successful treatment. The results suggest that the hypotensive response to pempidine when given alone runs parallel to the plasma concentration rather than to the total amount in the body; for, despite the fact that the hypotensive response is small and the plasma concentration negligible six hours after an oral dose of pempidine, more than 75% of the dose must still be in the body, because there is no evidence that the drug is metabolized.

Work on rats (Harington *et al.*, 1958; Muggleton and Reading, 1959) has shown that pempidine is concentrated in liver, kidney, and spleen, and it is reasonable to suppose that this may also apply in man. After oral administration of pempidine three processes will account for the characteristic shapes of the response curves obtained with isolated and maintenance doses. These are (1) absorption of the drug, (2) passage into the tissues, and (3) renal excretion. For a single dose the peak of the curve is sharp and the steep falling limb represents loss of drug from the blood by both (2) and (3) because the tissues initially contain no pempidine. With a maintenance dose, however, the curve is broader and initially less steep because the tissues already contain pempidine, so that (2) is relatively unimportant and (3) alone is largely responsible for removal of drug from the blood.

The two uraemic patients were given pempidine twice instead of four times a day. In one of them the peak plasma concentration of pempidine after 2.5 mg. was the same (30 $\mu\text{g.}/\text{ml.}$) as that found in patients with a normal renal function after the same dose. The plasma concentrations showed no tendency to rise from day to day, and, despite the severe impairment of renal function, there was no evidence of pempidine accumulating in the body.

Three-quarters of the out-patients had plasma concentrations of pempidine within $\pm 50\%$ of the expected value, many of the values being much closer. Only two patients had no pempidine in their blood, and one of these had a satisfactory level at a later examination. The sample may be unavoidably biased, since patients may be more inclined to take their doses of pempidine before attending the clinic than at any other times, knowing that a satisfactory pressure, with a good postural effect on standing, wins approval. In several cases where blood-pressure control was not satisfactory a low plasma pempidine concentration was expected, but this did not prove to be the case. Such instances of escape from drug control are known to occur from time to time.

The conscientiousness of patients on long-term regimes of treatment is an important problem of present-day medicine. Other studies, most notably with *para*-aminosalicylic acid in the treatment of tuberculosis, have suggested a greater tendency to depart from the prescribed dose regimes than was indicated by our results. Indeed, Dixon *et al.* (1957) concluded that less than half of their tuberculous patients who were supposed to be taking *para*-aminosalicylic acid were in fact excreting it in their urine. Many factors must play a part: the bulk and side-effects of the drug, the severity of symptoms before treatment, and, perhaps most important of all, the patient's attitude to his disease. Our results show a gratifying degree of co-operation by the patients. It must be remembered, however, that all had severe symptoms of hypertension before treatment; they were therefore probably more

conscientious than patients with only mild hypertension, who are less willing to accept the unpleasant side-effects of ganglion blockage. Careful follow-up in a special clinic where the patients always see the same doctors may also help to create a feeling of mutual trust.

Summary

A new sensitive method of estimation has allowed the measurement of plasma pempidine concentrations over the whole range of dosage used in practice. The plasma concentration, which was remarkably predictable for a given dose, was found to be closely related to the fall in blood-pressure on standing. Data from patients in hospital have been used to predict the plasma concentrations of the drug in out-patients: 75% were found to have concentrations within $\pm 50\%$ of the expected values, suggesting reasonably good co-operation by the patients.

We gratefully acknowledge the valuable technical assistance given by Mr. A. F. Ivens, who carried out the fluorescence measurements. Thanks are due also to Dr. H. W. Reading, who examined the urine samples, and to Dr. H. Campbell and Professor J. McMichael, F.R.S., for their interest and support.

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CHLOROTHIAZIDE IN TREATMENT OF HIGH BLOOD-PRESSURE

RESULTS OF A CONTROLLED TRIAL

BY

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Chlorothiazide has been stated by many observers to enhance the effects of a number of agents used in the treatment of patients with hypertension. Others have found that it reduced the blood-pressure when given by itself. A controlled trial of its effect when used with ganglion-blocking agents has not been carried out, nor, at the time when this work was started, had such a trial been carried out in which chlorothiazide was used alone. We present the results of a double-blind trial of the effect of chlorothiazide used both with ganglion-blocking drugs and alone in the treatment of high blood-pressure. Ganglion-blocking agents produce side-effects which are noticed by the patient and are reported to the observer. This difficulty is commonly held to invalidate an attempt at a controlled trial of these drugs, but in the group of patients here presented it proved not to be of importance.

