reasons. Thus, in our series of 24 patients a surprisingly high proportion of the psoriatics became completely free from eruption. (The provision of a pot of ointment without instructions in its use usually results in application of ointment at night only, and that erratically, with very little improvement in the psoriasis.) It seems that efficient occlusive dressings such as stockinet and tube-gauze have increased the chances not only of effective local medication but also of cutaneous absorption and clinical toxicity. In this connexion it may be noted that for the successful treatment of extensive psoriasis large quantities of ointment are required, many of our patients using between 1 and 2 lb. (450 and 900 g.) weekly.

Of the 24 patients thus treated, 22 had levels of urine mercury above the limit generally accepted as normal. If urine mercury levels of 300 μg. per litre or above are considered to be in the range where clinical toxicity is likely, 13 of the 24 cases were in the toxic range: in one specimen the level was as high as 3,300 μg. per litre, and readings of 1,000 μg. or more occurred in eight cases.

Nevertheless there were no clinical signs of toxicity. Every patient was inspected and interrogated weekly for at least six weeks, but most of those showing high levels were followed for five or six months and a few for longer than this. There were no cases of albuminuria except in the three isolated specimens of orthostatic albuminuria. In spite of the clinical absence of toxicity, the earlier observations of others are confirmed that in many cases increased urine mercury levels take many months to subside to normal.

It is difficult to explain this lack of toxicity in view of the published cases of mercury poisoning in industrial workers, nephrosis, and pink disease since the second world war. Allergy to mercury applications in skin diseases is well known and may be acute. Possibly some such manifestations occur, though rarely, internally, producing mercury poisoning associated with urine mercury levels which are well tolerated by normal psoriatic patients. If this view receives support we may have to become wary of treating psoriasis for long periods by mercury ointment, since the allergic reaction cannot be forecast. On the other hand, some mercury compounds may be more poisonous than others. The cases of pink disease and mercury nephrosis referred to above nearly always followed the use of calomel ("calomel disease"). Calomel is less often used in skin applications, and the more widely used hydrarg. ammon. or yellow oxide of mercury may be less poisonous. Calomel was apparently used for cutaneous application in syphilis, and mercury poisoning from such treatment was then common.

There seems to be no reason to give up using mercury ointments in psoriasis if they are prescribed with discretion. But there is a need for clinical investigation to decide how important mercury is in the treatment of psoriasis. The same ointments containing the tar without the mercury might be found to be as effective. On the other hand, mercury ointments having been used so widely for so long, clinical experience would allow them to be generally non-toxic, apart from allergic reactions limited to the skin.

In spite of the relative safety of mercury ointments, our findings indicate that they should not be used for treating a psoriatic under 5 years of age. They should probably not be employed for any length of time in anyone with a history of nephritis, or with albuminuria, or with impaired kidney function. Moreover, they should not be used in pregnant women, for mercury has been shown to pass to the foetus *in utero* through the placental circulation (Cushny, 1947).

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CONTROLLED TRIAL OF MEPROBAMATE

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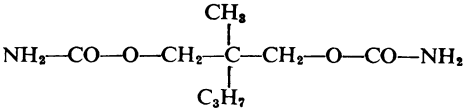
Meprobamate is another of the recently introduced tranquillizing drugs. It has been tried out and used in the United States since 1952 and has temporarily become the fourth most commonly prescribed drug there. It is now also available in this country under the trade names of "equanil," "miltown," and "mepavlon" in tablets of 400 mg. for oral use. Sedative or tranquillizing drugs are now so commonly prescribed that their cost is a large proportion of the national drug bill. The expense of the newer preparations makes an early assessment of their true value a matter of considerable economic as well as medical importance.

Meprobamate was synthesized in 1950 by Ludwig and Piech in the search for compounds resembling mephenesin chemically but having a longer therapeutic action. Meprobamate is 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate and has the following structural formula:



Berger (1954) has described meprobamate as a new interneuronal blocking agent, and showed that it acts,

as does mephenesin, on the central nervous system, depressing multineuronal but not monosynaptic reflexes. In animal experiments large doses produced reversible flaccid paralysis of skeletal muscles without significantly affecting the heart, respiration, or other autonomic functions. Smaller doses had general sedative and muscle-relaxant effects. The drug also protected animals against the convulsant effects of such drugs as picrotoxin, strychnine, and leptazol.

