Papers and Originals

Bethanidine, Guanethidine, and Methyldopa in Treatment of Hypertension: a Within-patient Comparison

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When a new agent is introduced into therapeutics it is important to obtain reliable comparison with existing drugs. Examination of the published reports on guanethidine, methyldopa, and bethanidine provides only an approximate estimate of their comparative merits. Most reports indicate that about 70% of patients achieve reasonable control of their blood pressure with each drug. However, the conditions of the trials varied in many respects, such as levels of blood pressure accepted as good and fair control, the severity of the hypertension in the patients treated, and the clinic routine. In addition, it is difficult to obtain a clear idea of the acceptability of these drugs by patients and of the incidence of side-effects. It was with these factors in mind that, following our initial studies with bethanidine (Johnston, Prichard, and Rosenheim, 1962, 1964), we designed a formal trial to compare bethanidine with the established drugs guanethidine and methyldopa.

Patients.—Details of the 30 patient-volunteers completing the trial are summarized in Table I; four of the original 34 patients were withdrawn (see below). The patients were selected solely by the criteria that it was thought necessary to treat them with potent hypotensive drugs and that they were able to attend regularly. All except one patient were on potent drugs before the trial—14 on bethanidine, 11 on guanethidine, and 4 on methyldopa.

Method

Summary of Trial

A within-patient comparison was designed in which each patient received bethanidine, guanethidine, and methyldopa. These drugs were prepared in identical capsules and were given in random order, the randomization being stratified according to the treatment the patient was receiving before the trial.

Patients were seen at two-weekly intervals during the trial (except for the intrusion of their holidays) under identical clinic conditions. At each visit patients were first asked standard questions and their symptoms recorded by physician A (B. N. C. P.), who knew the treatment they were receiving. Blood pressures were then taken by physician B (A. W. J.), who was unaware of the treatment being administered. Physician B gave instruction to physician A whether to increase, decrease, or continue at the present dosage of drug.

After careful consideration it was not thought desirable for physician A to be "blind." Safe and reasonably rapid adjustment of the dose was essential in order to avoid exposing the patients to unnecessary risk, and as the duration of action of the drugs varies different dose schedules have to be followed. The final decision on instructions to adjust the dose had to be tempered with the knowledge of any side-effects being experienced, most notably symptoms of postural hypotension. In addition, the drugs have several characteristic side-effects which would have permitted physician A in many instances to know which drug was being used.

Previous to the "period of assessment" (see below) on each of the three drugs there was a "run-in period." The run-in period was to enable the dose of each drug to be adjusted to obtain the optimal therapeutic effect. The run-in before the first drugs also served to familiarize the patients with clinic procedure, to ensure that they understood the "weekly symptom record sheet" (see below) which they kept, and, lastly, it went some way to ensure that the greater part of the hypotensive effect of increased interest by the physician became stabilized before the trial proper.

When therapy had been stabilized, control of the blood pressure, and the side-effects, were assessed over a period of three months (period of assessment), during which the patient visited the clinic seven times. During this period only spontaneous complaints of side-effects were recorded, but at the end of each period of assessment direct questions were asked to ensure that nothing was overlooked. The run-in period of the next drug was then begun.

A three-month period of assessment on each drug is not sufficient to enable an opinion to be formed on the comparative merit of these drugs with reference to the development of tolerance or the occurrence of any longer-term side-effects.

Drugs and Dosage

The drugs were presented in identical capsules, half and full strength. The capsule sizes were bethanidine 12.5 and 25 mg., guanethidine 10 and 20 mg., and methyldopa 125 and 250 mg.

Initially patients were started on small doses of the new drug —for example, guanethidine 10 mg. once or twice a day—the dose being gradually increased as required, while the previous drug was concurrently gradually reduced. Except where less than one of the half-strength capsules four times a day of the drug concerned was required to control the blood pressure, a four-times-a-day routine was used for each drug. A three- or four-times-daily schedule is usual with bethanidine and methyldopa, whereas guanethidine is usually given once daily in view of its longer duration of action. It seems unlikely that giving

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guanethidine in divided dosage would have adversely affected its efficacy.