Methods

Seventeen patients with essential hypertension, of whom 10 were being treated with mecamlamine and

seven with pentolinium, were chosen for the trial. They lived close enough to the hospital to be able to attend once a week without inconvenience. Two patients were later withdrawn; the particulars of the remaining 15 are given in Table I.

TABLE I.—Sex, Age, Blood-pressure Before any Treatment, and Duration of Preceding Treatment of Patients Used in Present Trial

Case	Sex and Age	B.P. Before Treatment	Duration of Treatment (Years)	Neuro-retinopathy Before Treatment
1	M 55	227/130	2½	—
2	M 46	180/125	1	—
3	M 55	200/120	½	—
4	F 48	240/120	5	—
5	M 48	280/150	1	—
6	F 47	220/140	1	—
7	F 59	270/130	1	—
8	M 57	225/125	2½	—
9	F 36	220/130	3	—
10	M 49	210/140	5	—
11	F 48	300/160	4	+
12	M 51	210/130	3	+
13	F 44	240/135	5	+
14	M 53	230/130	4	—
15	F 53	235/135	5	+

The trial lasted for 24 weeks. Each patient, for six weeks at a time, received one of four combinations of tablets. These were: (1) ganglion-blocker plus chlorothiazide; (2) ganglion-blocker plus dummy chlorothiazide; (3) dummy ganglion-blocker plus chlorothiazide; (4) dummy ganglion-blocker plus dummy chlorothiazide. Except that dummy ganglion-blocker was not given for any two successive periods, the order of treatment was random, and was not known to us until the trial was finished. No alteration was made in the diet of any patient.

In addition, and throughout the 24 weeks, each patient received supplementary potassium, initially in the form of 3 g. of potassium chloride as enteric-coated tablets. Later, when it was discovered that one patient was passing these unchanged per rectum, and when other patients were showing low levels of potassium in their plasma, a mixture of potassium chloride, potassium bicarbonate, and potassium acetate in water was given, so that each patient received a supplement of approximately 66 mEq of potassium daily.

The patients were seen once weekly, when the blood-pressure was taken twice in the standing and lying position and the averages for each posture were recorded. Blood samples for the estimation of plasma potassium were taken approximately once a month.

The interval between the last dose of tablets and the measurement of blood-pressure was not the same for all patients. Therefore, though each patient was seen each week at approximately the same time after his last dose of drugs, there was considerable variation in this interval between one patient and another.

Chlorothiazide was given in a dose of 250 mg. three times daily. Since it was unnecessary for our purpose, no attempt was made to give the patients the maximum tolerable dose of ganglion-blocking drug. The dose was not changed from that given before the trial began, except in special circumstances. It was decided that patients should be allowed to reduce the dose of ganglion-blocking agent, or of its dummy, if any started to experience troublesome symptoms of hypotension at any time. Conversely, if during any period the patient developed evidence of hypertensive neuroretinopathy or

a consistently very high diastolic blood-pressure, the dose of presumed ganglion-blocker should be increased. If this produced no fall in blood-pressure, the patient received the drug-combination schedule for the next period of the trial and took this for the ensuing six weeks.

Significance of Side-effects

At the beginning of the trial all patients were told that at some time they might experience dizziness, particularly on standing up, and they were asked to reduce their dose of presumed ganglion-blocking drug if this occurred. They were reminded of this at the beginning of each six-weeks period. No patient was asked about symptoms that might have been due to parasympathetic ganglion blockade, but a number volunteered such information. An analysis of symptoms reported by the patients is given in Table II, which shows how difficult it would have been to deduce from these reports whether or not a patient was taking active or dummy ganglion-blocker at the time.

