With this exception we have little experience of the combined action of bretylium tosylate with other drugs. The addition of pempidine or of trimethidinium in a very few cases seemed to confirm the favourable findings of Smirk and Hodge (1959), and we feel that the whole question of combined treatment with modern hypotensive drugs requires further study. For example, as bretylium increases the sensitivity of the blood-vessels to circulating noradrenaline, it would be of great interest to observe whether the addition of an adrenalytic agent would help in the control or resistant cases.

The mechanism of the minor but annoying side-effects that interfere with the usefulness of this valuable drug also requires further investigation. Although Boura *et al.* (1959) claimed that it has no central action, a severe general asthenia with tremor of the limbs recalling the central effect of mecamlamine occurred in one of our patients one week after she had changed from pentolinium to bretylium tosylate, the symptoms ceasing immediately on reversion to the former treatment. Evanson (personal communication) reports dysarthria associated with severe general muscular weakness in another case.

So far there has been no evidence of a toxic action on the liver, kidneys, or the haemopoietic system, and none of our patients has developed a dissecting aneurysm (Beaven and Murphy, 1956).

The freedom from the more serious side-effects consequent on parasympathetic blockade and depressant central action of other drugs is a conspicuous advantage in the use of bretylium tosylate, and many patients, especially those on high dosage, were most grateful for this relief. As will be seen from Table II, satisfactory and uneventful control of the blood-pressure has been achieved in 71% of our cases, and it must be emphasized that no case of mild or moderate hypertension has been included. We feel, indeed, that bretylium tosylate, with its powerful and sometimes unpredictable action, is out of place in dealing with uncomplicated moderate benign hypertension, especially if the patient is leading an active life.

Judged by the yardstick of its effectiveness in malignant hypertension, this drug has given an encouraging success rate of just over 50% during a period of six to nine months. It is without doubt an important advance in the treatment of severe hypertension.

Summary and Conclusions

By its selective action in blocking the peripheral sympathetic nerves without interfering with parasympathetic transmission, bretylium tosylate offers a new type of treatment in hypertensive disease that is free from some of the serious disadvantages of its predecessors.

Using this drug in 75 cases of severe hypertension over a period of nine months, we have obtained successful control in 71%, including 7 out of 13 cases of malignant hypertension.

The main disadvantages in its clinical use appear to stem from a marked variability in its absorption from the digestive tract. This may lead on the one hand to severe postural hypotension on low dosage or on the other to the necessity for very large doses which expose the patient to a number of minor side-effects. This effect can be countered to some extent by the adjuvant action of hydroflumethiazide. The frequent occurrence

of postural hypotension after physical effort in patients taking this drug makes it unsuitable for the treatment of uncomplicated moderate benign hypertension in active subjects. Its mode of action also makes it ineffective in the recumbent patient.

Administration of bretylium tosylate requires careful supervision, as a collapse of the blood-pressure with fainting is not uncommon when the drug is first introduced, and may occur unexpectedly later. For this reason we do not recommend its use in patients with established coronary or cerebral vascular disease.

We thank Dr. David Long, of the Wellcome Foundation, for supplies of bretylium tosylate (darenthin).

REFERENCES

- Arnold, P., and Rosenheim, M. L. (1949). *Lancet*, **2**, 321.
Beaven, D. W., and Murphy, E. A. (1956). *Brit. med. J.*, **1**, 77.
Bennett, G., Tyler, C., and Zaimis, E. (1957). *Lancet*, **2**, 218.
Boura, A. L. A., and Green, A. F. (1959). *Brit. J. Pharmacol.*, **14**, 536.
—, McCoubrey, A., Laurence, D. R., Moulton, R., and Rosenheim, M. L. (1959). *Lancet*, **2**, 17.
Dollery, C. T., Emslie-Smith, D., and McMichael, J. (1960). *Ibid.*, **1**, 296.
Evanson, J. M., and Sears, H. T. N. (1960). *Ibid.*, **1**, 544.
Harington, M., Kincaid-Smith, P., and McMichael, J. (1959). *Brit. med. J.*, **2**, 969.
Le Quesne, L. P., Hobsley, M., and Hand, B. H. (1960). *Ibid.*, **1**, 141.
Lowe, R. D., and Rosenheim, M. L. (1960). *Lancet*, **1**, 655.
Montuschi, E. (1957). *Proc. roy. Soc. Med.*, **50**, 514.
— (1959). *Lancet*, **2**, 462.
Smirk, F. H., and Hodge, J. V. (1959). *Ibid.*, **2**, 673.
Turner, R., and Lowther, C. (1960). *Ibid.*, **1**, 381.

