy only.

PERSONAL HISTORY

The patient was born and brought up in Kilbirnie, the fourth of six children of a steel worker. She enjoyed a happy home life as a child. She attended a Junior Secondary School where she took a non-academic course. Even at this level she did not do well. She left school at 15 and worked in a fish net factory until her marriage at 19, to a man of the same age. She did not want to marry her husband but was persuaded by her parents to do so because she was pregnant. Nonetheless their married life had since been reasonably happy. There are 3 sons of the marriage, aged 18, 15 and 7. All of them were well and gave their parents no particular cause for concern. The patient's husband was employed by the Admiralty in laboratory work connected with munitions. This had caused the family to have to move about a good deal but this had pleased the patient rather than the reverse. Her symptoms had started when they were living in Gibraltar and had persisted since their return. They were happy in Gibraltar and no precipitant could be

detected. The patient described herself as always being anxious and inclined to worry excessively. She appeared always to have been over-concerned about her own health and that of her family.

DRUGS PRIOR TO ATTENDANCE

In the two years of her illness Mrs. B had had a wide variety of minor tranquillisers and tricyclic antidepressants. When she attended the clinic she was having

Doxepin 25 mg. t.i.d.
Diazepam 5 mg. t.i.d.
Chlorpromazine 25 mg. nocte.

She smoked 20 cigarettes per day and drank occasionally.

AT INTERVIEW

She appeared significantly depressed. She was rather hostile and defensive. Anxiety was not a marked feature. Otherwise her mental state was normal.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (3).

During this lady's course of treatment her father died unexpectedly.

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	1	1	0	0	0	
Anxiety	1	1	1	1	1	1	1	
Phobias	0	0	0	0	0	0	0	
Obsessions	0	0	0	0	0	0	0	
Depressed	3	3	1	1	0	0	0	
Anxious	1	1	1	1	1	1	1	
Overall severity	12	12	6	6	3	3	3	

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	1	0	1	1
tremor	1	0	0	0	0
ataxia	0	1	1	1	0
sweating	2	0	2	1	1
constipation	1	0	1	0	0
faints/dizziness	1	1	1	2	0
micturition difficulty	0	0	1	1	0
blurred vision	0	1	1	1	0
Other	0	buzzing in ears 1	0	0	0
Total	7	5	6	7	2

Days 2 and 12 substituted for Days 3 and 13 for tryptamine assessment.

NAME	AGE	ACETYLATOR STATUS
Mrs. A. O'H.	29	Slow

OCCUPATION

Housewife

PRESENTING COMPLAINT

Patient complained of weepiness, inability to cope, headaches and light-headedness. These symptoms had all been present to some extent for about one year but had been very much worse in the three months before her presentation. In this three-month period she had given up working outside her home and in the last month her mother had had to take over her housework.

HISTORY OF PRESENTING COMPLAINT

These features had developed gradually over about one year and had steadily worsened during this time, becoming incapacitating in the last three months. Eighteen months prior to her attendance the patient had had a hysterectomy for carcinoma of the cervix, discovered on routine screening. This appeared likely to have precipitated her condition but the patient denied that she was in any way concerned about the possibility of recurrence and indeed she denied having any fears about her health. She complained also that she was very easily tired but that she slept poorly. She was unreasonably irritable towards her family and quarrelled a good deal. Her concentration had become very poor, to such an extent that she could not do her shopping at all. She felt sad and wept very easily. She felt a failure in many ways and she felt afraid of the future, although she was not able to be definite about this. She did not have any suicidal ideas. She worried a good deal about trivia and constantly brooded about how she would cope if her mother died, although she realised that this was a ridiculous preoccupation, her mother being a robust woman in her fifties. She had

entirely ceased going out but stated that this was due to apathy rather than fear. Her appetite had become very poor and she had lost over a stone in weight in the past year. The patient had always been rather dependent upon her mother and her husband. Her stress tolerance had always been poor but prior to this episode any symptoms provoked by stress had been fleeting. She had normally numerous interests outwith her home but had neglected these in the past year.

PAST PSYCHIATRIC HISTORY

Six years previously the patient had poisoned herself impulsively following a quarrel with her husband. She had been admitted to a medical ward because of this but psychiatric advice was not sought.

