to be admitted as the stigma against mental hospitalization still presents high. Delusions and hallucinations were usually associated with symptoms of the first group, and there was no patient who was admitted for these two symptoms alone.

SUMMARY

A series of the first 100 new cases admitted to Woodbridge Hospital were studied and the reasons for admission elicited. The majority were admitted because of abnormal behaviour, being aggressive and violent or disturbed or talking irrationally. Subjective symptoms which required admission were those of insomnia, depression, suicidal feelings, delusions and hallucinations.

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CARDIOVASCULAR HAZARDS FROM INTERACTIONS BETWEEN IMIPRAMINE AND CATECHOLAMINES

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SUMMARY

Though hypertensive crisis and sometimes death resulting from interactions between monoamine oxidase inhibitor (MAOI) antidepressants and catecholamines are well known, similar cardiovascular hazards are seldom reported with tricyclic antidepressants. Therefore interaction experiments were carried out in human volunteers between imipramine, a tricyclic antidepressant, and sympathomimetic amines in this study. It was found that imipramine potentiated the pressor effect of phenylephrine by two- to three-fold, that of noradrenaline by four- to eight-fold and that of adrenaline by two- to four-fold. There was no significant change in the response to isoprenaline. Dysrhythmias were recorded during adrenaline infusion after pretreatment with imipramine. It is recommended that patients taking imipramine or other tricyclic antidepressants must avoid using local dental anaesthetic containing noradrenaline, phenylephrine as nasal decongestant and subcutaneous adrenaline for the treatment of bronchial asthma as the resultant interactions may precipitate hypertensive crisis and serious arrhythmias.

The pressor effect of some sympathomimetic amines has been shown by Elis et al (1967) to be potentiated in subjects receiving monoamine oxidase inhibitor (MAOI) antidepressant. Hypertensive crisis and sometimes sudden death resulting from the above interactions are quite well known. However, similar cardiovascular hazards with tricyclic antidepressants are rarely reported in pharmaco-therapeutic textbooks and medical literature. Therefore the use of tricyclic antidepressants in the treatment of depression predominates in the clinical practice as they are regarded to be less dangerous and toxic than MAOI antidepressants. The ability of tricyclic antidepressants to potentiate the cardiovascular effect of noradrenaline was first suspected by Sigg in 1959 and was later confirmed in animal experiments by Kaumann et al in 1965. Recently Svedmyr (1968) showed that in human volunteers a tricyclic antidepressant, protriptyline, potentiated the pressor effect of noradrenaline and adrenaline. As sudden deaths have been reported recently to have occured in patients taking tricyclic antidepressants (Coull et al, 1970; Moir et al, 1972), the safety of using tricyclic antidepressants is now questioned by many physicians. The mechanism underlying this sudden death is still not certain but it can either be due to direct cardiotoxic action of tricyclic agents on the heart or due to interactions with concomitantly administered drugs (Moir, 1972). In

view of the serious cardiovascular hazards which may arise as a result of interactions, it appears to be of great value to carry out interaction experiments between imipramine, a commonly prescribed tricyclic antidepressant and catecholamines, in human volunteers.

Method

Four healthy human volunteers (age range 30 to 48) received intravenous infusions of phenylephrine, noradrenaline, adrenaline and isoprenaline under control condition and after taking imipramine 25 mg three times a day for five days. At each experiment, the four sympathomimetic amines were infused in random order without the subjects being aware of the order. Before infusion started, each subject rested supine until blood pressure and heart rate had reached a steady state. Throughout the experiment, the blood pressure was measured by the London School of Hygiene sphygmomanometer (Rose et al, 1964) which is designed to eliminate observer bias. The rate and rhythm of the heart were continuously monitored by Mingograph recorder. Infusions were given for a period of five minutes at each concentration (steady state usually occurring after three minutes), and the concentrations being increased in logarithmic fashion. Phenylephrine infusions were started at 50 ug/min, and at five minutes' interval, the rate of infusion was increased to 100 ug/min, 200 ug/min and 400 ug/min, etc. Noradrenaline and adrenaline infusions were started at 2 ug/min, and at five minutes' intervals, the rate of infusions was increased to 4, 8, 16, 32 ug/min, etc. Isoprenaline infusion was started at 1 ug/min and then increased to 2, 4, 8, 16 ug/min etc. at five minutes' intervals. It was decided that infusions should be terminated when systolic pressure exceeded 170 mmHg or when the heart rate increased by 40 beats per minute or when the subject requested.