DRUG PROPHYLAXIS IN MIGRAINE

A CONTROLLED CLINICAL TRIAL

BY

RODNEY GRAHAME, M.B., B.S., M.R.C.P.

Formerly Captain, R.A.M.C.; Junior Specialist in Medicine

From the Cambridge Military Hospital, Aldershot

Migraine, in common with other psychosomatic diseases, is subject to wide variation in severity during the patient's lifetime. The condition is exacerbated under the influence of adverse physical and psychological factors, and it is common experience that relief from these is sufficient in many patients to produce a remission. It follows, therefore, that assessment of any form of drug therapy aimed at the prevention or modification of attacks is beset with obvious practical difficulties: for not only is the disease influenced by many variable factors but also, as Graham (1956) has pointed out, it is "notorious for responding temporarily to any new and encouraging form of therapy."

It is therefore essential that any attempt to demonstrate the effect of drug treatment in migraine must be made with full statistical control by applying the technique of the double-blind trial.

Current Views

The idea that reserpine, an alkaloid contained in *Rauwolfia serpentina*, might be employed in the preventive treatment of migraine arose from light that has been shed on its pharmacology by recent research. Known and used in the Orient for centuries, and in recent years achieving universal use in the treatment of hypertension and a variety of psychiatric disorders, reserpine was thought to exert its effect on the central nervous system (Bein, 1953).

It has become increasingly clear since experiments initially conducted on rabbits and later applied to man by McQueen *et al.* (1955) that the peripheral vasodilatation is in part effected by direct action. Maxwell *et al.* (1956, 1957) concluded, using anaesthetized dogs premedicated with a ganglion-blocking agent, that the response to reserpine was by direct peripheral action on the vessels, and suggested an adrenaline release. Since then it has been conclusively demonstrated that reserpine depletes adrenaline and noradrenaline stores (Kroneberg and Schumann, 1957, 1958) in the adrenal gland (Carlsson and Hillarp, 1956; Mirkin, 1958; Molinatti *et al.*, 1958; Camanni and Molinatti, 1958; Camanni *et al.*, 1958), arterial wall (Burn and Rand, 1957, 1958), blood (Burger, 1956), brain (Holzbauer and Vogt, 1956; Brodie *et al.*, 1957; Shore *et al.*, 1957), sympathetic ganglia (Muscholl and Vogt, 1958), and the heart (Bertler *et al.*, 1956). Similarly, serotonin is released from a variety of different tissues, including the brain (Brodie *et al.*, 1957) and the intestine (Fletscher *et al.*, 1955).

In view of their finding of catechol amine release from arterial walls after the administration of reserpine, Burn and Rand suggested that this discovery might have clinical application in various disorders where the underlying mechanism is a paroxysmal vasoconstriction. Yet in studying the literature it is apparent that very little work has been done in this field. Scalfi *et al.* (1956) treated some 14 patients suffering from various disorders of the peripheral vasculature (including four with Raynaud's disease) with reserpine and, using photoplethysmography, noted an objective improvement in nine (including three of the patients with Raynaud's disease).

Friedman (1955) treated with reserpine 58 patients suffering from migraine, and only 22 of them showed an appreciable improvement. Of 12 patients given a control tablet, seven improved. Barrett and Hansel (1955) treated 21 patients suffering from various kinds of headache (including two with migraine) in an uncontrolled trial, and concluded that "reserpine appears to be effective in all vascular headaches regardless of their basic mechanism."

The value of sedatives alone in the prophylaxis of migraine has been pointed out by Kunkle and Wolff (1951), and in particular phenobarbitone has been strongly advocated by Brain (1951).

It was therefore decided to assess the relative merits of reserpine and phenobarbitone in the prevention of migraine attacks by comparing their effect with that of a placebo and with that of no treatment at all.