TABLE II.—Occurrence of Reported Side-effects During Treatment with Active and Dummy Ganglion-blocking Agents

	Ganglion-blocker Reduced Because of Orthostatic Dizziness	Dizziness, Ganglion-blocker Not Reduced	Dryness of Mouth	Blurred Vision	Constipation
No. of patients on active blocker	Mecamylamine, 4 Pentolinium, 4	1	1	0	2
No. of patients on dummy blockers	Mecamylamine, 4 Pentolinium, 2	1	1	3	1

The blood-pressure was recorded as lower than the mean control value for each patient on six of the nine occasions when orthostatic dizziness was reported by patients taking active blocking agents; it was not observed to differ from the mean control value in any of the seven patients taking dummy blocker except in two, who were taking active chlorothiazide. A fall in blood-pressure was recorded on all occasions when patients taking active ganglion-blocker reported symptoms of parasympathetic ganglion blockade: it was recorded in none of the five patients who reported these symptoms when taking dummy ganglion-blocking drugs.

Patients Taking Two Dummy Tablets.—After three weeks on this treatment, one patient (Case 4), whose blood-pressure had been consistently at a level of 210/138, developed a retinal haemorrhage, and she was accordingly given the next combination of drugs in her schedule (Table III). On the other hand, it is of interest that Cases 11, 12, 13, and 15 (Table IV), all of whom had had hypertensive neuroretinopathy some years previously, did not revert to high levels of blood-pressure.

Patients Taking Mecamylamine.—Of these 11 patients, one developed a generalized erythematous maculopapular rash after a few days on what was subsequently discovered to have been chlorothiazide. One patient of unstable temperament became convinced that chlorothiazide was exacerbating her emotional instability. These two patients were accordingly withdrawn from the trial. Table III shows that, in the remaining eight patients, mecamylamine when given alone produced a significant fall in the mean values of the standing systolic and diastolic blood-pressures for the group as a whole but no such change in the lying

blood-pressures. Of the individual patients, in six a significant fall in standing systolic blood-pressure was achieved, in four of whom the standing diastolic blood-pressure was significantly lowered. The systolic pressure in the lying position was lowered significantly in three patients and the diastolic pressure in one.

When chlorothiazide was added to the mecamlamine the mean fall for the group was much greater, and significant both for lying and for standing systolic and diastolic values. Of the individual patients, all showed a significant fall in their standing systolic and seven out of the eight in their standing diastolic blood-pressures. In the lying position, two failed to show a significant fall in the systolic pressure and three showed no such change in the diastolic pressure. One patient (Case 4) reduced the dose of mecamlamine from 75 mg. daily to 70 mg. Case 1 reduced the dose from 30 mg. to 22.5 mg.; Case 6 from 30 mg. to 7.5 mg.; and Case 7 from 35 mg. to 15 mg. daily, because of hypotensive episodes.

Patients Taking Pentolinium.—For reasons not apparent to us, the control values of the mean blood-pressure for each of these patients varied within much wider limits than did those of the group taking

mecamlamine. There was no evidence that pentolinium alone in the doses being used caused a significant reduction in the blood-pressure of any one of these patients in either the standing or the lying position (Table IV).

When Chlorothiazide was Added to Pentolinium.—One patient (Case 14) showed a pronounced fall in blood-pressure. Case 13 also showed a large fall, but this was no greater than that obtained when chlorothiazide alone was used (Table V).

Effect of Chlorothiazide Alone.—It seemed unlikely that the response of any patient to chlorothiazide alone would be determined by the type of ganglion-blocking agent that they might have been taking in the period before. Accordingly, the results obtained in the two groups of patients are presented together. Table V shows that chlorothiazide reduced the mean standing systolic pressure for the group by an amount which was barely significant, whereas the reduction achieved in the standing diastolic blood-pressures was significant. In the lying position the reductions in systolic and diastolic pressures were less than in the standing position. The systolic pressure was not significantly altered and the diastolic was scarcely so. Out of the

TABLE III.—Changes in Blood-pressure of Eight Patients when Taking Mecamlamine Alone and Mecamlamine Plus Chlorothiazide