Table I. Summary of results. Figures in parentheses are standard errors.

	Phenylephrine			Noradrenaline			Adrenaline			Isoprenaline		
	Before	After	P	Before	After	P	Before	After	P	Before	After	P
Average dose:	200 ug/min			9 ug/min			18 ug/min			5 ug/min		
Imipramine 25 mg t.d.s. for five days (n = 4) B.P.* Systolic	143(9.9)	173(0.6)	<0.05	131(6.4)	174(1.4)	<0.05	123(10.2)	153(16.1)	<0.025	109(8.7)	104(7.4)	N.S.
Diastolic	89(1.4)	108(4.8)	<0.05	84(5.6)	99(1.3)	0.05	60(5.4)	72(4.4)	<0.05	49(5.1)	50(3.7)	N.S.
Mean	107(4.3)	130(3.3)	<0.02	100(4.4)	124(0.8)	<0.01	81(6.9)	99(7.8)	<0.01	69(6.2)	68(4.7)	N.S.
Heart rate*	45(3.2)	50(4.0)	<0.01	63(5.2)	53(2.0)	N.S.	86(6.9)	95(12.2)	N.S.	121(5.2)	127(1.9)	N.S.

*The quoted levels of B.P. and heart rate are those produced by the maximum tolerated doses of sympathomimetic amines after antidepressant compared with those levels produced by similar doses under control conditions.

Results

The final (steady state) blood pressures and heart rates during infusions of each amine after the subjects had been pretreated with antidepressant were compared with the blood pressures and heart rates produced by equal concentrations of amines under control conditions. These results are summarised in table I. The significance of imipramine-induced modification of the response of blood pressure and heart rates to infusions of amines was determined by means of paired t tests. The p values quoted are derived from two-tailed tests.

Imipramine 25 mg three times a day for five days was associated with dry mouth, tachycardia in all subjects. There was a two-fold to three-fold potentiation of the pressor effect of phenylephrine ($P < 0.05$), a four-fold to eight-fold potentiation of noradrenaline ($P < 0.05$), and a two-fold to four-fold potentiation of adrenaline ($P < 0.025$). (See figs. 1, 2, and 3). Some potentiation of adrenaline-induced tachycardia occurred in subject 2, but not in the other three subjects. However, striking changes in rhythm occurred — three subjects developed noticeable sinus arrythmia, and the other subject (subject 1) developed numerous atrial ectopics, ventricular ectopics and runs of nodal rhythm. Isoprenaline-induced tachycardia was modestly potentiated (nearly two-fold) in one subject but was unaltered in the other three. There was no significant change in the response of blood pressure to isoprenaline.

DISCUSSION

The results obtained in our study agree fairly

well with those of Svedmyr (1968) who found that protriptyline potentiated the pressor action of noradrenaline approximately nine-fold and that of adrenaline three-fold when these catecholamines were intravenously infused in man. However a two- to three-fold potentiation of the pressor effect of phenylephrine observed in our study is not in agreement with the observations made by Costa et al (1966) who showed that the tricyclic antidepressant reduced the pressor effect of indirectly acting amine. This difference can be partly explained by the fact that phenylephrine is a sympathomimetic amine with both direct and indirect action.

The mechanism of this interaction is not clearly known. It had been shown by Iversen (1967) that tricyclic antidepressants inhibited the uptake of noradrenaline into adrenergic nerve endings. As this amine uptake mechanism is one of the most important pathways of inactivation of free noradrenaline at the receptor sites, its blocade will result in an increase in local concentration of noradrenaline at the adrenergic receptors and hence the increased pressor effect.

