effects on the bronchi and blood vessels. (2) Very little enters the brain. Whereas the brain/blood ratio at three hours after an oral dose in dogs is 7 for propranolol, it is only 0.13 for practolol, compared with heart/blood ratios of 2.5 for propranolol and 2.1 for practolol (Scales & Cosgrove 1970). While it is possible that this small amount of practolol entering the brain is sufficient to block central adrenergic receptors, it is more probable that its peripheral receptor blocking action in the heart is responsible for its effectiveness in alleviating anxiety. This would be consistent with interruption of a somatopsychic sequence of events which may well help to maintain anxiety in these patients. If so, then receptor blocking drugs such as propranolol and practolol would be expected to be of most value in those patients in whom somatic symptoms, particularly those referable to the heart, are prominent. It is of interest, therefore, that all 15 patients studied showed improvement with practolol, even though they were not selected in any way to exclude patients without such symptoms. Furthermore, Carlsson & Johansson (1971), in a double-blind study, found that propranolol 160 mg daily for eight days significantly decreased the incidence of tension symptoms in the abstinence phase of treatment of 44 chronic alcoholics.

These findings would suggest that somatic symptoms referable to the cardiovascular system occur in a majority of anxious patients even though routine questioning may fail to elicit them. This is consistent with the observation (Bonn, *see* above) that although patients spontaneously complained of cardiac irregularities or tachycardia during their 'natural' anxiety attacks, only 50% of them reported these symptoms in the experimental attacks produced by lactate infusion, even though there was objective evidence of tachycardia in all of them.

Although practolol is a selective β_1-antagonist, one patient had an asthmatic attack during treatment, and her plasma practolol was the highest among this group of patients, 3.20 μg/ml. This indicates that practolol's selectivity is relative, and that organs with a β_2 receptor population such as the bronchi may also be affected. This drug should, therefore, be used with caution in patients with a past history of asthma or airways obstruction.

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During the past ten years there has been a great deal of interest in the treatment and assessment of anxiety. The minor tranquillizers have largely replaced barbiturates for the treatment of anxiety states, in both general practice and hospital clinics.

The Benzodiazepines

The benzodiazepines are now one of the most widely used groups of psychotropic drugs. In a double-blind controlled trial of chlordiazepoxide, carried out at the Johns Hopkins Hospital, 15 randomly allocated anxious patients were treated with the active compound, and 15 with placebo capsules, for one week. A flexible dosage regime was used, with a mean dosage of 45 mg per day (Kelly *et al.* 1969). It was found that the observer and self ratings of global improvement were greater after chlordiazepoxide than after placebo.

The benzodiazepines appear to be particularly useful in reducing the background level of anxiety when given by mouth, but they can also be very effective sedative agents for overcoming acute anxiety when given intravenously. In a recent study at St George's Hospital, the effects of i.v. diazepam on 15 anxious patients were examined, to determine the psychological and physiological actions of the drug (Kelly, Pik & Chen 1973). The infusion, of 10 mg which lasted for ten minutes, was preceded by a similar 'placebo' infusion of diazepam solvent. It was found that on the Clyde Mood Scale the patients were significantly less 'Dizzy' (dizzy, jittery, shaky and sick to the stomach) and less 'Unhappy' (sad, downhearted, troubled and worried) at the end of the experimental procedure. It is likely that these changes

were due to diazepam. In the previous study, chlordiazepoxide by mouth also resulted in a significant decrease in the 'Dizzy' factor, which is composed of items generally associated with anxiety.

There was a significant reduction in observer and self ratings of anxiety after the diazepam infusion, and this was accompanied by a significant reduction in physiological arousal, as evidenced by a fall in forearm blood flow and heart rate. The maximal effect on these measurements was during the period 20–30 minutes after the administration of diazepam ended. Rosenberg & Buttsworth (1969) had also found a significant decrease in anxiety self-rating and forearm blood flow after i.v. diazepam. In our study diazepam produced cutaneous vasodilatation, as evidenced by an increase in finger pulse amplitude, but blood pressure, respiration and sweat gland activity were not significantly affected.

Diazepam, when given intravenously, may produce burning at the site of injection, with pain radiating down the arm. This occurred in 2 of our patients, although neither of them subsequently developed venous thrombosis. It is thought that pain is due to the acidity of the solution, producing irritation of the venous endothelium. Venous thrombosis can be a serious disadvantage if diazepam is used for repeated injections, e.g. for treating by systematic desensitization. One method of reducing pain at the site of injection, suggested by Mitchell-Heggs, is to withdraw venous blood into the syringe, so that it is well mixed with diazepam before it is injected.

Diazepam is thought to act on the limbic system and, in particular, on the hippocampus. Bilateral hippocampal lesions may result in amnesia, and it is interesting to speculate that diazepam may act on limbic circuits concerned with memory. In a preliminary trial before the above study, 10 mg of diazepam was given i.v. to a control subject, who subsequently experienced a period of amnesia. When diazepam is given orally, amnesia is usually not a problem, but amnesia during systematic desensitization with i.v. diazepam can occur and is not desirable.

