Close observation and attention to detail are necessary, and are time-consuming to both patient and doctor; there is still, in fact, a considerable price to pay for health. Nevertheless, guanethidine, usually in combination with an oral diuretic, is probably at present the treatment of choice for the majority of patients with severe hypertensive disease.

Summary

After preliminary assessment in hospital, 75 out-patients with moderate or severe hypertensive disease have been treated with guanethidine for periods up to three years.

An adequate fall in blood-pressure has been maintained in 80% of these patients throughout the period of observation, but in only half of them could the standing diastolic pressure be maintained at less than 100 mm. Hg.

In order to achieve these results more than half of the patients required the addition of oral diuretics and others were given pempidine, codeine, propantheline, or potassium salts to alleviate side-effects.

Side-effects were frequent but less troublesome than with any previous drug; they included morning dizziness or weakness, diarrhoea, frequency of micturition, and exertional dyspnoea. Variations of blood-pressure throughout the day and prolonged periods of hypotension were also encountered. Tolerance occurred in 10% of patients.

It is concluded that guanethidine in combination with an oral diuretic is better than previously available drugs for the long-term treatment of severe hypertension. It has, however, a number of disadvantages.

Addendum

Since the submission of this paper additional information bearing on the efficiency of guanethidine has become available. Of the original 75 patients, three moved away and no uniform follow-up has been possible, and two died, leaving a total of 70 about whom a further statement can be made.

Twenty-one (30%) stopped treatment, in most cases because side-effects became too troublesome and more promising drugs were available. Of the remaining 49 who are still on treatment, 24 have now been treated with guanethidine for three or more years and 39 have been treated for two years or more. The results in these 49 patients, by the criteria adopted above, are as follows: good, 28 (40%); fair, 15 (21%); and poor, 6 (9%).

Thus at the end of a long period of treatment worth-while results—that is, good or fair—are still maintained in 61% of our patients. During the increased period of follow-up late tolerance has appeared in only one additional patient and the average dose-level has remained almost unchanged. As is obvious, it is those patients least troubled by side-effects who have been able to continue taking the drug. These results continue to justify our conclusion expressed in the terminal paragraph of the Summary.

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METHYLDOPA AND HYDROCHLOROTHIAZIDE COMPARED WITH RESERPINE AND HYDROCHLOROTHIAZIDE IN HYPERTENSION

BY

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Reserpine and other rauwolfia alkaloids in combination with oral diuretics of the thiazide group are widely used in the treatment of patients with moderate hypertension. Reserpine causes drowsiness and reduction in mental alertness; hence this drug in combination is not the ideal treatment for symptomless patients who require hypotensive therapy.

Methyldopa lowers blood-pressure more effectively than either chlorothiazide or reserpine; patients who respond satisfactorily find treatment easy to tolerate (Irvine *et al.*, 1962; Dollery and Harington, 1962). Some patients find difficulty with the large number of tablets that are necessary, and minor side-effects, including dryness of the mouth and drowsiness, are still present. It seemed possible that a combination of methyldopa and hydrochlorothiazide might prove a better treatment for patients with moderate hypertensive disease. It was decided to compare these two drugs with a combination of reserpine and hydrochlorothiazide in a double-blind trial.

Method

Eighteen patients with high resting blood-pressure (9 males, 9 females) were selected; their ages ranged from 33 to 70 years. In seven there was an additional feature such as angina, previous hypertensive heart failure, or a cerebral vascular accident. All patients had hypertensive changes in the vessels of the retina; no patient had haemorrhages or exudates. Patients already on hypotensive therapy had their treatment stopped three weeks before entering the trial.

Patients attended the hypertension clinic between 11 a.m. and 1 p.m. Blood-pressures were recorded every 20 minutes for seven readings, with the patient recumbent after the first and every third reading. The blood-pressure was measured by the method recommended by the Committee for the Standardization of Blood-pressure Readings (1939). One doctor asked about side-effects at each visit.

Investigations at the beginning and end of the trial comprised haemoglobin, leucocyte count, blood urea, liver-function tests, chest *x*-ray examination, and electrocardiogram.

Identical capsules were supplied containing: (*a*) placebo powder; (*b*) methyldopa, 250 mg.; (*c*) methyldopa, 250 mg., and hydrochlorothiazide, 15 mg.; (*d*) reserpine, 0.167 mg., and hydrochlorothiazide, 15 mg.

A preliminary phase was necessary to determine the dose of methyldopa combined with hydrochlorothiazide required to achieve good control of blood-pressure by the criteria of Dollery *et al.* (1960). Patients were given initially one capsule of methyldopa and hydrochlorothiazide three times daily and attended the clinic at weekly intervals. At the second visit, if control of blood-pressure was good, they carried on for a further week and then entered the trial. If control of blood-pressure was inadequate a capsule of methyldopa was added each week, the aim being to achieve good control of blood-pressure for two visits. Table I shows the final dose of methyldopa and hydrochlorothiazide for the 18 hypertensive patients.