The hazards of administering catecholamine containing drugs to patients on tricyclic antidepressants treatment are very real indeed. But so far hardly any warning appear to have been made against the concomitant administration of catecholamine though similar warnings are repeatedly made in the case of MAOI antidepressants. As a matter of fact, in some pharmacology textbooks, noradrenaline drip is recommended for the treatment of hypotension caused by overdosage of tricyclic antidepressants in man. This is obviously hazardous as it may well turn hypotension into a hypertensive crisis.

Boakes et al (1972) reported a series of adverse reactions to local anaesthetics containing noradrenaline at a concentration of 1:25,000 (40 ug/ml) during the dental treatment of patients on tricyclic antidepressants. A steep rise in blood pressure can occur and is hazardous to life. Therefore this type of local anaesthetics should not be used. Though the potentiation of the pressor effect of adrenaline at lower concentration is not as marked as that of noradrenaline, it has the additional hazard of inducing arrhythmia in subjects pretreated with imipramine. Therefore the use of subcutaneous adrenaline 1:1000 at a high concentration (1000ug/ml) in the treatment of bronchial asthma may lead to hypertensive crisis and serious arrhythmia. As many asthmatics are often depressed, it is therefore quite common in clinical practice to put the asthmatics on tricyclic antidepressants as well. It is not surprising that these cardiovascular hazards arising out of the above interactions may account for some of the sudden unexpected death among the asthmatics. On the other hand, it appears that coincident administration of tricyclic antidepressants will not increase the hazards of isoprenaline inhalation in bronchial asthmatics as our present study fails to show any potentiation of cardiovascular response to isoprenaline infusions in subjects pretreated with imipramine.

As phenylephrine was potentiated two- to three-fold in its pressor effect, its indiscriminate use may lead to serious consequences. Unfortunately phenylephrine is very commonly used as nasal decongestant and finds its way into many patent preparations like Coricidin D, Dristan etc. There are not less than twenty proprietory remedies described in Drug Index in Malaysia and Singapore (1973) which have phenylephrine as part of the constituents. Therefore the patients on tricyclic antidepressants should be warned. The use of other indirect acting amines like ephedrine and phenylpropranolamine which are present in many cough and cold cures should also be cautioned in these patients until human experiments are done to substantiate the finding of Costa et al (1966) that tricyclic antidepressants actually reduce the pressor effects of indirectly acting sympathomimetic amines.

ACKNOWLEDGEMENT

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LEGENDS TO THE FIGURES

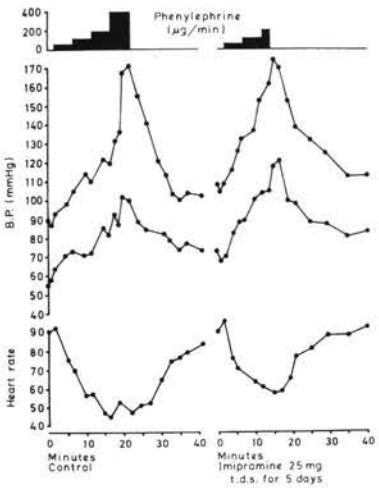

Fig. 1: Subject 2. Cardiovascular response to intravenous infusion of phenylphrine before and after imipramine.

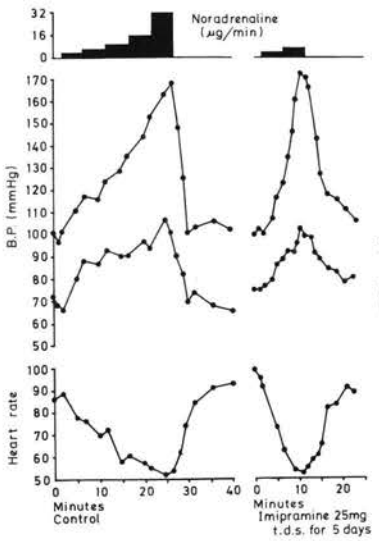

Fig. 2: Subject 2. Cardiovascular response to intravenous infusions of noradrenaline before and after imipramine.