Case		Control Blood-pressure ± S.E.		Fall in Blood-pressure			
		Standing	Lying	On Mecamlamine Alone		On Mecamlamine + Chlorothiazide	
				Standing	Lying	Standing	Lying
1	Systolic ..	178.0 ± 7.9	178.0 ± 10.6	16.4	7.7	55.4	25.9
	Diastolic ..	112.0 ± 6.8	108.0 ± 9.6	5.8	1.5	27.3	8.6
2	Systolic ..	175.8 ± 4.9	174.1 ± 6.7	11.8	16.1	35.8	25.6
	Diastolic ..	124.8 ± 4.4	117.6 ± 5.0	8.6	8.0	26.4	14.2
3	Systolic ..	159.3 ± 15.4	164.6 ± 1.6	40.5	16.3	45.6	25.6
	Diastolic ..	100.3 ± 8.8	96.0 ± 8.1	22.3	8.0	24.1	9.8
4	Systolic ..	210.0 ± 0.0*	206.6 ± 5.6	29.0	27.6	68.7	45.8
	Diastolic ..	138.6 ± 2.9	132.6 ± 6.4	12.4	10.0	42.5	26.3
5	Systolic ..	194.1 ± 5.2	195.0 ± 12.2	53.5	33.0	64.1	34.0
	Diastolic ..	133.0 ± 3.6	126.6 ± 5.1	36.0	26.8	38.2	30.6
6	Systolic ..	163.0 ± 9.1	178.6 ± 5.5	20.0	1.6	32.0	21.6
	Diastolic ..	113.0 ± 3.0	114.0 ± 5.5	12.6	-2.0	25.0	14.6
7	Systolic ..	210.6 ± 15.6	209.0 ± 16.0	9.8	0.7	48.1	30.7
	Diastolic ..	129.6 ± 7.6	127.2 ± 5.5	1.1	-1.1	35.3	24.7
8	Systolic ..	168.0 ± 7.5	145.0 ± 10.0	5	-22	27	3
	Diastolic ..	109.0 ± 7.4	92.0 ± 11.5	8	-12	12.4	2
Mean fall ..		{ Systolic .. Diastolic ..		23.2 ± 5.9 13.3 ± 3.9	10.1 ± 6.1 4.9 ± 4.1	47.0 ± 5.3 28.2 ± 3.4	26.5 ± 4.2 16.4 ± 3.5

* Mean of three readings. In this and the following tables, a minus sign before a figure means that there was a rise in blood-pressure.

TABLE IV.—Changes in Blood-pressure of Seven Patients when Taking Pentolinium Alone and Pentolinium Plus Chlorothiazide

Case		Control Blood-pressure (± S.E.)		Fall in Blood-pressure			
		Standing	Lying	On Pentolinium Alone		On Pentolinium + Chlorothiazide	
				Standing	Lying	Standing	Lying
9	Systolic ..	188.3 ± 6.0	185.0 ± 10.0	-2	-8.8	0.8	-15.8
	Diastolic ..	114.6 ± 4.5	109.0 ± 8.0	-4	-9	-4.7	-6.3
10	Systolic ..	181.8 ± 26.6	179.6 ± 11.3	2.6	-12	-3.4	-12.4
	Diastolic ..	136.2 ± 5.0	137.4 ± 7.5	-6.8	-9.2	-1.2	-0.6
11	Systolic ..	181.0 ± 16.4	193.0 ± 14.8	7	6	-1	6.4
	Diastolic ..	112.8 ± 7.1	113.2 ± 6.9	8.2	2.4	12.2	15
12	Systolic ..	180.8 ± 12.4	180.0 ± 11.4	-3.4	-19.2	16.7	5
	Diastolic ..	114.3 ± 6.4	113.8 ± 8.0	0.8	-10.9	8	2.2
13	Systolic ..	185.0 ± 27.2	194.6 ± 10.8	3.7	8	52	42.6
	Diastolic ..	119.6 ± 11.6	120.5 ± 15.7	5.8	12.4	34.6	31.5
14	Systolic ..	158.3 ± 19.7	181.6 ± 27.3	26.2	19.1	62.3	47.6
	Diastolic ..	95.0 ± 16.5	112.1 ± 11.2	-2.4	-6.7	21	27.5
15	Systolic ..	185.0 ± 18.7	192.1 ± 25.7	-4.6	-19.5	15	18.1
	Diastolic ..	112.6 ± 10.9	107.5 ± 11.5	4.1	2	14.6	10.9
Mean fall ..		{ Systolic .. Diastolic ..		4.2 ± 4.0 0.4 ± 2.2	-3.7 ± 5.7 -2.7 ± 3.2	20.3 ± 10.1 12.0 ± 5.0	13.0 ± 9.4 11.4 ± 5.3