Clinical trials of oral meprobamate in patients were first reported in the United States by Selling (1955) and Borrus (1955). They showed that it is effective in the treatment of anxiety and tension states. Collomb *et al.* (1956), in France, report favourable although not such marked effects in the psychoses. The anticonvulsant action of meprobamate was found to be helpful in the treatment of petit mal but not in grand mal.

Claims are made that meprobamate is only one-fifth as toxic as the barbiturates. It is said not to cause addiction or undue dependence, and no withdrawal symptoms are said to occur when the drug is stopped. Selling (1955) described the effects of deliberate overdosage by two patients. A man took a total of 40 g. in 24 hours, 25 times the normal therapeutic dose. A woman took about half this amount in 24 hours. Both recovered without serious after-effects. No serious toxic effects have as yet been reported in the literature. Drowsiness often occurs, but can disappear without the dose of meprobamate being reduced. Skin rashes and generalized sensitivity reactions are recorded by Selling.

Three separate trials are reported in this paper. The first is a straight trial assessing the effects of meprobamate on patients attending the psychiatric out-patient department at St. Thomas's Hospital. In addition two "double blind" trials were carried out—the first to compare the superiority of meprobamate over the effects of an inert tablet, the second to compare meprobamate with sodium amylobarbitone.

Results of the Straight Trial

Meprobamate was given to 165 patients, but 14 either did not attend again or did not take the drug as prescribed. The remaining 151 patients (76 men, 75 women) were of an average age of 41, and they received meprobamate in doses ranging from 400 mg. twice a day, up to 800 mg. (two tablets) three times a day, with another 800 mg. at night. They were followed for periods of a fortnight to four and a half months. The usual dose given was 400 mg. three times a day, with another 400 mg. at night if insomnia was a problem. Where no effect occurred on this dose it was increased in stages to a maximum of 2 g. a day, after which side-effects usually appeared without any increase in the therapeutic effect.

In Table I "anxiety and tension states" is a broad classification, and includes patients of hysterical or obsessional personality, the main essential being that they should be experiencing tension, "being strung up inside," "unable to relax," having "a tight feeling over the scalp"; or complaining of phobias or states of apprehension without known cause, and showing such overt signs of anxiety as tremor, tachycardia, or sweating, etc. "Hysterical reactions" include such conditions as aphonia, globus hystericus, fugue states, etc., where anxiety is not an obvious feature.

Of the 62 patients who had been classified as anxious and tense, 36 (58%) improved, and meprobamate was noticeably most effective in this group. In a similar group Selling (1955) found that 68 of 72 (95%) improved, and Borrus (1955) that 52 of 67 (78%) improved. Our results are therefore less favourable to the drug than those of the American workers. This may be due to differing case material or different assessment of degree of improvement. Nevertheless in our trial meprobamate did appear to be exerting a definite therapeutic effect.

No very striking effects, however, were noted on tension headaches, only about a quarter of the patients suffering from them experiencing relief, although Selling (1955) reports very favourably on meprobamate in this connexion. The voracious appetite and marked weight gain reported by Barnard and Barnard (1956) were seen in only two patients—one woman with chronic anxiety with an aggressive personality and one man with withdrawal symptoms due to chronic alcoholism. Most patients showed no change of weight during the trial, and three who were already losing weight continued to do so.

TABLE I.—*Results in Straight Trial*

	Much Improved		Improved		Unchanged		Worse		Total
	M	F	M	F	M	F	M	F	
Anxiety and tension states		2	15	19	11	10	3	2	62
Depression:									
Reactive ..	1		3	5	4				13
Endogenous ..			1	1	3	5			10
Hysterical reactions			1	3	2	4	1	2	13
Obsessive-compulsive states			2	3	3	5	1		14
Psychopaths ..	1		6	2	2				11
Schizophrenia ..			1	2	3	1			7
Miscellaneous (muscle spasms, occupational neurosis, stammer, neurodermatitis, etc.) ..			3	2	9	7			21
Total	2	2	32	37	37	32	5	4	151

It was interesting to note that the overt somatic manifestations of anxiety, such as tremor, sweating, and tachycardia, showed very little change with meprobamate, even though the patients said they felt better and more relaxed. It was curious that meprobamate with its allegedly muscle-relaxant action did not have a more potent effect in abolishing tremor, presumably a sign of increased muscular tension. Meprobamate was also disappointing when used in conditions of muscle spasm such as spasmodic torticollis, hysterical spasms, and writer's cramp.