Patients Investigated

In January, 1959, a migraine clinic was set up at the Cambridge Military Hospital in order to conduct the trial. All medical officers in the Aldershot area were requested to refer suitable patients, and of those interviewed, 43 were originally regarded as suitable. Criteria for inclusion were strict, and the decision rested on a firm diagnosis of migraine coupled with a high order of frequency of attack at the commencement of the trial. In 15 cases the six-months trial period was not completed. In some instances this was because the men were posted away from the area. The remainder withdrew at their own request.

Twenty-eight patients (26 males and 2 females) completed the six-months observation period, the women

being wives of serving soldiers. The ages varied from 15 to 46 years, average 23.8 years. Details of the group are as follows:

Age distribution	{	15-9	20-11	25-3	30-1	35-2	40-1	45-49
Rank	..	Boys	Privates	N.C.O.s	Officers			
		2	16	6	2			
Length of service	{	<1 year		1-2 years		10-20 years		
		17		5		4		
Enlistment	..	Regular	Short service	Nat. Service	Boy soldiers			
		6	1	17	2			

At the initial visit a full history and clinical examination was undertaken. Physical examination, which included blood-pressure estimation and listening for an intracranial bruit, did not reveal any abnormality.

The headache was unilateral in 25 cases and bilateral in three. Of the former, 21 experienced the attack on one side only, the other four being affected on either side, with a predilection for one side in three of these. Of the 21 patients who were able to locate the onset of the pain, the sites were: frontal, 9; retro-orbital, 8; temporal, 3; and occipital, 1.

Nausea was experienced in 23 patients and was severe in 12. Vomiting occurred invariably in 10 patients and occasionally in a further five. It was absent in 13.

Of the visual disturbances, the characteristic fortification spectra were experienced in 17 patients; photophobia was severe in 18 cases; and significant blurring of vision occurred in five. Field effects occurred in five patients (homonymous hemianopia in four, and bitemporal hemianopia in one). Other focal neurological symptoms were encountered, four patients complaining of focal numbness, three of focal paraesthesiae, one of focal pain, and two experienced transient hyperacusis. Complete absence of visual or neurological symptoms with the onset of the attack occurred in only one patient.

A possible relevant past history was forthcoming in only three patients (meningitis, head injury, and "nervous breakdown" in one each). A family history of migraine was elicited in 13 patients (mother in nine, father in one, aunt in two, and grandmother in one).

The frequency of attack at the onset of the trial was one or more per week in 22 cases, and between one and three per month in the remainder.

An inquiry into previous treatment revealed that five had had no previous medical treatment, 14 had been treated with ergotamine, nine with phenobarbitone, four with aspirin, and one with pethidine.

All patients were asked to mention any precipitating factors: nine mentioned anxiety, two relaxation, three travel, five concentration or study, five physical exertion, and one constipation.

Method

In the first half of the trial the patient's response to maintenance therapy with reserpine (0.25 mg. three times daily after meals) over a six-weeks period was compared with that of an identical inert tablet over the same period of time. Thus the patient was acting as his own control. Half the patients received reserpine over the first period, the other half receiving the placebo. Random selection of cards from a pack determined whether the patient began with the drug or the placebo. At the end of six weeks, those who had been given the reserpine were switched to the control, and vice versa. The identity of the tablets that the patients were receiving during this half of the trial was closely guarded by the pharmacists from me until the trial was

completed. Each patient was seen in the clinic at fortnightly intervals to record progress and to keep a watch for the possible appearance of toxic manifestations.

At the end of this half of the trial each patient was given a third yet identical tablet containing phenobarbitone ($\frac{1}{2}$ gr. (32 mg.) three times daily, after meals) and the progress recorded. In the final six-weeks period the patient was observed while receiving no maintenance therapy. During the whole period under trial the patients were asked to note in a diary each attack as it occurred, and in this way an accurate record of both frequency and severity of the migraine attacks was available. In view of the fact that this was an evaluation of prevention of attacks, no special restrictions were placed on symptomatic treatment of the individual migraine headache with aspirin, codeine, or ergotamine tartrate. The patients' medical officers were requested to refrain from prescribing any other regular treatment, particularly barbiturates, during the trial. Clearly, as in any investigation of this nature, one had to place complete reliance on the patients to take their prescribed tablets. It should be pointed out, however, that in the present trial there was no instance in which there was the slightest reason to doubt the patient's integrity.