TABLE V.—Changes in Blood-pressure of 15 Patients Taking Chlorothiazide Alone

Case		Control Blood-pressure (±S.E.)		Fall in Blood-pressure on Chlorothiazide Only	
		Standing	Lying	Standing	Lying
1	Systolic ..	178.0 ± 7.9	178.0 ± 10.6	1.4	6.4
	Diastolic ..	112.0 ± 6.8	108.0 ± 9.6	5.6	0.3
2	Systolic ..	175.8 ± 4.9	174.1 ± 6.7	19.8	8.1
	Diastolic ..	124.8 ± 4.4	117.6 ± 5.0	16.2	4.0
3	Systolic ..	159.3 ± 15.4	164.6 ± 16.0	7.5	4.2
	Diastolic ..	100.3 ± 8.8	96.0 ± 8.1	2.7	4.2
4	Systolic ..	210.0 ± 0.0*	206.0 ± 5.8	63.7	47.9
	Diastolic ..	138.6 ± 2.9	132.6 ± 6.4	35.0	27.4
5	Systolic ..	194.1 ± 5.2	195.0 ± 12.2	27.1	9.0
	Diastolic ..	133.0 ± 3.6	126.6 ± 5.1	15.2	13.8
6	Systolic ..	163.0 ± 9.1	178.6 ± 5.5	22.9	29.0
	Diastolic ..	113.0 ± 3.0	114.0 ± 5.5	16.6	11.7
7	Systolic ..	210.6 ± 15.6	209.0 ± 16.0	-22.4	-15.0
	Diastolic ..	129.6 ± 7.6	127.2 ± 5.5	-1.0	-2.4
8	Systolic ..	168.0 ± 7.5	145.0 ± 10.0	20.0	-3.8
	Diastolic ..	109.0 ± 7.4	92.0 ± 11.5	10.0	-1.0
9	Systolic ..	188.3 ± 6.0	185.0 ± 10.0	-13.7	-23.0
	Diastolic ..	114.6 ± 4.5	109.0 ± 8.0	-3.2	-8.2
10	Systolic ..	181.8 ± 26.6	179.6 ± 11.3	-17.4	-7.0
	Diastolic ..	136.2 ± 5.0	137.4 ± 7.5	-3.5	-3.1
11	Systolic ..	181.0 ± 16.4	193.0 ± 14.8	-14.0	-3.7
	Diastolic ..	112.8 ± 7.1	113.2 ± 6.9	2.3	1.6
12	Systolic ..	180.8 ± 12.4	180.0 ± 11.4	7.8	-13.3
	Diastolic ..	114.3 ± 6.4	113.8 ± 8.0	4.1	-3.7
13	Systolic ..	185.0 ± 27.2	194.6 ± 10.8	51.7	37.1
	Diastolic ..	119.6 ± 11.6	120.5 ± 15.7	28.8	18.9
14	Systolic ..	158.3 ± 19.7	181.6 ± 27.3	36.7	34.1
	Diastolic ..	95.0 ± 16.3	112.1 ± 11.2	9.4	14.6
15	Systolic ..	185.0 ± 18.7	192.1 ± 25.7	6.1	-11.2
	Diastolic ..	112.6 ± 10.9	107.5 ± 11.5	8.8	2.5
Mean fall ..		{ Systolic .. Diastolic ..		13.2 ± 6.5 9.8 ± 2.9	6.5 ± 5.5 5.3 ± 2.5

* Mean of three readings.