The blood pressure was unaffected, both at raised and at normal levels. In six elderly patients with hypertension of the order of 220/120, who were also suffering from anxiety, two months' treatment with meprobamate did not alter the level of the blood pressure at all.

We were able to confirm the findings of other workers that this drug helps tense and anxious patients to get off to sleep without their having to take other medication. We also noticed that those tense and anxious patients who had symptoms of undue irritability were particularly helped by meprobamate, both generally and when the irritability was associated with pre-menstrual tension. Five women with pre-menstrual tension experienced definite relief from the drug. These findings in the latter syndrome must be accepted with some reserve in view of the good response of this condition to a variety of drugs. The irrational irritability and outbursts of temper in five psychopaths also seemed to be helped by meprobamate. As psychopaths are so notoriously difficult to treat it would appear that further work is merited to confirm whether in fact this drug would be of help over a longer period of time.

A quite general finding was that severe anxiety states did not respond as well as the milder ones. In these more severe cases, increasing the dose often caused side-effects, usually drowsiness or "limpness," without relief of anxiety symptoms. As a rule, when no therapeutic effect resulted from the usual dose, it did not do so by increasing the dose. The exceptions to this were strongly built patients with considerable "inner tension," three of whom tolerated 800 mg. of meprobamate three times a day, with another 800 mg.

at night, without side-effects. In general no serious side-effects were observed. Tiredness was sometimes complained of, and in five patients transient urticarial rashes occurred soon after taking the first tablet, thus suggesting a primary or cross sensitivity reaction rather than an acquired allergy.

Although patients in the anxiety and tension group were helped most, some benefit occurred in other groups. This benefit was noted in reactive, although not in endogenous, depression. Meprobamate was also tried in 15 patients with endogenous depression as a premedication for modified electric convulsion therapy, 400 mg. being given an hour before the treatment. No marked effect was noted in the allaying of apprehension in these patients nor in the shortening of the post-E.C.T. period of confusion, although Thal (1956) reports favourably on meprobamate in this respect. Thal was, however, reporting on straight E.C.T. in psychotic patients.

Only minor improvement was noted in hysterical reactions, this improvement being confined to three women with globus hystericus who felt worse when the drug was discontinued. When treatment was resumed with inert tablets no benefit was noted, although this occurred as soon as the active drug was reintroduced.

In the classical type of obsessive-compulsive neurosis, a slight improvement occurred in some patients with obsessional thinking. They became less aware of the obsessional thoughts or found the tension associated with them diminished. The motor forms (compulsive handwashing, etc.) were unaffected. Feelings of unreality were slightly relieved in one man; in six other patients they were unchanged.

Double Blind Trial Comparing Meprobamate with an Inert Tablet

The degree of improvement we found in the group of anxiety and tension states (58%), although greater than in the other groups, need not be due to the pharmacological effect of meprobamate, but could be due to the total therapeutic situation of the patient attending hospital and receiving advice. It is often said that any degree of improvement involving up to one-third of the patients might be due to placebo effects, and above one-third to a specific drug effect. In fact Wolf and Pinsky (1954) reported an improvement in 20–30% of patients acting as their own controls, irrespective of whether they were receiving mephenesin or inert tablets. Tibbetts and Hawkings (1956) reported a 60% rate of improvement irrespective of whether an active or inert substance was given. Our figure of 58% improvement might therefore lie within the range of a purely placebo response.

To decide whether meprobamate had any pharmacological superiority over an inert tablet in chronic anxiety states, a double blind trial was carried out; meprobamate and an inert tablet indistinguishable from it in appearance were given alternately to 26 patients with symptoms of anxiety and tension, who thus acted as their own controls. There were 11 men and 15 women, whose average age was 39. The criteria for selection were that they should not be taking other drugs at the time of the trial and that their illnesses should not have fluctuated appreciably over the preceding year.