Results

Reserpine and Placebo

The number of migraine headaches experienced by the individual patients during the first half of the trial are recorded in Table I. The numbers in parentheses refer to mild attacks.

TABLE I

Case	Reserpine	Placebo	Case	Reserpine	Placebo
1	0	4	15	16	17
2	0 (1)	0 (2)	16	2 (1)	10 (3)
3	3 (2)	1 (1)	17	4 (1)	1 (2)
4	0	4	18	0	2
5	0 (1)	3	19	1 (1)	2 (6)
6	0 (2)	0 (4)	20	2 (4)	9
7	29	21	21	42	41
8	2	4	22	1	0
9	0	0 (2)	23	1	1 (5)
10	13	15	24	22	21
11	0	7	25	8	6
12	1 (1)	7	26	4 (2)	5 (1)
13	2 (5)	7 (2)	27	3	8
14	7 (2)	6	28	7 (1)	7 (1)

It will be appreciated that this half of the trial represents the fully randomized part of the investigation. It follows, therefore, that it is the only part of the trial that would be likely to yield any statistically valid comparisons.

The choice of the most suitable method of interpretation of the results posed a problem. At first sight it might appear that a formal "t" test using the differences in the numbers of headaches should be adopted. However, because the sample consisted of patients with such a wide variation in the number of attacks, those with the largest numbers would give undue bias to the results as a whole. For example, Patient No. 7 experienced 29 attacks while on reserpine compared with 21 on the placebo. Though his frequency of attack was reduced on the latter by only 36%, by virtue of the numerical difference of eight he would effectively cancel out, say, Patients Nos. 1 and 4, both of whom were kept free of migraine while receiving reserpine. In view of this tendency the "t" test was not regarded as appropriate for this type of sample.

Instead, the degree of improvement derived from reserpine as compared with placebo, or vice versa, was

expressed as a percentage reduction in frequency of attack. Since a prophylactic drug that failed to reduce the frequency by one-half was unlikely to be of much clinical value, *the chosen arbitrary criterion of improvement was a reduction of 50% or more in the frequency of attack.* Anything less than 50% was regarded as unchanged. For the purposes of calculation a mild attack was counted as being equivalent to one-half of a severe one.

If these criteria were applied to the results the following observations may be made.

Comparison of reserpine with the placebo (crossover trial) showed:

Improved by reserpine	..	..	..	14 (50%)
Improved by placebo	..	..	..	3 (10.7%)
Unchanged	..	..	..	11 (39.3%)
				28 (100%)

If this result is applied to the significance chart for percentages devised by Rosenbaum (1959) the difference between reserpine and the placebo is significant at the 5% level of significance.

Phenobarbitone and Placebo

In the third six-weeks period all patients received phenobarbitone. The number of attacks occurring in this period is shown in Table II. For the purposes of comparison the corresponding numbers relating to the period on the placebo are also shown. Patients Nos. 13 and 27 were posted away from the area, so that their response to phenobarbitone could not be tested. As they both had already provided useful information in the remainder of the trial, it was not thought justifiable to reject them. In both cases the results relating to the final stage were later made available by letter.

TABLE II

Case	Phenobarbitone	Placebo	Case	Phenobarbitone	Placebo
1	0	4	15	19	17
2	1	0 (2)	16	2	10 (3)
3	0	1 (1)	17	3	2 (2)
4	0 (1)	4	18	0	2
5	0 (1)	3	19	1 (2)	2 (6)
6	2	0 (4)	20	3 (6)	9
7	23	21	21	41	41
8	4	4	22	0	0
9	1	0 (2)	23	0	1 (5)
10	11	15	24	22	21
11	0	7	25	12	6
12	0	1	26	3 (1)	5 (1)
13	—	7 (2)	27	—	8
14	10	6	28	1 (1)	7 (1)

Comparison of the placebo with phenobarbitone after a period of time had elapsed (six weeks in half the patients and three months in the remainder) showed:

Improved by placebo	..	..	..	1 (3.85%)
Improved by phenobarbitone	..	..	..	11 (42.3%)
Unchanged	..	..	..	14 (53.85%)
				26 (100%)

The difference is significant at the 5% level of significance and could be a true effect. Since the two phases of treatment bore a constant time-relationship with each other and not a randomized one, the result could also be due to the passage of time.