The final dose level achieved in each patient was that which gave the desired level of blood pressure control, with no or with tolerable side-effects. No arbitrary upper dosage level was fixed.

Any other hypotensive drugs—for example, reserpine, thiazides—were stopped before the start of the trial.

Chlorothiazide with potassium supplements was added to the regimen if it was not possible to achieve good control of the blood pressure with the primary drug alone. At the time of changeover to the next drug chlorothiazide therapy was withdrawn. Dosage was adjusted to the optimum during the run-in period, but adjustments were also made as necessary during the period of assessment.

Initial Assessment and Levels of Blood Pressure Control

At the first visit to the trial clinic, before the first run-in period, the history was summarized, each patient was examined, and the following investigations were carried out: chest *x*-ray examination, E.C.G., haemoglobin, blood urea, and urine analysis. These details were recorded on the " clinical detail sheet."

Then the range of standing diastolic pressure was decided which in that patient would be regarded as satisfactory during the trial in the light of the clinical features ; this was recorded on the clinical detail sheet. Thus, for example, if the patient was a 40-year-old man with uncomplicated hypertension therapy was adjusted to give a standing diastolic pressure in the range 80–89 mm. Hg provided that this could be achieved without unacceptable side-effects, otherwise 90–99 mm. Hg would be regarded as satisfactory. If levels down to 70–79 mm. Hg chanced to occur no action was taken if there were no side-effects, otherwise the dose of drug was reduced. In an older patient no attempt to lower the diastolic blood pressure below 90–99 mm. Hg was made, and in certain patients the range 100–109 mm. Hg was also regarded as satisfactory, 90–99 mm. Hg being accepted only if side-effects were absent or mild. This category was devised to include patients who had had previous strokes, but was rarely invoked during the trial. Levels of fair control of the blood pressure would be 10 mm. Hg above the range deemed good in the particular patient concerned. The treatment was recorded as a failure when it was not possible to reach even the "fair" range or else when sufficient drug to produce the desire control of blood pressure resulted in intolerable side-effects.

Clinic Routine

Patients were asked to swallow the capsule(s) whole with water on rising, before the midday meal, before the evening meal, and on going to bed. They kept a weekly symptom record sheet. On this sheet the day was divided up into four periods, space was provided for recording postural symptoms on rising, and, throughout the day, exertional symptoms, headaches, and bowel motions ; a space was also provided for patients' comments.

At visits subsequent to the first, patients were seen first by physician A, who recorded their replies to standard questions, recorded any side-effects complained of, and summarized data from the two-weekly symptom record sheet. Physician B then saw the patient in a separate room. He was given the patient's clinical detail sheet and a separate observer sheet for each visit, on which he recorded blood pressures. He did not have available any previous blood pressure readings. Blood pressure was taken one minute and three minutes after the patient had lain on the couch, then again one minute after standing. The supine blood pressures quoted in Table I and subsequent tables are those taken after three minutes on the couch. Pulse rates were recorded before each blood pressure reading. Blood pressure was also taken after ascending and descending 18 stairs. Blood pressures were taken on the London School of Hygiene sphygmomanometer (Rose, Holland, and Crowley, 1964). This device ensures that the observer is unaware of the actual level of blood pressure at the time he auscultates, and it eliminates digit preference. In the light of the level of blood pressure recorded and the levels defined on the patient's clinical detail sheet, physician B instructed physician A whether to increase or decrease the dose of drug or keep it at its present level. Physician A, who knew the blood pressure readings, followed these instructions unless side-effects prevented this ; the reasons for any deviation from the instructions were recorded.

Patients were seen at the same time (afternoon) at each visit. The capsules were dispensed in the clinic to minimize delay and retain the patients' co-operation.