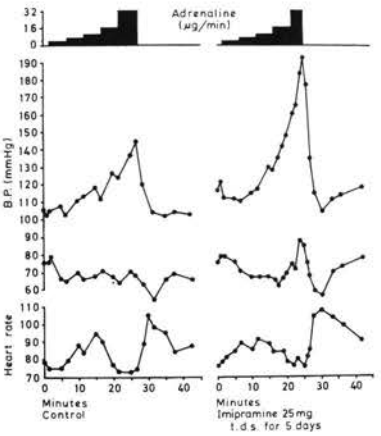

Fig. 3: Subject 4. Cariodvascular response to intravenous infusion of adrenaline before and after imipramine.

PSYCHOTROPIC MEDICATION FOR ANXIETY

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Anxiety is an ubiquitous existential symptom. Different era and culture not only have different sources of anxiety but also different manifestations and management. Anxiety also occurs as a symptom in almost any psychiatric syndrome or organic disease. A clinician may encounter different degrees of anxiety. Free-floating anxiety does not seem to relate to any stress-factor. Anxiety may be manifested via numerous somatic symptoms. Restlessness of increased tone of the musculature may proceed intense anxiety state known as panic.

Psychotropic Drugs Influencing Anxiety

In every category of psychotropic drugs, there are those which show, to a greater or lesser extent, an anti-anxiety effect. One should however differentiate drugs having a predominant effect on anxiety, i.e. minor tranquillizers, from those in which this effect is secondary, as exemplified by some antihistamines, hypnotics, major tranquillizers (neuroleptics) and antidepressant drugs. In the subsequent discussion, we shall see that for anxiety associated with various clinical features some of these psychotropic medications are indicated for the associated anxiety.

Minor tranquillizers, through their demand by patients and doctors had a lucrative market.

But marked tendency to produce addiction and seizure if withdrawn suddenly and lack of efficacy had resulted in the disappearance of a number of them from the markets. (Tan, 1970). The group that has the greatest success and is still being improved on is the Benzodiazepine (Hurlimann, 1972). Included under this group are Chlordiazepoxide (Librium) and Diazepam (Valium). The side effects of the benzodiazepine include nausea, drowsiness and paradoxical excitement.

Rationale for Treatment of Anxiety

Dally (1967) distinguished between a primary anxiety state from anxiety which is secondary to, and may mask depression, schizophrenia, organic disease or an early state of dementia.

To quote Cazzullo (1969): "The particular character of anxious phenomena, whether occurring in isolation or in conjunction with other symptoms, presents a range of problems which are appropriate to other treatments as well as pharmacotherapy. The *first* problem is the discrimination between degrees of anxiety, the *second* the relationship of anxiety with other clinical pictures and a *further point* is the distinction between the various phenomenological features of anxiety, psychic as well as somatic. The second and third points are obviously closely connected."

Rothman (1963) always used supportive psychotherapy first. Kielholz (1969) wrote that psychopharmacotherapy without psychotherapy was pointless. Kusumanto (1972) in "The Problems of Anxiety in a Non-Western Society." advocated a combined chemo- and psychotherapeutic approach to anxiety. The two methods must be co-ordinated: the more the anxiety is generated by emotional factors, the greater will be the part played by psychotherapy. A 'medical model' (psychopharmacotherapy) of managing anxiety is thus combined with a 'behavioural educational model' (psychotherapy).