Placebo and No Treatment

The results of the final phase of the trial are shown in Table III, together with the corresponding results relating to the placebo.

TABLE III

Case	No Treatment	Placebo	Case	No Treatment	Placebo
1	2	4	15	3	17
2	2	0 (2)	16	0 (6)	10 (3)
3	1 (1)	1 (1)	17	5	1 (2)
4	0	4	18	0	2
5	1	3	19	3 (1)	2 (6)
6	1	0 (4)	20	7	9
7	3 (5)	21	21	5 (16)	41
8	5	4	22	0	0
9	0	0 (2)	23	4	1 (5)
10	7	15	24	20	21
11	0	7	25	12	6
12	1	7	26	1 (3)	5 (1)
13	4	7 (2)	27	5	8
14	8	6	28	5	7 (1)

Comparison of the placebo with no treatment after a period of time (either three months or four-and-a-half months) showed:

Improved by placebo	..	..	3 (10.7%)
Improved by no treatment	..	..	14 (50%)
Unchanged	..	..	11 (39.3%)
			28 (100%)

The result is statistically significant at the 5% level of significance, and similarly could be a true effect or be due to the effect of the passage of time.

Other Comparisons

The other possible comparisons—namely, phenobarbitone with no treatment, reserpine with no treatment, and reserpine with phenobarbitone—do not reveal any significant differences.

If the combined reserpine and phenobarbitone results are compared with those with the placebo, and the most favourable drug is taken in each case, the following observations may be made.

Improved by reserpine or phenobarbitone	16 (57.2%)
Improved by placebo	0
Unchanged	12 (42.8%)

This result is significant at the 1% level of significance, though, as before, when phenobarbitone is taken the possibility that the effective improvement could be due to the passage of time cannot be ruled out.

Side-effects

Side-effects were noted in 13 patients at some time during the trial. Without exception they were trivial in nature and tended to occur during the first days of treatment. In no case was it necessary to interrupt the trial on their account. In fact, they were rather more common with the control than with either of the drugs. They may be summarized as follows:

Reserpine.—Mild depression, 1; mild indigestion, 1; feeling of well-being, 1; feeling "shaky," 1; nasal congestion, 1; slight dazed feeling, 1.

Phenobarbitone.—Slight dizziness, 1; tiredness, 2.

Placebo.—Mild depression, 1; dizziness on rising, 2; feeling on edge, 2; slight ingestion, 1; feeling tired, 2; bad dreams, 1.

Discussion

It will be appreciated that this series differs in two important respects from a completely unselected series of patients suffering from migraine. Firstly, there was an overwhelming preponderance of males (93%) in a disorder where 70% of the sufferers are female. Secondly, there was a high order of frequency of attack—namely, 21% experienced attacks less often than once

a week compared with 55% in an unselected series (Friedman *et al.*, 1954). While the former discrepancy was unavoidable in a Service population, the latter was deliberate because of the limited duration of the trial.

The results suggest that both reserpine and phenobarbitone are of value in reducing the frequency of migraine in certain patients as compared with a dummy tablet. In this trial the proportions improved were 50% and 42.3% respectively. With regard to the reserpine the effect is a true one, whereas with phenobarbitone, because its administration was not randomized, the effect could be due to the passage of time. However, as there is no apparent reason why such a large number of patients should all develop a remission at that time, the effect is likely to be a true one.

It is further suggested that a larger percentage of migraine sufferers (in this trial 57.2%) might benefit from one or other of these two drugs administered over different periods. It is observed that of the 15 not improved by phenobarbitone, five were improved by reserpine; and of the 14 unchanged by reserpine, three improved on phenobarbitone. A point of interest is that among 10 patients unresponsive to either form of therapy were the five most severe cases, these experiencing between two and seven attacks a week.

It is perhaps surprising to find that patients were worse on the placebo tablet and when they received no maintenance therapy. Again this could possibly be a time effect, and, for the same reasons mentioned above in connexion with phenobarbitone, this cannot be ruled out. Should it be a true effect it would appear to produce the opposite result to the one expected. Possibly the mere taking of frequent tablets, constantly reminding the patient of his complaint, might be the mechanism of the increased frequency. This might also explain the increase of reported side-effects with the placebo. The coinciding of the onset of the warm summer of 1959 with the final stage of the trial is another possible explanation of the general improvement.