TABLE I.—*Details of Patients and Average Blood Pressures from Periods of Assessment (Seven two-weekly Visits over 12 Weeks for Each Drug)*

Case No.	Age and Sex	Type of B.P.	Presenting		Start of Trial			Bethanidine				Guanethidine				Methyldopa			
			Supine B.P.	Fundus	Fundus	E.C.G.–L.V.	Urea (mg./100 ml.)	Blood Pressure (mm. Hg)			Chlorothiazide	Blood Pressure (mm. Hg)			Chlorothiazide	Blood Pressure (mm. Hg)			Chlorothiazide
								Supine	Standing	Exercise		Supine	Standing	Exercise		Supine	Standing	Exercise	
1	M 41	E	190/140	I	I	+	54	177/116	97/72	95/62	–	167/110	118/86	116/72	–	151/107	121/96	129/92	+
2	M 56	E	180/130	III	II	–	32	173/103	164/92	142/79	–	175/97	156/89	144/76	–	151/87	121/79	135/73	+
3	M 66	E	240/130*	II	II	+	24	203/93	165/81	170/75	–	212/88	187/84	201/88	–	179/80	153/79	173/75	+
4	F 54	E	210/150	I	I	–	63	199/116	133/95	106/69	–	176/105	136/100	123/82	+	161/98	128/91	130/83	+
5	M 52	E	220/150	III	II	+	46	155/98	119/84	126/84	+	186/106	105/77	97/71	–	†			
6	M 51	E	250/150	II	II	+	31	200/114	139/87	140/81	–	202/112	128/78	129/75	–	184/105	130/74	140/67	–
7	M 64	E	240/150	0	I	+	60	211/122	137/102	111/80	–	204/117	153/99	113/76	–	188/106	145/99	131/89	–
8	M 43	R	—	IV	III	+	44	159/113	114/86	112/79	+	156/106	117/81	116/70	+	155/115	129/93	123/87	–
9	F 39	R	245/160	IV	II	+	58	187/123	119/96	111/82	+	203/124	139/97	112/91	–	162/115	112/89	121/89	+
10	M 43	R	170/120	I	II	+	36	220/124	170/107	129/74	–	187/101	133/87	133/71	+	†			
11	M 54	E	230/130	III	III	–	43	170/110	149/105	141/95	–	156/101	130/92	124/81	–	144/98	132/97	137/92	–
12	M 46	R	180/130	I	0	+	25	154/116	112/89	114/84	–	152/110	129/98	123/83	–	139/100	124/95	124/90	–
13	M 55	E	190/140	II	I	+	38	188/108	144/91	142/82	–	168/99	134/84	124/73	–	153/97	129/87	145/87	–
14	M 36	?R	190/130	IV	II	+	65	179/119	127/99	122/84	–	165/108	121/92	121/81	–	152/104	126/102	141/102	–
15	F 44	E	210/135	II	I	+	31	193/104	173/97	179/92	–	193/103	169/96	175/92	–	165/95	161/94	174/92	–
16	F 68	R	180/130	IV	III	+	57	207/115	167/99	170/91	–	190/106	175/91	178/82	–	189/101	170/99	179/93	–
17	F 50	R	180/130	I	II	+	68	183/105	133/93	117/73	–	199/104	144/85	110/64	–	181/103	118/90	118/81	–
18	M 55	E	200/135	III	II	+	48	171/111	139/103	146/98	+	160/106	139/104	157/103	+	†			
19	F 52	E	220/115	II	I	–	36	195/114	168/102	146/89	–	191/105	176/94	166/89	–	153/102	125/87	135/87	+
20	M 45	R	215/150	IV	IV	+	52	210/118	145/99	151/92	–	220/116	170/98	163/95	–	192/113	147/94	157/93	–
21	M 39	E	190/140	II	I	+	43	208/134	150/105	110/78	–	189/108	149/97	106/69	–	†			
22	M 49	E	200/125	II	III	+	41	169/109	136/93	143/87	+	174/108	141/93	143/87	+	158/106	129/94	133/85	+
23	F 49	E	190/130	I	I	–	31	153/103	112/85	115/84	–	148/98	117/84	120/83	–	119/87	98/79	110/81	–
24	F 50	E	220/140	II	I	–	55	172/109	130/93	123/81	+	187/113	161/100	158/95	+	154/102	130/98	142/99	+
25	M 48	R	220/160	III	II	+	53	196/121	111/88	101/70	–	187/119	136/104	127/88	+	†			
26	M 51	R	210/130	IV	II	+	26	183/100	141/86	114/63	–	176/94	147/79	130/50	–	†			
27	M 49	R	260/170	III	II	+	63	229/150	117/83	99/62	–	193/127	124/94	91/60	–	166/123	124/95	110/79	+
28	F 57	E	240/125	IV	II	+	48	217/136	130/97	133/93	+	223/130	161/110	157/97	+	196/117	139/101	148/94	+
29	M 56	R	160/130*	I	I	+	63	170/116	136/105	94/72	+	†				121/91	111/91	117/87	+
30	M 43	R	245/135	I	I	–	33	159/88	129/83	131/74	–	152/92	129/85	135/80	–	128/88	118/87	123/79	–