The drug and inert tablets were prescribed under code names, the true identity of the tablets being known only by the pharmacist until the end of the trial. Half the patients were given the active drug to begin with, half the inert substance. At each attendance the alternative substance was substituted. The dose given initially was one tablet three times a day with one or two tablets at night if necessary. Where adjustments had to be made in the dosage for therapeutic effect or because of side-effects (and side-effects were reported by patients both on the active and on the inert tablets) the corresponding adjustment was made in the dose of the other substance at the patient's next attendance. No other drugs were allowed during this trial, which lasted six weeks.

The number of comparative observations on meprobamate and inert tablet fell short of those theoretically possible. Some patients did not attend again, others did not take the tablets regularly or discontinued them because of side-effects, or took other drugs in addition. However, 71 comparative observations were obtained, as shown in Table II.

TABLE II

	Meprobamate	Control	Total
Benefit	21	12	33
No benefit ..	14	24	38
Total ..	35	36	71

$\chi^2 = 5{\cdot}05$. d.f. = 1. $P = 0{\cdot}025$.

These results show a statistically significant superiority of meprobamate over the inert tablet under the particular conditions of this trial. They would suggest that our results in the uncontrolled clinical trial were due, at any rate in part, to a specific pharmacological effect of the drug.

Double Blind Trial Comparing Meprobamate with Sodium Amylobarbitone

At the time we started to use it, meprobamate cost our hospital dispensary about 24 times as much as an approximately equivalent therapeutic dose of a short-acting barbiturate. It is important, therefore, to try to find out whether it has sufficient therapeutic superiority to make its use in place of much cheaper drugs worth while.

Selling (1955) reported that 19 of his patients who had previously taken phenobarbitone were given meprobamate and all came to prefer the new drug. Although we found that meprobamate is an acceptable drug to most patients, nevertheless 17 asked to return to the drugs they had previously taken; these were mostly barbiturates or chlorpromazine; and two patients also stated that they found a bromide mixture more effective. On the other hand, 21 patients reported that meprobamate was the most effective drug they had had.

Some of these preferences could be due to prejudice, chance, or undesirable dependence. We therefore decided to compare the effects of meprobamate with those of sodium amylobarbitone on a double blind basis, neither doctor nor patient knowing which drug was being given, and the true identity of the substances being known only to the pharmacist. The tablets used were identical in appearance. The doses in each tablet were 1 gr. (65 mg.) of sodium amylobarbitone and 400 mg. of meprobamate. These doses were thought to be comparable in therapeutic effect after a small pilot trial during which patients reported about equal relief of symptoms on these doses given successively.

Fifty-one patients with psychoneurosis were treated, 20 men and 31 women, with an average age of 41. They had not been included in the other trials and were mostly new patients. The dose of both substances given was one tablet three times a day, with one or two tablets at night. The patients again acted as their own controls, half being given meprobamate first and half sodium amylobarbitone. The alternative substance was given at each attendance until a comparison was obtained.

Ten patients fared best when receiving sodium amylobarbitone and nine when receiving meprobamate, although some relief was experienced from both drugs. Three were symptom-free only when they were having meprobamate, four only when receiving sodium amylobarbitone. Nine received about equal benefit from both preparations and 16 no benefit from either. There were no significant differences in sleep, eight patients stating that they slept better while having meprobamate, five when taking sodium amylobarbitone (corrected $\chi^2 = 0.61$; $P = 0.44$). In the remainder no difference was noted.

These results seem to indicate that if either drug is given for short periods to most patients with anxiety and tension about equal benefit will accrue. Some few patients do benefit, however, from meprobamate only and others from sodium amylobarbitone only.

Only longer trials can show whether meprobamate is superior to barbiturates in effectiveness and in freedom from toxicity when given over longer periods. There is little doubt that short-acting barbiturates can become drugs of dependence and addiction; some patients need to go on increasing the dose, and a barbiturate-induced tension state finally results. Barbiturates are also often used in attempts at suicide. If, on longer trial, meprobamate proves to be free from such defects, it could be a useful alternative to other tranquillizing drugs. It is unlikely, however, that any drug which relieves anxiety will ever be entirely free from the disadvantages of producing dependence or causing symptoms on withdrawal.