TABLE I.—*Final Dose of Methyldopa and Hydrochlorothiazide for 18 Hypertensive Patients Entering the Double-blind Trial*

	Capsules of Methyldopa (250 mg.) and Hydrochlorothiazide (15 mg.) Daily	Capsules of Methyldopa (250 mg.) Daily
10 patients	3	0
4 patients	3	3
3 patients	2	0
1 patient	3	1

During the trial patients were seen at intervals of two weeks. For the first four weeks all patients were given placebo capsules at the same dose-rate as was finally established for good control of blood-pressure in the preliminary phase. The remainder of the trial comprised two eight-week periods of treatment. In one the patients were given methyldopa and hydrochlorothiazide at the dose-rate previously established; and in the other, one capsule of reserpine and hydrochlorothiazide was given thrice daily, together with sufficient placebos to make the total number of capsules the same for both periods. The two eight-week treatment periods were randomly allocated. The doctor asking about side-effects and the technician recording the blood-pressure were unaware of the allocation; the patients did not know about the placebo capsules or the change of treatment. Because of the prolonged action of reserpine it was decided, before the trial started, to compare blood-pressures at the fourth, sixth, and eighth weeks in each treatment period.

Results

Effects on Blood-pressure.—Table II gives the average standing, lying, and lowest blood-pressure for 17 hypertensive patients (one patient not having finished the trial). Pressures while on placebo have been compared with

TABLE II.—*Average Blood-pressures (mm. Hg) of 17 Hypertensive Patients Treated with Placebo, Methyldopa with Hydrochlorothiazide, and Reserpine with Hydrochlorothiazide*

	Standing	Lying	Lowest
Placebo	184/116 (S.D. 17·2/8·8)	178/104 (S.D. 18·0/13·3)	166/107 (S.D. 15·3/9·9)
Methyldopa and hydrochlorothiazide	139/93 (S.D. 15·2/7·8)	146/86 (S.D. 16·0/6·9)	122/82 (S.D. 14·8/8·0)
Reserpine and hydrochlorothiazide	139/91 (S.D. 19·3/7·1)	144/84 (S.D. 19·7/7·8)	124/80 (S.D. 19·8/8·9)

pressures at the fourth, sixth, and eighth weeks of treatment periods. The lowest pressure was taken as the average of the lowest of the seven standing readings at any visit. The average standing pressure while on placebo was 184/116 mm. Hg, on methyldopa with hydrochlorothiazide 139/93 mm., and on reserpine with hydrochlorothiazide 139/91 mm. A statistical analysis of the differences between the blood-pressures during the two treatment periods is shown in Table III. No significant differences were found. The average fall of pressure with treatment was 45/24 mm. Hg standing, and 33/19 mm. lying. The blood-pressures of all patients were well controlled by both methyldopa combined with hydrochlorothiazide and reserpine with hydrochlorothiazide.

TABLE III.—*Statistical Analysis of Average Blood-pressures of 17 Hypertensive Patients Treated with Methyldopa and Hydrochlorothiazide (Mean 1) and Reserpine with Hydrochlorothiazide (Mean 2)*

	Systolic Blood-pressure (mm. Hg)				Diastolic Blood-pressure (mm. Hg)			
	Mean 1	Mean 2	t value	P	Mean 1	Mean 2	t value	P
Standing	139·1	138·9	0·03	>0·9	92·6	90·5	0·82	0·5>P >0·4
Lying	145·6	143·8	0·30	0·8>P >0·7	86·0	84·4	0·63	0·6>P >0·5
Lowest	122·5	123·6	0·20	0·9>P >0·8	82·4	80·1	0·77	0·5>P >0·4

Clinical Effects.—One patient developed a hemiparesis while her blood-pressure was well controlled. She made a rapid recovery and was continued in the trial. There was no change in the clinical state of the other 17 patients. In one patient there was increased T-wave inversion in the electrocardiogram during the trial; and in one there was a significant improvement with less evidence of T-wave inversion.

Side-effects.—Assessment of side-effects was reliable because of the double-blind character of the trial. At the end of the second phase the patients were given an explanation of the basis of the trial and were asked to express a preference for one or other of the treatments. The most significant finding was that all patients felt much better on the placebo capsules than on either form of treatment. The patient who did not finish the trial had marked side-effects from both treatments. Table IV shows the occurrence of side-effects and the preferences of the other 17 patients. Five patients expressed no preference, nine thought they were better on reserpine with hydrochlorothiazide, and three preferred methyldopa with hydrochlorothiazide. Drowsiness and lethargy were the most troublesome side-effects with the combination of methyldopa and hydrochlorothiazide. These effects were most severe in the first two weeks of therapy, but five of the eight patients were troubled by drowsiness and lethargy throughout the eight-week trial. Five patients had side-effects, including mild depression and nasal congestion with reserpine and hydrochlorothiazide.