PAST MEDICAL HISTORY

Hysterectomy in 1972.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

None.

PERSONAL HISTORY

The patient was born and brought up in Kilbirnie in Ayrshire. Her parents both worked in unskilled capacities. She had one younger brother. She was not regarded as being unduly nervous as a child and had no neurotic traits. She attended a Junior Secondary school. She enjoyed this although she was not academically successful and she left at 15, going to work in the dyeing department of a thread factory. She was employed there until her marriage at 18, to a man 12 years her senior. There were three children of the marriage - sons aged 11, 8 and a daughter of 5 years. The husband was employed in a semi-skilled capacity. They had no financial worries. The patient depended on her husband in most matters and the marriage was happy. She was closely involved in the activities

of various ladies' organisations. She had worked for brief periods during her married life between the births of her children. She went back to work in November, 1972 but had had to give up because of her symptoms in April, 1973.

DRUGS PRIOR TO ATTENDANCE

Chlordiazepoxide 10 mg. t.i.d.
Amitriptyline 20 mg. nocte
The patient smoked 10 cigarettes per day. She did not drink alcohol.

AT INTERVIEW

She was very tense, anxious and indecisive. She wept frequently, constantly sought reassurance and had no confidence in her ability to answer even the simplest question accurately. Her mental state was otherwise normal.

She was physically entirely well. Because of her history of recent surgery for malignancy she was extensively investigated for recurrence before inclusion in the study. No evidence of any abnormality was found and 15 months later she remained free of recurrence.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (2).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	2	2	2	1	0	0	0	0
Anxiety	2	2	2	2	1	1	1	0
Phobias	1	1	1	1	0	0	0	0
Obsessions	2	2	2	1	0	0	0	0
Depressed	2	3	2	1	0	0	0	0
Anxious	3	3	3	1	0	0	0	0
Overall severity	17	19	17	9	1	1	1	0

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	1	0	0	0
tremor	1	2	1	1	1
ataxia	1	2	2	1	0
sweating	0	1	2	2	1
constipation	0	2	2	2	0
faints/dizziness	0	1	1	1	0
micturition difficulty	0	1	1	0	0
blurred vision	1	1	1	1	0
Other	0	0	0	0	0
Total	5	11	10	8	2

NAME	AGE	ACETYLATOR STATUS
Mrs. C.M.	40	Slow

OCCUPATION

Driver

PRESENTING COMPLAINT

Patient complained of a loss of interest in all pursuits and a feeling of sadness. These symptoms had been present for six months. For three weeks prior to her attendance she had been unable to work.

HISTORY OF PRESENTING COMPLAINT

The patient's symptoms developed gradually following a road traffic accident which took place some six months before her attendance. No-one was injured in the accident which was the patient's fault. After it she very much lacked confidence in her driving abilities and this lack of confidence gradually became more generalised. She became more and more lacking in interest and became constantly sad. On direct questioning she admitted that she felt easily tired, and that she slept badly. Her insomnia was early and severe. She was quarrelling a good deal with her relatives but this was at least to some extent a habitual trait. Her concentration was extremely poor and she felt that she had become incapable of attending even to the simplest matter. This depression was severe and at times she thought about suicide. Her depression was not associated with self blame. She had always been an anxious person but in the six months prior to her attendance this tendency had become much more severe so that she was worried all the time. She had become very indecisive, principally because she lacked confidence in her ability to make any correct decisions. Her appetite had become poor and she had lost over a stone in weight.

PAST PSYCHIATRIC HISTORY

Occasional attendance at general practitioner for anxiety symptoms intermittently over 20 years. No previous episode of lasting depression. No previous hospital attendance.

PAST MEDICAL HISTORY

Oophorectomy several years ago for ovarian cyst. Otherwise nil.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS.

Nil.