15 patients five (Cases 2, 4, 5, 6, and 13) showed a marked fall in their blood-pressure. In Case 4 the reduction in blood-pressure produced by chlorothiazide was almost as great as when this drug was combined with mecamlamine. Of these five patients, all except Case 6 showed a greater fall in systolic blood-pressure when standing than when lying. A similar postural difference in the diastolic blood-pressure was shown by all.

Relationship of Time Interval Between Last Dose of a Drug and Change in Blood-pressure

No attempt was made to ensure that all the patients took their drugs at the same time before their blood-pressure was recorded, though for each individual patient the interval between taking the tablets and attendance at the clinic remained approximately the same throughout the trial. Since this interval was an uncontrolled variable that might have affected our observations, it seemed of interest to see whether there was any relationship between it and changes in the blood-pressure.

The time that had elapsed since the last dose of drugs was recorded each time the blood-pressure was observed; the time was ascertained for all the patients when they were taking ganglion-blocking agents, but for only 9 of the 15 patients when they were taking chlorothiazide alone. For each patient the average interval was calculated for each of the three periods when active drugs were taken, together with the difference between the average standing systolic blood-pressure in the control period and each of the other periods. The two values were plotted against one another and regression lines were calculated. The results of these calculations were significant only for

the period when chlorothiazide was used alone. The Chart shows the regression line obtained, the slope of which is significant ($0.02 < P < 0.05$). Between two and six hours after the last dose of chlorothiazide the fall in systolic blood-pressure in the standing position is progressively greater.

Discussion

In a controlled trial it must be shown that the observations of the investigator have not been invalidated by a knowledge of what substances were being prescribed at any one time. In this trial, knowledge of the patients' plasma potassium levels and of the side-effects produced by mecamlamine and pentolinium could both have influenced the figures which we recorded as the patients' blood-pressures. In three patients, of whom only one was found to have a reduced blood-pressure when taking chlorothiazide alone, low potassium levels led us to suppose that chlorothiazide was being used during the first two weeks of the trial. After this a solution of mixed potassium salts was substituted for enteric-coated tablets of potassium chloride, and no patient was found to have a low plasma potassium level subsequently.

The possible influence of the patients' complaints of side-effects from mecamlamine and pentolinium is a much more important and interesting point. It had always seemed to us that the method of the double-blind trial was not suitable for assessing the effects of substances that produced symptoms in the patient, since the observations of the investigator would be influenced if the patient mentioned his symptoms. This argument seemed particularly cogent in the case of the ganglion-blocking drugs, which produce symptoms so unpleasant that the physician cannot remain unaware of them. In fact, the patients in this trial made complaints suggesting the side-effects of mecamlamine or pentolinium more often when they were taking dummy ganglion-blocking tablets than when they were taking the real drugs. Chlorothiazide cannot have been responsible for this, since only two patients were taking it when these symptoms were reported.

It can be objected that, had an effective dose of pentolinium been used, symptoms would have been reported more often when active ganglion-blockers were given. But, though mecamlamine treatment was effective in all the patients concerned, the dose of active tablets was reduced no more frequently than that of the dummy tablets. An analysis of the blood-pressure readings at the time of these complaints shows that on no occasion was a reduction in blood-pressure observed when neither active ganglion-blocker nor active chlorothiazide was being taken, and that such a reduction was not always seen when one or both of these substances were being used. Thus there was no evidence that the patients' reports of side-effects influenced our measurements of their blood-pressure. It is clear, therefore, that it is possible to conduct a double-blind trial of ganglion-blocking agents, at least in a group of patients who have already been treated with them for some time, and when the active or dummy tablets are used for a succession of short periods.

Hall and Owen (1959), in a controlled trial, found that chlorothiazide reduced the blood-pressure of hypertensive patients when used alone. The present investigation, which was begun before their report was published, confirms their conclusion and shows that in 5 out of 15 patients chlorothiazide alone produced

considerable falls in blood-pressure. In two patients (Cases 4 and 13) no extra effect was produced by the addition of a ganglion-blocking drug. Case 4 had a grossly raised blood-pressure during the time she was receiving two dummies and developed a retinal haemorrhage within three weeks. The usefulness of chlorothiazide is therefore not confined to patients with only moderate degrees of hypertension.