TABLE IV.—*Side-effects and Preferences of 17 Hypertensive Patients Treated in the Trial*

Side-effects	No Preference	Preferred Reserpine and Hydrochlorothiazide	Preferred Methyldopa and Hydrochlorothiazide
None	5	1	0
From both treatments	0	2	0
From methyldopa and hydrochlorothiazide	0	6	0
From reserpine and hydrochlorothiazide	0	0	3

Toxic Effects.—No toxic effects were seen. There was no significant alteration in haemoglobin, leucocyte count, blood urea, or liver-function tests.

Discussion

Patients with serious hypertensive disease require treatment with potent drugs; mild or labile hypertension needs sensible general management without prolonged use of drugs. There is, however, a large group of patients with high resting blood-pressures and mild secondary changes

in which the blood-pressure should be lowered to improve prognosis (Turner, 1962; Smirk, 1962). These patients are usually symptomless, so that treatment should be free of side-effects.

Many of these patients are treated with a combination of reserpine and a diuretic of the thiazide group. Such a combination is not free from side-effects, and it was thought that the addition of hydrochlorothiazide to the new hypotensive drug methyldopa might lower the blood-pressure to the same extent with less side-effects. A double-blind trial on 18 patients with moderate hypertension comparing methyldopa combined with hydrochlorothiazide and reserpine with hydrochlorothiazide has not supported this idea. Both combinations satisfactorily reduced the blood-pressure of all patients, but in every case the patient felt better on placebo than on either form of treatment. When comparing the two treatments in the 17 patients who completed the trial, nine preferred the reserpine with hydrochlorothiazide, three methyldopa with hydrochlorothiazide, and five had no preference.

Methyldopa is a potent hypotensive agent; the optimum daily dose for any patient can vary between 750 mg. and 3 g. (Irvine *et al.*, 1962). Because of this variable response it was thought necessary to have a preliminary phase to the trial to find the optimum dose of methyldopa with hydrochlorothiazide for each patient. This dose of methyldopa was compared with the maximum satisfactory dose of reserpine (0.5 mg. a day) (Smirk, 1957).

The ideal drug for the hypertensive patient without symptoms who needs treatment should be free from side-effects. Methyldopa is an effective hypotensive drug, but often a large number of tablets are needed and minor side-effects are present. A combination of hydrochlorothiazide and methyldopa produces good control of blood-pressure with a reduced number of tablets. This combination caused significant side-effects in 9 out of 18 patients. The margin of difference between the two regimes of treatment was small, and related only to the incidence and severity of side-effects. The most striking finding in our patients was that they all felt much better on placebo. Neither methyldopa with hydrochlorothiazide nor reserpine with hydrochlorothiazide is ideal treatment for moderate hypertension.

Summary

Eighteen patients were treated in a double-blind trial to compare methyldopa with hydrochlorothiazide and reserpine with hydrochlorothiazide (one patient did not finish the trial). Both combinations satisfactorily reduced blood-pressure; the average falls were 45/23 mm. Hg standing and 32/18 mm. lying with methyldopa and hydrochlorothiazide and 45/25 mm. Hg standing and 34/20 mm. lying with reserpine and hydrochlorothiazide.

Nine patients preferred reserpine with hydrochlorothiazide, three methyldopa with hydrochlorothiazide, and five had no preference. All felt much better on placebo. Neither combination is ideal treatment for symptomless patients who require hypotensive drugs.

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HAEMODYNAMIC EFFECTS OF OCCLUSION OF ABDOMINAL AORTA DURING NITROGEN MUSTARD THERAPY

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Alkylating agents have been used extensively in the chemotherapy of cancer. Occlusion of the abdominal aorta was developed in order to increase the tumour dose of nitrogen mustard (methyl-*bis* (β-chloroethyl) amine) (Duff *et al.*, 1961; Lawrence *et al.*, 1961; Miller *et al.*, 1962). By using this method the pelvic bone-marrow is adequately protected against the effects of the drug, and since approximately 45% of the body circulation is cut off (Duff *et al.*, 1961; Lawrence *et al.*, 1961) the drug is more concentrated in the remaining body area.

In our experience, after release of the occlusion of the aorta a profound fall in blood-pressure occurred which lasted for as long as two to three days. Since no studies of the haemodynamics of patients undergoing occlusions had been made, the present investigation was undertaken.

Methods

The investigation was carried out on 20 adult African patients with cancer of the head and neck. The main study was made on 12 patients, in all of whom the femoral-artery pressures were ascertained. In eight of these patients the right atrial pressure was measured, in five measurement was made of the pulmonary-artery pressure, in one the pulmonary wedge pressure, and in six the cardiac output. The other investigations reported were undertaken in a further eight patients.

Anaesthesia.—All patients were anaesthetized with 0.5 g. of thiopentone, paralysed with 120 mg. of gallamine triethiode, intubated, and then maintained on positive-pressure respiration by means of the Radcliffe pump. The duration of the anaesthesia was approximately 20 minutes.

Catheterization.—Before the patient was anaesthetized a cardiac catheter size 7 or 8 was passed under local analgesia through the right antecubital vein into the right side of the heart. The site of pressure recording was as stated above. Right atrial pressures were recorded on two separate occasions in two patients. All recordings were made with a Sanborn pressure-transducer, using a Sanborn