PERSONAL HISTORY

The patient was born and brought up in Glasgow, the only child of a self-employed furniture salesman. She had a happy childhood, being somewhat indulged by her parents. She was not regarded as a particularly nervous child and she had no neurotic traits in childhood. She attended a Senior Secondary school, taking a two language course but left at 15 to become a clerkess in an office. She was married at 19 and the marriage broke up after one year. She was "torn between her husband and her mother" and returned to her parental home a few weeks before the daughter of the marriage was born. She was divorced by her husband on grounds of desertion. Some years later she remarried but this marriage was not a success either. There are three children of the second marriage, aged 15, 11 and 4½. Her husband only saw the youngest child once or twice. Most of the time the family resided in the patient's parental home, the patient not wishing to leave to stay in the house her husband had provided for her. She was divorced by her second husband on grounds of desertion. At the time of her attendance she was living with her mother as she had really always done. She operated a mobile grocery shop. She had been employed in this type of capacity for many years. She had few hobbies or interests although she had always greatly

enjoyed any type of social occasion. She has always been of an anxious disposition and had a dependent and ambivalent relationship with her mother.

DRUGS PRIOR TO ATTENDANCE

Chlordiazepoxide 10 mg. q.i.d. for six months.

She smokes 20 cigarettes per day and drinks socially - about 2 measures of spirits per week.

AT INTERVIEW

She was obviously depressed. She was slow to answer questions or to respond in any way. She was tense and constantly twisted a handkerchief between her fingers. There was no other abnormality in her mental state.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (5).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	4	4	2	2	2	2		
Anxiety	4	4	2	2	2	2		
Phobias	0	0	0	0	0	0		
Obsessions	1	1	1	0	0	0		
Depressed	3	3	3	2	2	2		
Anxious	3	3	2	2	2	2		
Overall severity	21	21	15	12	12	12		

In view of her failure to respond the patient was removed from the study on the 24th day and treated with a course of 12 ECT which produced little improvement. She responded very slowly to a course of imipramine and chlorpromazine given thereafter and after eight months was able to return to work.

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	2	2	2	2
tremor	0	1	1	1	0
ataxia	0	1	1	1	1
sweating	1	0	0	1	0
constipation	1	0	1	1	1
faints/dizziness	0	1	1	1	0
micturition difficulty	0	0	0	0	0
blurred vision	0	1	1	1	1
Other	0	0	0	0	0
Total	4	6	7	8	5

NAME	AGE	ACETYLATOR STATUS
Mrs. C.S.	42	Slow

OCCUPATION

Unemployed/Housewife.

PRESENTING COMPLAINT

The patient complained that she felt miserable and upset all the time. In addition her life-long fear of rats and mice had become very much worse and as a result of this she had become afraid to go out.

HISTORY OF PRESENTING COMPLAINT

All of the patient's symptoms had arisen about one year prior to her attendance. They appeared to have been precipitated by her distress over the fact that her daughter had had to get married because she was pregnant. The patient regarded this as a reflection on the way that she had brought up her daughter and blamed herself for the situation. Her symptoms had worsened over the year and she had given up two jobs because of them. When she attended she had been unable to work for one month. In addition to the above spontaneous complaints, on direct questioning she admitted to frequent headaches, lack of energy, marked early insomnia, irritability and failing concentration and interest. The depression was marked and constant. She wept a great deal and locked herself in the bathroom when she could not control her outbursts of tears. She felt hopeless about the future and at times wished that she was dead although she had no suicidal intent. She felt guilty about her recent failure to cope at work and about her falling capacity to cope with her domestic responsibilities, and she blamed herself for her daughter's illegitimate pregnancy. She was never free from anxiety. All her life she had had an unreasonable fear of rats and mice, but this had not limited her life in any way. Since her other symptoms had developed this fear had become much more pronounced

and she was constantly preoccupied with the idea that rats or mice might be present. She lacked confidence in her ability to do things properly and repeatedly checked doors, gas taps, etc. She had become indecisive. She was not eating and she had lost one and a half stones in a year.

PAST PSYCHIATRIC HISTORY

Nil.

PAST MEDICAL HISTORY.

Hysterectomy for menorrhagia in 1970.

FAMILY HISTORY OF PSYCHIATRIC ILLNESS

A sister had had inpatient psychiatric treatment. There was no clear description of her symptomatology.