Summary

Meprobamate is a new tranquillizing drug which in a clinical trial on 151 psychiatric out-patients produced some relief of symptoms in 58% of patients with chronic anxiety and tension states. The drug was not as effective, however, when anxiety or agitation were severe.

A double blind trial was also carried out on 26 patients with states of anxiety and tension, so as to compare the effects of meprobamate with an inert tablet. There was statistically significant therapeutic superiority of meprobamate over the inert tablet.

In a separate double blind trial, meprobamate was also compared with sodium amylobarbitone in a further 51 patients mostly suffering from anxiety and tension states. No marked differences were found in effectiveness between these two drugs. However, clinically, meprobamate often seemed more useful than a barbiturate where irritability was a marked feature.

No serious side-effects were observed, but transient skin rashes occurred in five of the patients treated (2.5%).

We thank Dr. William Sargant for helpful advice, the hospital dispensary staff for their co-operation in carrying out the double blind trials, and John Wyeth Ltd. for generous supplies of "equanil" and control tablets.

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This year the Royal Women's Hospital, Melbourne, celebrated its centenary, the main feature of the celebrations being a week-long scientific and clinical meeting in August on topics of obstetrical and gynaecological interest. Among the distinguished contributors was Professor A. M. CLAYE, of Leeds, who has been working in the hospital during its centenary year. On the last day of the meeting there was a full discussion on obstetric infections. The importance of spore-bearing anaerobes was stressed, and Professor Claye made the point that in Australia the fall in obstetric mortality due to infection did not occur until the introduction of penicillin, whereas in England the sulphonamides achieved this result some years earlier. In Australia the care of the newborn, it appears, is usually left to the obstetrician, and at the meeting much enthusiasm was shown for keeping the babies with their mothers as a means of preventing neonatal sepsis.

THE HYPOTENSIVE ACTION OF MECAMYLAMINE

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Hypotensive therapy with ganglion-blocking compounds, alone and in combination with the rauwolfia alkaloids, has greatly improved the prognosis in malignant hypertension (McMichael and Murphy, 1955; McQueen and Smirk, 1956) and in many patients with severe non-malignant hypertension (Doyle and Smirk, 1955). Most agree that pentolinium is the most generally effective single substance at present available; it has largely replaced hexamethonium as the ganglion-blocking drug of choice in most cases of hypertension, for it has a longer action than hexamethonium; furthermore, it can be successfully used by mouth in 60–70% of patients with hypertension (Doyle and Smirk, 1955), whereas oral hexamethonium controls the blood pressure adequately in only 20–25% of patients (Kilpatrick and Smirk, 1952). Even with pentolinium, however, control of blood pressure can be more easily obtained by parenteral administration than by mouth, for, like hexamethonium, it is poorly absorbed, the oral dose being up to 20 times as great as the parenteral dose (Smirk, 1953; Freis *et al.*, 1954). Moreover, some patients, more especially those requiring large doses, may develop severe constipation with diminished response; this is often followed by diarrhoea with episodes of hypotension, due presumably to increased intestinal absorption.

The reports of Freis (1955) and Ford *et al.* (1956) that a new ganglion-blocking compound, mecamylamine, was fully absorbed from the gastro-intestinal tract, and that it had been successfully used in the treatment of hypertension, were of considerable interest.

Mecamylamine ("inversine") is 3-methylamino*iso*-camphane, a secondary amine which has been reported to be rather less active than pentolinium in dilating the pupils, but to be more active than pentolinium in abolishing nicotine convulsions in mice (Stone *et al.*, 1956).

We report here the preliminary results of a clinical trial of this substance in 45 hypertensive patients for periods of up to 10 months. Twenty-five have been treated for 6 to 10 months, and 15 for from three to six months. The remaining five discontinued treatment within one month of beginning it.

Methods

We have studied the hypotensive action and the side-effects of oral mecamylamine and have compared them with the effects of subcutaneous and, in some instances, oral pentolinium. Some of the patients selected to

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