It is not possible to comment on the basis of this work or whether the beneficial effect of reserpine in migraine is mediated through its central sedative action or through its effect of catechol amine release from peripheral arterial walls.

Summary

In a controlled clinical trial the response of 28 patients suffering from severe migraine to prophylactic maintenance therapy with reserpine, phenobarbitone, and a placebo tablet was assessed. The response to reserpine and phenobarbitone was favourable in 14 and 11 patients respectively. 16 patients were improved with one of the two drugs administered over different periods. There was a slight increase in the severity of the condition using a placebo compared with that observed without maintenance therapy.

The recent pharmacology of reserpine is reviewed.

I am indebted to Dr. A. Barham Carter, Adviser in Neurology at the War Office, for his encouragement and guidance in the preparation of this trial and paper; to Mr. S. Rosenbaum, of the War Office, for statistical advice; to the Commanding Officer and pharmacists of the Cambridge Military Hospital for their invaluable co-operation; and to Messrs. British Drug Houses for generous supplies of the tablets specially prepared for use in this trial.

REFERENCES

- Barrett, B. M., and Hansel, F. K. (1955). *Ann. N.Y. Acad. Sci.*, **61**, 250.
- Bein, H. J. (1953). *Experientia (Basel)*, **9**, 107.
- Bertler, A., Carlsson, A., and Rosengren, E. (1956). *Naturwissenschaften*, **43**, 521.
- Brain, R. (1951). *Diseases of the Nervous System*, 4th ed. Oxf. Med. Publ., London.
- Brodie, B. B., Olin, J. S., Kuntzman, R. G., and Shore, P. A. (1957). *Science*, **125**, 1293.
- Burger, M. (1956). *Helv. physiol. pharmacol. Acta*, **14**, C. 13.
- Burn, J. H., and Rand, M. J. (1957). *Lancet*, **2**, 1097.
- (1958). *Brit. med. J.*, **1**, 903.
- Camanni, F., Losana, O., and Molinatti, G. M. (1958). *Experientia (Basel)*, **14**, 199.
- and Molinatti, G. M. (1958). *Acta endocr. (Kbh.)*, **29**, 369.
- Carlsson, A., and Hillarp, N. A. (1956). *K. fysiogr. Sölsk. Lund Förh.*, **26**, 8.
- Fletscher, A., Shore, P. A., and Brodie, B. B. (1955). *Science*, **122**, 374.
- Friedman, A. P. (1955). *Neurology*, **5**, 805.
- von Storch, T. J. C., and Merriitt, H. H. (1954). *Ibid.*, **4**, 773.
- Graham, J. R. (1956). *Treatment of Migraine*, Little, Brown, Boston.
- Holzbauer, M., and Vogt, M. (1956). *J. Neurochem.*, **1**, 8.
- Kroneberg, G., and Schumann, H. J. (1957). *Arzneimittel-Forsch.*, **7**, 279.
- (1958). *Arch. exp. Path. Pharmacol.*, **234**, 133.
- Kunkle, E. C., and Wolff, H. G. (1951). In *Modern Trends in Neurology*, edited by A. Feiling. Butterworth, London.
- McQueen, E. G., Doyle, A. E., and Smirk, F. H. (1955). *Circulation*, **11**, 161.
- Maxwell, R. A., Plummer, A. J., Osborne, M. W., and Ross, S. (1956). *J. Pharmacol.*, **116**, 42.
- Ross, S. D., Plummer, A. J., and Sigg, E. B. (1957). *Ibid.*, **119**, 69.
- Mirkin, B. L. (1958). *Nature (Lond.)*, **182**, 113.
- Molinatti, G. M., Camanni, F., and Losana, O. (1958). *Arch. int. Pharmacodyn.*, **116**, 483.
- Muscholl, E., and Vogt, M. (1958). *J. Physiol. (Lond.)*, **141**, 132.
- Rosenbaum, S. (1959). *Appl. Statist.*, **8**, 45.
- Scalfi, L., Jacono, A., and Iuliani, G. (1956). *G. Clin. med. (Parma)*, **37**, 1635.
- Shore, P. A., Olin, J. S., and Brodie, B. B. (1957). *Fed. Proc.*, **16**, 335.