E = Essential. R = Renal. L.V. = Left ventricle. * On treatment. † Drug not tolerated (see Table II).

Other Observers

In most assessment periods patients were seen throughout by physicians A and B. Occasionally other observers deputized for physician A or B, never for both at one time. This occurred in not more than two instances in any individual period of assessment. In these patients the average blood pressure figures for all visits were compared with those for visits (at least five of the seven) where the patient was seen by physicians A and B, visits with other observers being excluded ; in no instance was there any significant difference in the supine, standing, or post-exercise blood pressure. The figures quoted are therefore from all visits.

Results

The results are outlined in Table I.

Withdrawals from Trial.—Thirty-four patients originally entered the trial. Four were withdrawn at an early stage. In one patient explosive diarrhoea occurred with methyldopa, which chanced to be the first drug, and he declined to continue in the trial. The other three patients did not complete the trial for reasons which are unlikely to be related to the particular drug they were receiving ; one patient (not the driver) was killed in a road accident, one died from a dissecting aneurysm, and one suffered a myocardial infarct and was withdrawn.

TABLE II.—*Failures of Treatment.* (*Total* 30 *Patients*)

(1) Bethanidine, 0	
(2) Guanethidine, 1	(diarrhoea)
(3) Methyldopa, 6	Depression, 2
	Severe tiredness, 2
	Diarrhoea, 1
	Rash, 1
	Poor control, blackout 1

Withdrawal from Individual Drugs.—The reasons for withdrawal from individual drugs are given in Table II ; in all except one, failure was due primarily to side-effects rather than poor blood pressure control. The patient withdrawn because of diarrhoea experienced this symptom in a severe form in spite of full doses of codeine phosphate.

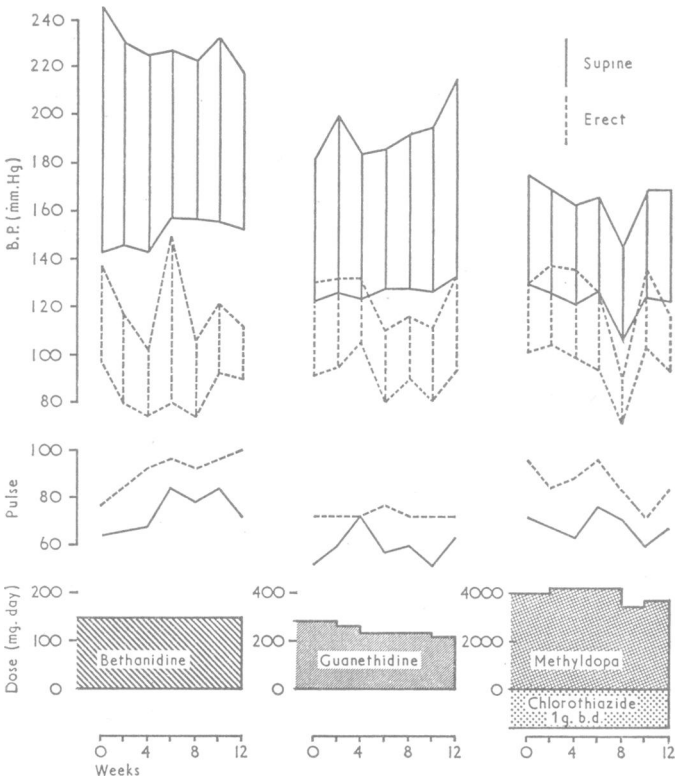

FIG. 1.—Example of blood pressure control in assessment periods (Case 27).

