during the day. In almost all cases there was a 12-hour interval during the night when no treatment was given. This dose was regarded as adequate for boys weighing 4½–7 st. (28.6–44.5 kg.). A few very big boys weighing 7–9 st. (44.5–57.2 kg.), and some with complications, were given 500 mg. q.d.s. Treatment was continued for five days in uncomplicated cases of pharyngitis, and for a week or 10 days in those with complications. The treatment was stopped in two cases (see Table I).

Blood for penicillin levels was taken once from each boy during treatment. The intervals between the previous dose of phenethicillin and venepuncture varied from 10 to 310 minutes. The concentration of antibiotic in the blood was determined by the tube-dilution method, using the Oxford H staphylococcus, and standard solutions of penicillin G and phenethicillin for comparison. The control solutions of penicillin G and phenethicillin gave identical results in every case.

TABLE II.—*Penicillin Levels in Blood*

Case No.	Age (Years)	Weight		No. of Doses of Phenethicillin Before Bleeding	Interval Between Previous Dose and Bleeding (Minutes)	Blood Penicillin (μg./ml.)
		lb.	kg.			
1	8	64	29.0	9	10	4
2	11	89	40.4	13	25	4
3	10	70	31.8	9*	30	2
4	11	71	32.2	17	40	2
5	12	81	36.7	5	40	4
6	8	66	29.9	5	50	8
7	12	106	48.1	9	65	4
8	9	71	32.2	7*	70	8
9	10	75	34.0	9	75	4
10	10	79	35.8	2	78	4
11	9	72	32.7	9	80	8
12	10	70	31.8	9	85	8
13	11	60	27.2	7	100	16
14	10	98	44.5	4	105	4
15	10	87	39.5	4*	108	16
16	10	66	29.9	4	185	2
17	9	67	30.4	4	190	1
18	12	110	49.9	3	195	0
19	9	63	28.6	4	220	1
20	8	62	28.1	4	220	0.25
21	11	66	29.9	4	230	0.5
22	8	64	29.0	4*	230	0.5
23	12	95	43.1	12	255	1
24	12	91	41.3	4	255	0.5
25	11	90	40.8	16	265	0
26	10	75	34.0	16	270	0.12
27	9	82	37.2	4	285	0
28	13	84	38.1	6	290	0
29	9	100	45.4	6	295	0
30	11	85	38.6	2	300	0
31	10	68	30.8	4	310	0

*These doses were 500 mg. All other doses were 250 mg. up till the time the blood was taken.

Results

The results are recorded in Table II, from which it will be seen that the blood level rises rapidly after taking the tablets, and drops again between three and four hours to very low or undetectable levels, regardless of the number of doses previously given. The absorption is obviously rapid, and the blood levels attained are comparable with those of penicillin G injected parenterally.

The clinical response to phenethicillin was very satisfactory. The patients with uncomplicated pharyngitis were afebrile and asymptomatic within 48 hours. The boy with lobar pneumonia responded as well as one would have expected had he been treated with penicillin by injection. The other complications cleared quickly (see Table I), except the cases of sinusitis. Three boys were afebrile within 48 hours, and symptoms settled after a further few days. Three boys did not respond to phenethicillin in a dose of 250 mg. four-hourly, and in two the fever remained high in spite of increasing the dose to 500 mg. q.d.s. From both, penicillin-resistant staphylococci were isolated, and they made rapid recovery when treated with erythromycin and

tetracycline respectively. Few objections were raised by any of the boys to the new drug. The prospect of not having to have injections (of which several boys had had previous experience) overshadowed the discomfort of one venepuncture for estimation of the blood penicillin level.

Side-effects.—Two boys complained of nausea soon after taking the tablets on an empty stomach, but this passed off after a few days. Three boys had diarrhoea; in two it was very mild, and in one who was receiving 500 mg. q.d.s. it was fairly severe, but it stopped when the dose was halved. In every case the diarrhoea ceased when the course of tablets was completed. One child was lethargic while receiving phenethicillin, but this ceased after treatment.

Summary

In a residential preparatory school an outbreak of severe pharyngitis affected 31 boys, 14 of whom had some complications. Group A β -haemolytic streptococci were isolated from most of the patients. All patients were treated with phenethicillin, and the clinical results were satisfactory. Blood levels of penicillin during therapy were equivalent to those expected from parenteral administration of penicillin G. Phenethicillin was rapidly absorbed, and concentrations up to 16 μg./ml. were obtained. The concentration fell to very low levels after four and a half hours.

We thank Miss N. Lovett, S.R.N., matron of Summer Fields School, for her valuable assistance, and we are grateful to Beecham Research Laboratories, Ltd., for the supplies of "broxil" used in this study.

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A TRIAL OF A NEW MONOAMINE OXIDASE INHIBITOR IN ANGINA PECTORIS

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Dramatic relief of angina pectoris with iproniazid (1-isonicotinyl-2-isopropylhydrazine; "marsilid") was reported by Cesarman (1957). Other early reports were also favourable (Cossio, 1958; Towers and Wood, 1958). The serious risk of liver necrosis from iproniazid later became recognized (*New Engl. J. Med.*, 1958), and recent double-blind trials have shown no improvement of angina (Dewar *et al.*, 1959; Snow and Anderson, 1959; Fife *et al.*, 1960). Iproniazid inhibits monoamine oxidase, and the alleged effect on anginal pain was ascribed to this action. As early enthusiasm for iproniazid has waned, other monoamine inhibitors have been tried in angina, and we here describe a double-blind trial of one of them.