The following classification of anxiety and its associated symptoms aids in the selection of the appropriate psychotropic drugs:—

I. *Primary Anxiety State*

When anxiety is a normal reaction to some unpleasant circumstances i.e. mild reactive anxiety, or existential anxiety, no medication is needed. In anxiety neuroses paroxymal, acute anxiety may be felt or shown by an individual without apparent reason or out of all proposition to the supposed cause. The patient may be physically and mentally affected by his anxiety to such a degree that he cannot cope with routine activities. This engenders even more anxiety and a vicious circle is set up. Treatment should aim to break this vicious circle: to reduce anxiety to a level at which the patient can function efficiently and deal with his problems. Once this is done, treatment can usually be tailed off and stopped. For primary anxiety, chlordiazepoxide (Librium), 5—10 mg per dose, daily dose range 10—80 mg or Diazepam (Valium), 2—10 mg per dose, daily dose range 6—30 mg may be used. The aims of medication here are these:—

(1) it facilitates contact with and communication with the patients;
(2) it helps to break down resistance which could not otherwise be overcome;
(3) it utilizes the action of the drug in relieving patients from unbearable anguish.

The efficiency of a tranquillizer upon anxiety symptoms should be apparent within a few days. It is reasonable to double the dosage if symptoms are unrelieved after a week, and to change if there is no improvement after a further week. Some claim that diazepams, with its more prominent muscle relaxant activity, is superior to chlordiazepoxide when both are given in a dosage of 10 mg three times a day, but that diazepam has a greater tendency to cause drowsiness.

Sometimes it is only necessary to treat the insomnia resulting from anxiety. A benzodiazepine, Nitrazepam (Magadon) 10—20 mg is a useful hypnotic.

An important determinant in the success of any treatment will be the personality of the patient. McDonald (1967) explored the effects of personality type on drug response. For the chronically inadequate group of patients suffering from anxiety, there is as yet no proper physical treatment. Sargant (1969) warned that these might be helped by sedative drugs at the expense of causing their increasing addiction and deterioration under them. In predisposed individuals, e.g. alcoholic, habituation and addiction to Meprobamate and Chlordiazepoxide may occur, although less likely than barbiturates. Overdosage with meprobamate or diazepam derivatives is unlikely to be fatal.

II. *Anxiety with Depression*

The relationship between anxiety and depression is very complex, depending on the features and the individual meaning of the depressive experience, with depression often being a final step in the dynamics of anxiety. Simon (1966) found that all thirty-seven patients hospitalized at the Psychosomatic and Psychiatric Institute,

Chicago with a diagnosis of depressive reaction ranked feelings of tenseness, focused anxiety, and sadness and blueness among their top initial concerns. The anxiety factor mean scores were highest. Hollister et al (1967) studied one hundred and one newly admitted depressed male psychiatric patients who were treated with amitriptyline (Elavil, Laroxyl, Tryptanol), perphenazine (Trilafon) or a combination of the two drugs over a four week period, using blind controls. They confirmed all of the following hypothesis which were the results of observations from previous studies: amitriptyline would be most efficacious in patients classified as retarded depressions; perphenazine would be the drug of choice for patients with anxious depressions and the combinations would be effective in both types, as well as in hostile depressions but would not offer any special advantage over the indicated single drug.

The therapeutic effect of amitriptyline may be delayed up to two to three weeks. If the suicidal risk is high, ECT may have to be used first. The danger of attempted suicide with amitriptyline should be borne in mind. Lethal dose has varied from 1,250 mg to 1,500 mg. Williams and Sherter (1971) described two cases of unresponsive cardiac standstill secondary to toxicity of tricyclic antidepressants. These drugs are contra-indicated in patients receiving drugs that deplete cardiac catecholamines (e.g. guanethidine).

Sargant (1969) found that a group of mixed anxiety, depressive and anguish states with an adequate previous personality and with low basal forearm blood flow responded to an MAOI group of antidepressant drugs e.g. Phenelzine (Nardil).

III. *Secondary anxiety or anxiety bound to different ideas and thought representations such as phobias, obsessions, hypochondrical ideas and delusions.*

When anxiety symptoms are secondary to the main picutre of the illness present e.g. schizophrenia, minor tranquillizers are effective only for this symptom, but not on the others. This lack of anti-psychotic effect distinguishes it from the group of major tranquillizers e.g. phenothiazines and butyrophenones. Cazzullo (1969) sometimes combined chlorpromazine with high dosages, 100 to 250 mg a day, of chlordiazepoxide, given intramuscularly.