Dosage.—The mean of the average dose used in the three-month period of assessment was bethanidine 112 mg. (S.E. 23.7 mg.), guanethidine 70 mg. (S.E. 8.8 mg.), and methyldopa 2,326 mg. (S.E. 308.2 mg.). Over the three months there was an average increase of 19.6 mg. (S.E. 10.4 mg.) in the dose of bethanidine required to control the blood pressure, of 2.8 mg. (S.E. 4.2 mg.) in the dose of guanethidine, and of 244.8 mg. (S.E. 192.3 mg.) in the dose of methyldopa. These increases were not statistically significant.

Levels of Control

The average levels of blood pressure attained during the three-month period of assessment on each drug in each patient are shown in Table I. An example of the actual levels of blood pressure at each visit is shown in Fig. 1 (Case 27). Table III summarizes the levels of control achieved on each drug, and Table IV gives the average for all the patients on each of the three drugs. The standing diastolic pressures are similar on each drug (Table IV), as aimed at in planning the trial.

TABLE III.—*Levels of Standing Diastolic Pressure ; Mean for Three Months on Each Drug*

Control		Bethanidine	Guanethidine	Methyldopa
Good	(a) 100 mm. Hg or less	23	26	22
	(b) 101–110 mm. Hg. Systolic 150 mm. Hg or less	5	2	2
Fair, 101–110 mm. Hg		2	1	0
Fail		0	1	6
Total		30	30	30

TABLE IV.—*Average Blood Pressure*

		Blood Pressure (mm. Hg)		
		Supine	Standing	Exercise
Bethanidine (30 patients)	S.E.	184/114 (4·50)(2·31)	137/93 (3·65)(1·57)	128/80 (4·09)(1·76)
Guanethidine (29 patients)	S.E.	182/107 (3·82)(1·83)	142/92 (3·81)(1·57)	134/80 (4·81)(2·20)
Methyldopa (24 patients)	S.E.	160/102 (4·40)(2·15)	130/91 (3·29)(1·53)	136/87 (3·86)(1·67)

(Readings from seven visits over three months in each patient.)

Values of P

	Supine		Standing		Exercise	
	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.
Differences between:						
Bethanidine and guanethidine	<0·20	<0·001	<0·10	<0·50	<0·20	<0·80
Guanethidine and methyldopa	<0·001	<0·001	<0·001	<0·80	<0·90	<0·025
Methyldopa and bethanidine	<0·001	<0·001	<0·10	<0·50	<0·50	<0·02

Probabilities calculated from differences in logarithms of the blood pressures of patients who received both drugs of the pair being considered.

This picture is not substantially changed by including estimates for the missing observations (in Table I) derived by the standard method for a randomized block analysis with missing observations. It should be noted that these estimates might be misleading, since the observations were missing owing to intolerance of the drug under test and not to some reason unconnected with the trial. However, the proportion of missing observations is fairly small, and it seems most unlikely that the overall picture could be misleading as a result of this.

Side-effects

The actual side-effects experienced are listed in Table V. They are divided into those complained of spontaneously during the period of assessment and the total, including those elicited by direct questions at the end of the three-month period. In the top part of the Table the data from the weekly symptom