Newer benzodiazepines include oxazepam (Serenid-D), and medazepam (Nobrium). Both are useful drugs, but neither appear to have striking advantages over the older benzodiazepines, chlordiazepoxide or diazepam. Some patients, however, appear to favour one benzodiazepine, and obtain little or no benefit from others. Nitrazepam (Mogadon) is a useful hypnotic for anxious patients.

Other Tranquillizers

Benzoctamine (Tacitin), which has been introduced recently, is related to the benzodiazepines, but it has no anticonvulsant properties; 10 mg of benzoctamine three times daily is equivalent to 5 mg of diazepam three times daily. Side-effects include drowsiness, dry mouth, headache and dizziness.

The phenothiazines, such as perphenazine, are sometimes helpful in controlling severe anxiety, but their side-effects limit their usefulness for outpatient treatment. Oxypertine (Integrin) has some structural affinities to the phenothiazines, and in small doses, such as 10 mg three times daily, it can be a useful minor tranquillizer for treating anxiety states. The barbiturates, which affect the cortex, have the disadvantages of inducing sleepiness and producing addiction, and are much more dangerous when taken as an overdose. These properties have been responsible for their decline in popularity in spite of their cheapness.

Antidepressants for Treating Anxiety States

MAOIs and tricyclics are complex substances and have other effects besides their antidepressant action.

Monoamine oxidase inhibitors: Sargant (1960) and West & Dally (1959) have long advocated the value of MAOIs in what was called 'atypical depression', in which phobic anxiety was a prominent symptom. Clinical experience suggests that minor tranquillizers, such as the benzodiazepines, have less value in preventing panic attacks, which are so often seen in phobic anxiety states, but that antidepressants are often very useful for this purpose.

In a previous uncontrolled study, anxious patients treated with a MAOI alone, or combined with a benzodiazepine, were found to be less phobic, less depressed and to have an improved social adjustment rating one month, and one year, after starting treatment (Kelly *et al.* 1970). Of the St Thomas' outpatients 90% had panic attacks initially, 42% had lost their panic attacks a month after starting treatment, and 58% at one year. Panic or anxiety attacks play an important role in the generalization and avoidance behaviour of phobic patients. During a panic attack the patient experiences acute apprehension, associated with marked autonomic concomitants, such as tachycardia, sweating, a dry mouth, tremor and a feeling of dizziness or weakness with difficulty in breathing. These feelings often lead the patient to believe that he is about to die or lose his self-control. The experience is so dramatic

that he subsequently tries to avoid the circumstances associated with the attack. It is thought that the benefit of MAOIs in the treatment of anxiety states is largely due to their ability to block panic attacks, and hence to let the patient gradually re-enter situations which had formerly been avoided, for fear of precipitating an attack. Wolpe (1964) stressed the importance of persisting panic attacks, in phobic patients, as an important obstacle to the success of behaviour therapy.

Anxiety attacks have been precipitated experimentally by the intravenous infusion of sodium lactate in a high percentage of anxious patients (Pitts & McClure 1967, Kelly *et al.* 1971). We subsequently treated with phenelzine a small number of patients who had anxiety attacks precipitated by i.v. sodium lactate. It was found that the patients who showed substantial clinical improvement had many fewer symptoms when they were given a second sodium lactate infusion. Clinical improvement in anxiety appears to raise the threshold at which a panic attack can be precipitated by sodium lactate.

In a double-blind controlled trial of phenelzine, carried out at the Maudsley and St George's Hospitals, patients were selected who had severe primary agoraphobia (fear of going out alone), or social phobias, which had been present continuously for at least one year (Tyrer *et al.* 1973). Fourteen patients had phenelzine for two months, on a flexible dosage regime, and 14 prospectively matched controls had placebo. The overall assessment indicated that the patients on phenelzine were significantly more improved than those on placebo ($P<0.001$). The patients on phenelzine had decreased scores on the Anxiety and Phobic Scales of the Middlesex Hospital Questionnaire (MHQ), and on the Taylor Scale of Manifest Anxiety. Their work adjustment rating also improved significantly. Depression as a symptom correlated negatively with improvement, so it would be difficult to assume that this population was primarily depressed, or that phenelzine was exerting an antidepressant effect.

The relationship between anxiety and depression is usually close, however. It is a common observation that when a patient becomes depressed, he also becomes anxious, and panic attacks may start for the first time; as the depression lifts panic attacks often disappear. At present it is not known if MAOI antidepressants have a direct 'blocking-effect' on panic attacks, which seems likely, or if it is their sedative action which brings this about, which seems unlikely, because drugs like phenelzine in most patients do not produce significant sedation.

Pollitt & Young (1971) discussed the possibility that anxiety states responsive to MAOIs are a form of depression, and that the different clinical picture is due to chronological age.