PERSONAL HISTORY

The patient was born and brought up in Glasgow. Her father was a semi-skilled engineer. She was one of five siblings and enjoyed a very happy home life. She had no neurotic traits in childhood. She spent a good deal of time at dancing school as a child and left her Junior Secondary school at 14 to become a professional dancer. She was thus employed until her marriage at the age of 18 to a postman, five years her senior. The marriage had always been very satisfactory. They had twins, now aged 23, both married and away from home. The patient's symptoms developed following her daughter's precipitate marriage. The patient was normally cheerful and outgoing. She and her husband attended dances at clubs every week and they were very sociable. She was a keen sewer and normally made all her own, and her daughter's clothes and all her household furnishings. Since becoming unwell she had stopped all these activities. At best she tended to "over-react to stress" and she had always had a fear of rats and mice.

DRUGS PRIOR TO ATTENDANCE

Chlordiazepoxide 10 mg. t.i.d.)
Nitrazepam 10 mg. nocte) for one year.

AT INTERVIEW

She was very tense. She talked rapidly and under pressure. She was depressed but this was a less marked feature than her tension. Otherwise her mental state was normal.

Physically she was entirely well.

During her course of phenelzine she had no other drugs.

At the time of the initial assessment her score on the neurotic/endogenous rating was (4).

MODIFIED GOLDBERG SCORE

	0	0	1	2	3	3½	3½ + 4	3½ + 8
Depression	3	3	1	1	0	0	0	0
Anxiety	4	4	2	1	0	0	0	0
Phobias	3	3	3	1	1	1	0	0
Obsessions	2	2	1	0	0	0	0	0
Depressed	2	3	2	1	0	0	0	0
Anxious	3	3	2	1	1	0	0	0
Overall severity	22	24	15	7	3	1	0	0

After her course of phenelzine was finished this patient had a course of behaviour therapy for her residual phobic anxiety.

MODIFIED SIDE EFFECTS SCORE

	0	1	2	3	3½
insomnia	2	0	1	1	0
tremor	2	1	1	1	1
ataxia	0	0	0	2	0
sweating	2	0	0	0	1
constipation	1	0	0	1	0
faints/dizziness	0	1	2	2	1
micturition difficulty	0	0	0	0	0
blurred vision	1	1	1	1	1
Other	0	0	0	burning of skin 1	burning of skin 1
Total	8	3	5	9	5

APPENDIX II

Mrs. S.H.
Modified Goldberg Score
urinary tryptamine µg/24 hrs.
mm on Visual Analogue Scale (sum of 3 scales anxiety, tension & depression)
Side effects & symptom score
Goldberg
Vas morning
Vas evening
Tryptamine
Side effect
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. M.B.
Goldberg
Vas morning
Vas evening
Tryptamine
Side Effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side Effects
8 Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mr. J. McK.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side Effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. M.C.
Goldberg
Vas morning
Vas evening
Tryptamine
Side Effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side Effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Miss A.B.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression).
Side Effects
& Symptom score
Duration of Study in Days

Mr. G.H.
Modified Goldberg Score
urinary tryptamine
µg/24 hrs.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side Effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mr. J.A.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side Effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. J. McD.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
Duration of Study in Days
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side Effects
& Symptom score

urinary tryptamine
ug/24 hrs.
Modified Goldberg score
Miss M.M.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Miss J.M.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
8 Symptom score
Duration of Study in Days

Mrs. M.S. (1)
Modified Goldberg Score
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Goldberg
Vas morning
Vas evening
urinary tryptamine
µg/24 hrs.
Side effects
& Symptom score
Tryptamine
Side effects
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. M.G.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side Effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mr. J.F.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. A.J.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