Preliminary Communications

Ethionamide

The Clinical Trials Committee of the Research Committee of the British Tuberculosis Association has for the past 12 months been investigating the use of ethionamide (2-ethylthioisonicotinamide; "1314") with cycloserine or pyrazinamide in patients with advanced pulmonary tuberculosis in whom treatment with streptomycin, P.A.S., and isoniazid has failed. The results will be published in full when the study has been completed; but some important findings have already emerged and justify a preliminary report at this early stage.

Treatment.—All patients have been treated initially in hospital. None of them have previously received the two drugs with which they were treated in this investigation. They have received 500 mg. of ethionamide daily in two doses of 250 mg. in enteric-coated tablets morning and evening, with either cycloserine (0.5 to 1 g., according to body weight in two equal doses daily) or pyrazinamide (2–3 g., according to body weight in two equal doses daily).

Bacterial Resistance.—All resistance tests have been carried out in the same laboratory.

Sensitivity Before Treatment.—Sensitivity tests have been done on pretreatment cultures from 26 patients in the pyrazinamide/ethionamide group. The cultures obtained from two patients had resistance ratios (R.R.)* to ethionamide of 4 and 8 respectively; the cultures were sensitive to pyrazinamide (R.R. $\frac{1}{4}$ and $\frac{1}{2}$). They

were treated with ethionamide and pyrazinamide, and in both cases sputum remained positive and the cultures became less sensitive to pyrazinamide (R.R. >8 , >16). The cultures from three patients had resistance ratios to pyrazinamide of 4, >16 , and 32 respectively, but were sensitive to ethionamide (R.R. 1 in each case). They were treated with ethionamide and pyrazinamide, and in all three cases the sputum remained positive and the cultures became less sensitive to ethionamide (R.R. 16, >8 , 32).

Sensitivity tests have been done on pretreatment cultures from 20 patients in the cycloserine/ethionamide group. No cultures had resistance ratios of 4 or more to either cycloserine or ethionamide.

Sensitivity During Treatment.—Cultures with resistance ratios of 4 or more have so far been obtained at some stage of treatment in 10 out of 29 patients in the pyrazinamide group. Decreased sensitivity to pyrazinamide has appeared in nine cases and to ethionamide in five; in most cases change of pyrazinamide sensitivity has appeared first. In the cycloserine group there has been no apparent change in cycloserine sensitivity of any of the cultures; but cultures with decreased ethionamide sensitivity have appeared in 9 out of 23 patients.

In both treatment groups some of the patients from whom resistant cultures had been obtained have later had negative cultures.

Changes in Bacillary Content of the Sputum.—In the pyrazinamide group 13 out of 25 patients had a negative culture at the end of the third month and 8 out of 15 at the end of the sixth month. The corresponding figures in the cycloserine group were 18 out of 21 and 7 out of 11. So far nine of the pyrazinamide and seven of the cycloserine group have had negative cultures for one month or more.

Drug Intolerance.—Gastro-intestinal symptoms attributed to ethionamide have caused interruptions of treatment in many of the patients, and two had to stop treatment entirely because of them. Cycloserine toxicity in two patients and hepatitis attributed to pyrazinamide in six patients have resulted in these eight patients having to stop treatment.

CONCLUSIONS

The investigation was not designed to compare the results of treatment with certain doses of ethionamide and cycloserine and of ethionamide and pyrazinamide. The patients were not randomly allocated to the treatment groups, and from the information at present available it is not known how similar the groups were. It is not justified to compare the results with published results of treatment with cycloserine or pyrazinamide and other drugs. It seems, however, reasonable to draw the following conclusions from this preliminary analysis.

1. Cultures from patients who have not previously received either pyrazinamide or ethionamide may have decreased sensitivity to one or other of them. In such patients, treatment with either drug in combination with another may be unsuccessful and lead to resistance to the companion drug. Whenever possible, therefore, it is desirable to wait for the results of sensitivity tests before starting treatment with either pyrazinamide or ethionamide.

*Resistance ratio is the ratio of the minimum inhibitory concentration of the drug for the test organism to that for the standard sensitive strain (*Myco. tuberculosis* H₃₇Rv).