TABLE V.—*Side-Effects*

	Bethanidine (30 Patients)		Guanethidine (29 Patients)		Methyldopa (24 Patients)	
	Average of One or More/Week	Less than Average of One/Week	Average of One or More/Week	Less than Average of One/Week	Average of One or More/Week	Less than Average of One/Week
I. Recorded on weekly symptom record sheet:						
1. Dizziness postural: on rising ..	6 (20%)	15 (50%)	6 (21%)	14 (48%)	1 (4%)	7 (29%)
2. „ „ during day	2 (7%)	6 (20%)	0 (0%)	8 (28%)	1 (4%)	6 (25%)
3. „ exercise	5 (17%)	17 (57%)	4 (14%)	13 (45%)	0 (0%)	8 (32%)
4. Headaches	8 (27%)	17 (57%)	4 (14%)	18 (62%)	7 (29%)	15 (63%)
	Average of less than five/week	Average of more than 15/week	Average of less than five/week	Average of more than 15/week	Average of less than five/week	Average of more than 15/week
5. Bowel motions	2 (7%)	1 (3%)	0 (0%)	4 (14%)	1 (4%)	2 (8%)
	Spontaneous	With direct questions	Spontaneous	With direct questions	Spontaneous	With direct questions
II. Other side-effects:						
Dreams	0 (0%)	3 (10%)	0 (0%)	4 (14%)	4 (17%)	9 (38%)
Difficulty in sleeping	0 (0%)	3 (10%)	0 (0%)	6 (21%)	1 (4%)	3 (13%)
Tiredness	3 (10%)	15 (50%)	5 (17%)	15 (52%)	18 (75%)	20 (83%)
Mild depression	0 (0%)	2 (7%)	0 (0%)	6 (21%)	0 (0%)	3 (13%)
Shortness of breath	1 (3%)	6 (20%)	1 (3%)	6 (21%)	1 (4%)	7 (29%)
Nasal obstruction	2 (7%)	6 (20%)	6 (21%)	12 (41%)	0 (0%)	2 (8%)
Cold extremities	3 (10%)	10 (33%)	0 (0%)	7 (24%)	0 (0%)	5 (21%)
Dry mouth	0 (0%)	5 (17%)	4 (14%)	8 (28%)	1 (4%)	8 (32%)
Unpleasant taste	2 (7%)	2 (7%)	1 (3%)	1 (3%)	1 (4%)	2 (8%)
Sore tongue	0 (0%)	0 (0%)	0 (0%)	3 (10%)	0 (0%)	1 (4%)
Pain angle of jaw	1 (3%)	2 (7%)	1 (3%)	2 (7%)	0 (0%)	1 (4%)
Diarrhoea	2 (7%)	3 (10%)	15 (52%)	19 (66%)	2 (8%)	3 (13%)
Constipation	3 (10%)	4 (13%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)
Nocturia	3 (10%)	16 (53%)	3 (10%)	16 (55%)	1 (4%)	8 (32%)
*Failure ejaculation	6 (30%)	14 (70%)	9 (47%)	15 (79%)	0 (0%)	2 (14%)
*Poor erection	3 (15%)	8 (40%)	2 (10%)	5 (26%)	0 (0%)	1 (7%)

* 20 male patients on bethanidine, 19 on guanethidine, 14 on methyldopa.
In addition: (1) Ankle swelling complained of (C.O.) spontaneously by 1 patient on methyldopa, with direct questions (D.Q.) 2 patients. (2) Anorexia, D.Q. 1 patient on bethanidine, C.O. 1 patient on methyldopa. (3) Nausea, D.Q. 1 patient on guanethidine, C.O. 1 patient on methyldopa. (4) Pain in chest on exertion, D.Q. 1 patient on bethanidine, C.O. 1 patient on guanethidine. (5) Lack of concentration, C.O. 1 patient on guanethidine. (6) Urgency of micturition, C.O. 1 patient on guanethidine.

record sheets are summarized. A numerical score was given to the side-effects experienced by the patients in order to effect comparison between the drugs. The side-effects listed in Table V, part II, were each scored 1, with the exceptions of mild depression, diarrhoea, and the sex disturbances, which were scored 2. If a patient complained of a symptom spontaneously it scored an additional 2. The four recorded symptoms of dizziness on rising, during the day, or on exertion, and headaches were averaged over the three-month period of assessment; an average of half or less attack per week scored 1, up to two attacks scored 2, up to five attacks scored 3, over five scored 4. In addition, patients were asked at the end of the period of assessment how they had felt overall during the previous three months. They were given four alternatives, in the following order: "well" (scored 5), "only fair" (scored 15), "very well" (scored 0), "ill" (scored 20). The last category was not chosen at all. All these scores were added together, the mean from the patients tolerating the drug concerned being shown in Table VI, A. Table VI, B, is the total from those side-effects spontaneously mentioned and those in response to direct questions, *excluding* dizziness, headache, and the patient's general assessment. A low score therefore indicates few side-effects and a large score many.