1-Pivaloyl-2-benzylhydrazine ("tersavid") is chemically related to iproniazid. Animal experiments have shown equally powerful inhibition of monoamine oxidase, but it is less toxic than iproniazid. Relief of angina has been reported in preliminary trials.

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Method of Trial

Twenty patients (2 women and 18 men) took part in the trial. Their mean age was 59.5 years (range 46–70 years). All had typical severe angina due to coronary artery disease, constant in degree for at least two months before the trial. Aortic stenosis was also present in two patients, rheumatic aortic incompetence in one, and mitral stenosis in one. The electrocardiogram was abnormal in 16 patients, with evidence of infarction in eight and of ischaemia in the remaining eight. Eleven patients were previously receiving anticoagulants and continued them throughout the trial.

A double-blind cross-over technique was used, each patient acting as his own control. The 20 patients were allocated to two equal groups by a random method. One group took tersavid for a month followed by identical inert tablets for a second month, and the other group took inert tablets followed by tersavid. No other alteration of treatment was made during the period of the trial. At the start of the tersavid period treatment was begun with 150 mg. daily. If there was no improvement in angina after one week, the dose was increased to 250 mg. daily and continued at this level for the next three weeks. The dose of inert tablets was similarly increased if angina continued unchanged after one week of the control period. The patients were seen at fortnightly intervals throughout the trial, when the severity of angina and the number of trinitrin tablets required were recorded. Weight, blood-pressure, evidence of fluid retention, and side-effects were also noted. An electrocardiogram was taken and serum glutamic-oxaloacetic and glutamic-pyruvic transaminase levels were estimated at monthly intervals.

Results

One patient, a man on anticoagulant treatment, died of recurrent myocardial infarction after three days on control tablets. Of the remaining 19 patients, only the one man with aortic incompetence reported improvement in angina with tersavid and no benefit from the inert tablets. Seven patients improved during both trial periods, and in the remaining 11 patients there was no significant change in angina. Three patients had associated intermittent claudication. In one of these—the one patient who reported benefit from tersavid—leg pain also decreased. The other two patients found no change in angina or leg pain.

No side-effects occurred apart from slight dizziness in two patients. There was no change in weight or blood-pressure, and no evidence of fluid retention. The electrocardiograms were also unchanged, and the transaminase levels remained normal.

Discussion

There is real need for a drug capable of producing prolonged relief of angina. The most widely prescribed remedy, pentaerythritol tetranitrate (P.E.T.N.), we have recently tried in high dosage on a double-blind basis with negative results. Twelve patients with angina received 60 mg. of P.E.T.N. three times daily for a month and identical inert tablets for another month. None found improvement on P.E.T.N. and not on control tablets. Similar negative results were reported by Dewar *et al.* (1959).

Recent experience with iproniazid is disappointing, and it may be doubted whether other monoamine

oxidase inhibitors will relieve angina if iproniazid does not. The present trial, in which only 1 out of 19 patients improved while on tersavid and not during the control period, does not indicate that this drug is valuable in angina. However, in a recent trial of β -phenylisopropylhydrazine ("cavodil") (MacKinnon *et al.*, 1960) our experience has been less encouraging. Hepatic damage, with jaundice, developed in one of the 12 patients treated with it.

Summary

A monoamine oxidase inhibitor, tersavid, has been tried on a double-blind basis in 19 patients with angina. Only one patient appeared to benefit.

We are grateful to Dr. Horace Joules and Dr. Keith Ball for help with this trial. The tersavid and control tablets were kindly supplied by Roche Products Ltd.

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Medical Memoranda

Megimated Barbiturates

Partly owing to the wider prescription of barbiturates the mortality and morbidity from overdosage, accidental or suicidal, has risen considerably over the last decade. We are faced with a serious problem: 2,800 hospital cases of barbiturate poisoning were treated in 1949 and 6,000 in 1958. We can, with reasonable certainty, expect an even greater rise over the years ahead. There are two alternatives to combat this rise: either to stop using barbiturates or to safeguard their use. Some measures have, of course, already been taken to control their prescription and use. However, something more is needed, since the number of deaths continues to rise despite these statutory measures.

Attempts have been made to make barbiturates less dangerous by combining them with emetics and stimulants. These combinations appear to have had little success in practice. Following the work on bemegride ("megimide") by Shaw and his co-workers in 1954, over 200 articles appeared on its use in the treatment of barbiturate overdosage. These articles provided confirmation of the effectiveness of bemegride as a functional barbiturate antagonist. It seemed possible, therefore, that a combination of bemegride with barbiturates might lower the potential toxicity of overdosage from barbiturates. Trautner *et al.* (1957) and Gershon and Shaw (1957) were able to show that 10–20% bemegride with barbiturate in tablet form reduced or even prevented the development of coma or of prolonged sleep in doses of up to 2.6 g. of barbiturate. Quite naturally the critical test of whether this combination is effective in preventing death due to gross overdosage can never be performed