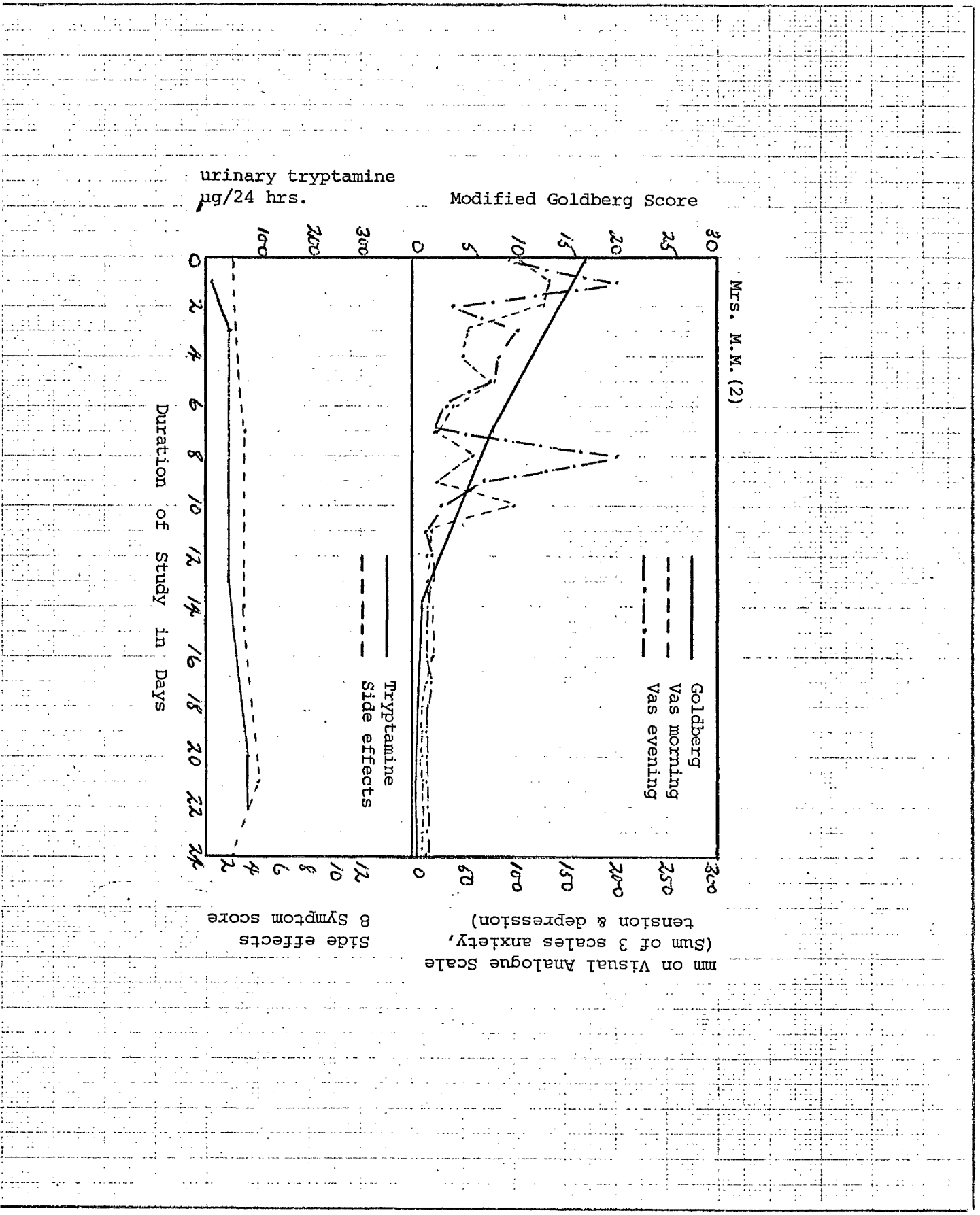
urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. M.S. (2)
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
ug/24 hrs.
Modified Goldberg Score
Miss M.W.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side Effects
& Symptom Score
Duration of Study in Days

urinary tryptamine
ug/24 hrs.
Modified Goldberg Score
Mrs. M.M. (1)
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Miss J. McQ.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. A. McG.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days


urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. M.M. (2)
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. M.F.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
8 Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. H. McD.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

Mrs. A. McI.
Modified Goldberg Score
urinary tryptamine
µg/24 hrs.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. M.D.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mr. P.F.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. C.G.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. E.B.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side Effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. A. O'H.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(sum of 3 scales anxiety
tension & depression)
Side Effects
& Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg Score
Mrs. C.M.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
mm on Visual Analogue Scale
(Sum of 3 scales anxiety,
tension & depression)
Side effects
8 Symptom score
Duration of Study in Days

urinary tryptamine
µg/24 hrs.
Modified Goldberg score
MRS. C.S.
Goldberg
Vas morning
Vas evening
Tryptamine
Side effects
Duration of Study in Days
mm on Visual Analogue Scale
(sum of 3 scales anxiety,
tension & depression)
Side effects
& symptom score