It can be seen (Table VI) that in those patients tolerating the drugs the mean of the scores for bethanidine for side-effects A and B, 16.3 and 7.9, is similar to the mean scores with methyldopa, 16.7 and 8.8 respectively. The score obtained with guanethidine for A, 22.9, is significantly larger than those obtained with the other two drugs, and for B, 12.2, is significantly larger than on bethanidine.

TABLE VI.—*Mean Side-effect Scores*

	Bethanidine n = 30	Guanethidine n = 29	Methyldopa n = 24
A. Total side-effect score ..	16·3 S.E. 1·73	22·9 S.E. 1·62	16·7 S.E. 1·97
B. Side-effects (less score for dizziness and headaches and patients' general assessment)	7·9 S.E. 1·05	12·2 S.E. 1·22	8·8 S.E. 1·20
Failures of treatment (not allowed for in scores)	0	1	6

For differences:
Between bethanidine and guanethidine for side-effects A and B, $P < 0.001$.
Between guanethidine and methyldopa, A $0.005 > P > 0.001$, B $0.10 > P > 0.05$.
Between bethanidine and methyldopa not significant (A $0.90 > P > 0.80$, B $0.975 > P > 0.950$).
Probabilities calculated as in Table IV for A; for B the log of the score plus 1 was taken, as some patients scored zero.

At the end of the trial patients were asked to place in order of preference the capsules they had received. These preferences are summarized in Table VII. They follow the same pattern as seen with the side-effect scores, bethanidine and methyldopa being preferred more often than guanethidine.

TABLE VII.—*Patients' Order of Preference for the Drugs*

Order of Preference	Bethanidine	Guanethidine	Methyldopa
1	12	4	10
1 =	1	2	1
2	5	11	4
2 =	5	5	2
3	5	5	5
No preference ..	2	2	2
Fail	0	1	6
Total ..	30	30	30

Effect of Order of Administration of the Drugs on Blood Pressure Control and Side-effects

Drugs were given in random order. Bethanidine was given first 11 times, second 9 times, and third 10 times; guanethidine 10 times for each order; methyldopa first 9 times, second 11 times, and third 10 times.

Table VIIIa shows that the levels of blood pressure control were not significantly different as the trial progressed. The figures for individual drugs were also examined, and for each of the three drugs blood pressure control was not affected by their order of administration.

When the total side-effect scores (A) are considered (Table VIIIb) the score for the second and third drug was significantly

TABLE VIIIa.—*Effect of Order of Administration of Drugs on Blood Pressure Control*

		Order of Administration		
		1st Drug	2nd Drug	3rd Drug
Supine B.P.	Mean	181/109	175/107	176/108
	S.E.	3·77 2·55	5·12 2·12	4·64 2·19
Standing B.P.	Mean	136/90	137/94	137/92
	S.E.	3·74 1·70	3·90 1·53	3·59 1·38
Exercise B.P.	Mean	130/79	134/84	134/84
	S.E.	4·54 2·05	4·14 2·04	4·42 1·70
n		29	28	26

None of the differences reach 5% level of significance. Probabilities calculated as in Table IV.

lower than for the first, 0.02>P>0.01. When postural and exertional hypotension, headaches, and the patient's own assessment are eliminated (score B) the trend remains but loses its statistical significance. The patients themselves showed a pronounced preference for the third drug (Table VIIIc). When this apparent reduction in side-effects as the trial proceeds is considered it must also be remembered that four patients could not tolerate the third drug, against only one patient for the first drug.

TABLE VIIIb.—*Effect of Order of Administration of Drugs on Side-effect Scores*

	Order of Administration		
	1st. n = 29	2nd. n = 28	3rd. n = 26
A. Total side-effects	22·9 S.E. 1·96	17·1 S.E. 1·69	15·8 S.E. 1·55
B. Side-effects (less score for dizziness and headaches and patients' general assessment)	11·97 S.E. 1·32	8·82 S.E. 1·13	8·50 S.E. 1·03
Failures of treatment	1	2	4

Side-effects A:
For differences between 1st and 2nd, and 1st and 3rd drugs, 0·02 > P > 0·01.
For differences between 2nd and 3rd, 0·60 > P > 0·50.