In obsessional neuroses, anxiety may still persist in spite of displacement. Diazepam may be used. When obsessional thinking is related to a cyclothymic background, thereby assuming the character of a depressive equivalent, the association of antidepressant drugs (amitriptyline)may be of value. In the case where compulsive phenomena become autonomous, losing their emotional charge and tendency to stereotype, it is necessary to potentiate the treatment with butyrophenones (Cazzullo, 1969).

In alcoholic withdrawal state and delirium tremens, adequate dosage of tranquillizing drugs to allay the patient's excitement and fear must be given. If the patient has not gone into the state of frank acute organic brain syndrome but shows evidences of development in that direction, phenothiazines or butyrophenones in large doses should be prescribed. The tremulous, very anxious patient might be given a 50 to 100 mg of intravenous chlordiazepoxide for some immediate relief as well as to facilitate the diagnostic interview. Medication will be required for the next 4 days and most reliable control can usually be obtained with the use of phenothiazines (Hankoff, 1969).

Other Factors Influencing Outcome of Medication

Other elements which are important in influencing the anti-anxiety treatment: (1) The functions and the personality of the therapist, (2) the specific quality of the doctor-patient relationship and (3) the environment in which the treatment is carried out. In this connection also (4) the problem of the placebo effect cannot be overlooked and therefore great caution is necessary in evaluating the anti-anxiety effect of any drug (Cazzullo, 1969).

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TRIAL OF LITHIUM CARBONATE IN THE PREMENSTRUAL TENSION SYNDROME

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INTRODUCTION

Good results with the use of Lithium salts in the premenstrual tension syndrome have been reported (Sletten and Gershon, 1966; Rossman 1969). These observations however await confirmation. The value of Lithium is suggested by its known capacity to affect water and electrolyte balance which are implicated in the pathophysiology of the syndrome, and its efficacy in psychiatric disorders characterised by periodicity. (Gjessing, 1967; Schou, 1968, Forssman and Walinder, 1969; Hanna *et al.*, 1972). We therefore undertook a controlled study on the efficacy of lithium in the syndrome.

Methods

The study compared lithium with placebo, was double-blind with multiple random cross-over, and involved 19 Chinese out-patients. It lasted up to 8 menstrual cycles for each patient. The first cycle involved open lithium for dosage adjustment; thereafter the allocation to either lithium or placebo for a cycle was randomized so that a patient did not necessarily have equal numbers of lithium and placebo periods. Lithium was dispensed in capsules of 250 mg (6.8 mEq) of the carbonate salt. Dosage was flexible, ranging from 750–1000 mg daily and aiming at maintaining serum concentration at 0.8 – 1.3 mEq/1. Lithium estimation by flame photometry was carried out at least once a month when patients were interviewed. Dosage was regulated by the interviewing psychiatrist on the basis of serum lithium values reported to her from the laboratory, true values for the lithium periods and fictitious values within the same range for the placebo periods.

Patients were selected on the basis of symptoms being temporarily related to the menstrual period – marked emotional tension (irritability, anxiety, depression) and various somatic features, as originally described by Frank (1931). They had also to promise not to become pregnant during the trial.

They were not permitted to take diuretics or hormones, excepting oral contraceptives; other psychiatric medication including antidepressants (8 patients) and tranquillizers (18 patients) was maintained at fixed levels throughout. Excluded from the study were patients with brain damage, active somatic disease, alcoholism, character disorders, as well as those in whom lithium therapy was for one reason or another contraindicated. The majority (17) of the subjects had, at onset of trial, moderate to severe symptoms of premenstrual tension which had either not responded to medication or whose slight response had stabilised for long periods. Their ages ranged from 20 to 44 years (mean 32.3)

Concomitant psychiatric conditions were diagnosed in accordance with the U.K. Glossary of