Tricyclic antidepressants: The sedative effects of the tricyclic antidepressants can be used for treating anxiety states. A single dose of amitriptyline or trimipramine at night is often preferable to a barbiturate for night sedation, or a small dose, e.g. 10 mg three times daily, may produce a reduction in anxiety during the day, without the danger of habituation or addiction. Some patients may tolerate a large dose of amitriptyline during the day without feeling sleepy. Doxepin (Sinequan), one of the new tricyclic antidepressants, is useful as a minor tranquillizer, although its antidepressant properties do not appear to be as great as those of imipramine or amitriptyline. Klein (1964) found tricyclic antidepressants were also valuable for treating panic attacks, and this has also been my experience, although they do appear to be less effective than MAOIs.

Intravenous clomipramine (Anafranil) has been found to be of benefit in the occasional severe chronic anxiety state. We are investigating the properties of this drug when given by intravenous infusion, but it is too early to say if it will establish itself as an accepted type of treatment. It is also used for depression and obsessional neurosis.

Combined antidepressants: Combining tricyclic antidepressants with a MAOI is controversial, but in a recent paper by Schuckit *et al.* (1971) the world literature on the adverse effects of combined antidepressants is reviewed. The authors conclude that there is 'no convincing evidence that the antidepressant combination taken in therapeutic doses was responsible for the illnesses reported'. Occasionally it is helpful, when treating severe anxiety states, to combine a sedative tricyclic at night with a MAOI during the day. Confusional states can occur if the second drug is not introduced slowly. Clomipramine should never be given within fourteen days of a MAOI.

Modified narcosis: Modified narcosis combined with an antidepressant and ECT has been found to be of value in severe anxiety states (Walter *et al.* 1972). It is a specialized type of treatment which is best carried out in a unit with considerable experience of this technique.

Limbic Leucotomy

If anxiety is intractable, in spite of every other type of treatment, and if incapacity is severe, then psychosurgery may benefit the patient. Modified leucotomy carried out free-hand has the dis-

Table 1

The mean psychometric values before and six weeks after limbic leucotomy
N = 35. Four patients were unable to complete the forms because of language difficulties and one patient was too disturbed

	Mean psychometric values		
Scale	*Before leucotomy*	*Six weeks after leucotomy*	*P*
MPI:			
Neuroticism	30.8	23.1	< 0.001
Extraversion	12.9	14.2	NS
Depression:			
Beck	26.4	18.7	< 0.001
Hamilton	21.5	10.5	< 0.001
Anxiety:			
Taylor	31.9	24.1	< 0.001
Hamilton	22.2	12.3	< 0.001
MHQ:			
Anxiety	11.6	10.0	< 0.01
Phobic	7.1	5.7	< 0.01
Obsessional	11.3	10.2	< 0.05
Somatic	8.2	5.5	< 0.001
Depressive	10.6	7.9	< 0.001
Hysteric	5.3	4.7	NS

advantage that large numbers of fibres have to be divided between the cortex and the target site to enable an adequate section of the lower medial quadrant of the frontal lobe to be made. Stereotactic techniques now enable small lesions to be placed with considerable accuracy. Mr A E Richardson, at Atkinson Morley's Hospital, uses a Leksell stereotactic frame, and makes cryogenic lesions in the lower medial quadrants of the frontal lobes, at sites of physiological activity. Before the lesion is made the target area is stimulated while respiration, heart rate, finger pulse amplitude, forearm blood flow and sweat gland activity are being monitored continuously (Kelly 1972). The target site may be moved a few millimetres if no physiological changes are obtained. This procedure is used to increase the accuracy of lesion placement. Lesions are made in the lower medial quadrant to disconnect some frontolimbic pathways, and in the cingulate gyrus to interrupt one of the important limbic circuits of Papez (Kelly, Richardson & Mitchell-Heggs 1973).

The results of stereotactic limbic leucotomy have been assessed psychologically and physiologically at six weeks (Kelly, Richardson, Mitchell-Heggs, Greenup, Chen & Hafner 1973).

The patients, who were mainly suffering from obsessional neurosis, depression and anxiety, had a mean duration of symptoms of eleven years, with a mean number of hospital admissions of 4.5. Thirty-six of the 40 patients had been treated previously with ECT, 27 had received psychotherapy and 24 modified narcosis; 11 had made a determined suicidal attempt.

Postoperative assessment showed a significant reduction in anxiety (Taylor, Hamilton, MHQ), depression (Beck, Hamilton, MHQ) neuroticism (Maudsley Personality Inventory) and obsessions (MHQ) (Table 1). The postoperative IQ assessment showed a significant *increase* in the mean full-scale and performance IQ on the Wechsler Adult Intelligence Scale. This was probably due to a practice effect, but on none of the subscales of the WAIS was there a significant decrease in postoperative score. The patients are being re-evaluated psychologically and physiologically at one year, and are being seen by an independent psychiatrist before and one year after operation.

During the past ten years a greater understanding of the nature of pathological anxiety has been achieved, and several new types of treatment are now available for its alleviation. The work of assessing these will be a slow but worth-while endeavour.

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The benzodiazepines are the mainstay of treatment of the milder forms of anxiety in general practice; this may be because of the safety factor, since they are free of the danger of death by overdose. Nevertheless, I believe that the benzodiazepines are specifically better than the barbiturates, as was demonstrated in a trial undertaken by the General Practitioner Research