The Chart shows the correlation between the time that had elapsed since the last dose of chlorothiazide alone and the reduction in the standing systolic blood-pressure. A relationship of this kind may vitiate the results of any trial in which blood-pressure is recorded

Relationship between changes in standing systolic blood-pressure and the time since the last dose of chlorothiazide in nine patients.

infrequently. In this instance there was an even distribution of times between dosage and blood-pressure measurement, so that the results may be representative of the effect of chlorothiazide alone.

There was no evidence that the arterial pressure was affected in patients taking pentolinium alone. In all but one the initial arterial pressure, three to five years

previously, was much higher than that recorded in the control period of the present trial, and four of them (Cases 11, 12, 13, and 15) presented with hypertensive neuroretinopathy. It is impossible, on the available evidence, to prove that this reduction in blood-pressure was due to the drugs used. But, if it were so, the question would arise whether such treatment, for a limited period, may not effect a remission in the course of the disease.

Summary

It has been shown that it is possible to carry out a double-blind controlled trial of ganglion-blocking agents, since the incidence of side-effects was no less when dummy tablets were used than when active drugs were employed. Reports of side-effects by the patients did not influence the readings of the blood-pressure.

Chlorothiazide produced a significant fall of blood-pressure in 5 out of 15 patients when given alone in a dose of 250 mg. three times daily.

Chlorothiazide enhanced the reduction of blood-pressure achieved by mecamlamine in all of eight patients, and increased the effect of pentolinium in one of seven patients.

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RELATIVE ANTIBACTERIAL ACTIVITY OF THREE PENICILLINS

BY

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A new oral penicillin, the potassium salt of 6-(alpha-phenoxypionamido) penicillanic acid, has recently been marketed in this country under the name "broxil." The only published information about it relates to its absorption, which is claimed to be much more nearly complete than that of phenoxymethylpenicillin (penicillin V); the blood levels attained are about double those produced by the same dose of penicillin V, and equivalent to those produced by an intramuscular injection of the same dose of benzylpenicillin (penicillin G) (Knudsen and Rolinson, 1959). Information about its antibacterial activity was communicated to the Seventh Annual Antibiotics Symposium in Washington in November last, but is not yet in print. Some of this information suggested a superior action against penicillin-resistant staphylococci, apparently owing to its slower inactivation by penicillinase (Report, 1959).

Since broxil, which is referred to here as penicillin B, is recommended for use in a wide variety of infections, further assessment of its activity against not only staphylococci but other bacteria is evidently called for, and the following preliminary observations were made with this object. Comparison was made with penicillins G and V. It is known that these two are not identical in activity. G is more active against streptococci and V against some staphylococci, but differences hitherto recorded have been only of the order of twofold (Martin, Nichols, and Heilman, 1955; Zischka, 1956; Lund, 1957).

Methods

The plate-dilution method, with a dilute inoculum, described by Garrod and Waterworth (1956), was used for all species, the medium being nutrient agar for non-exacting species, with the addition of saponin-lysed horse blood for *Str. pyogenes* and *Str. pneumoniae*, and "chocolate" agar for *H. influenzae*. The inoculated areas were separated by ditches in tests of *Proteus*.

A second series of tests was done with penicillin-resistant strains of *Staph. pyogenes*. 2.5 ml. of broth containing concentrations of penicillin falling by four-fold from 512 $\mu\text{g./ml.}$ being inoculated with one 0.02-ml. drop of undiluted broth culture and read for presence or absence of turbidity after 18 hours. When this large inoculum is used the result is determined by whether preformed penicillinase in the inoculum, the amount of which varies greatly between different strains, can destroy the penicillin before it exerts its bactericidal effect. Penicillin-sensitive strains of this organism were also tested by this method, the concentrations falling by twofold from 0.12 $\mu\text{g./ml.}$

All the organisms used were recently isolated from clinical material except some strains of *Str. pyogenes* and *Str. pneumoniae*.

Results

Staph. Pyogenes. — The findings obtained with sensitive strains were so uniform as only to require description in general terms. In the plate-dilution test