Side-effects B:
For differences between 1st and 2nd drug, 0·20 > P > 0·10.
For differences between 1st and 3rd drug, 0·05 > P > 0·10,
For differences between 2nd and 3rd drug, 0·40 > P > 0·50.
Probabilities calculated as in Table IV.

TABLE VIIIc.—*Effect of Order of Administration of Drugs on Patients' Preference*

Order of Preference	Order of Administration		
	1st	2nd	3rd
1	2	9	14
1=	1	2	3
2	11	7	1
2=	6	3	3
3	7	5	3
No preference ..	2	2	2
Fail	1	2	4
Total ..	30	30	30

Chlorothiazide

It can be seen from Table I that eight patients on bethanidine (of 30), eight on guanethidine (of 29), and 10 on methyldopa (of 24) required chlorothiazide in addition to their main drug. In three patients it was needed on all three drugs, and in a further two it was required for the two drugs that these patients received when the third drug was not tolerated. In three patients it was required on two of the three drugs, and seven received chlorothiazide once. Hence 15 of the 30 patients received chlorothiazide at least once.

There is no significant difference (Table IX) between the systolic or diastolic blood pressure in patients taking chlorothiazide and those not, in the case of each of the three drugs. Though individual changes are not significant, it will be noted that in all patients on chlorothiazide, except after exercise in those on guanethidine, there is a lower systolic pressure whether diastolic pressure is the same or slightly raised. The effect of chlorothiazide on the pulse pressure is summarized in Table X. In each of nine instances of supine, standing, and exercise blood pressures on the three drugs the mean pulse pressure on patients receiving chlorothiazide in addition to the basic drug is less than on those on the basic drug alone. In the case of bethanidine supine and standing pulse pressure this is significant.

TABLE IX.—*Effect of Chlorothiazide on Blood Pressure Control*

			Blood Pressure (mm. Hg)		
			Supine	Standing	Exercise
Bethanidine	Alone .. n = 22	S.E.	188/113 5·51 2·85	140/93 4·68 1·95	129/79 5·13 2·10
	Plus chlorothiazide.. n = 8	S.E.	175/114 6·88 3·97	128/95 3·31 2·60	124/85 6·18 2·88
Guanethidine	Alone .. n = 21	S.E.	183/106 4·58 2·16	143/89 4·94 1·53	132/78 6·28 2·43
	Plus chlorothiazide.. n = 8	S.E.	181/111 7·33 3·34	141/97 5·16 3·40	139/87 5·96 4·20
Methyldopa	Alone .. n = 14	S.E.	162/99 6·43 2·60	134/91 5·09 2·26	141/86 5·92 2·38
	Plus chlorothiazide.. n = 10	S.E.	157/105 5·81 3·59	124/92 2·65 1·97	130/87 3·62 2·36

None of the differences reach levels of significance.

TABLE X.—*Effect of Chlorothiazide on Pulse Pressure*

		Pulse Pressure (mm.Hg)		
		Supine	Standing	Exercise
Bethanidine	Alone n = 22 ..	77·1 S.E. 3·47	47·4 S.E. 3·86	50·7 S.E. 4·02
	Plus chlorothiazide.. n = 8	60·6 S.E. 3·55 P = 0·01	33·3 S.E. 2·14 0·05 > P > 0·025	39·0 S.E. 3·812 0·20 > P > 0·10
Guanethidine	Alone n = 21 ..	77·2 S.E. 4·31	53·4 S.E. 4·60	54·6 S.E. 5·26
	Plus chlorothiazide.. n = 8	70·3 S.E. 5·14 0·40 > P > 0·30	43·1 S.E. 3·55 0·20 > P > 0·10	50·1 S.E. 4·71 0·70 > P > 0·60
Methyldopa	Alone n = 14 ..	62·6 S.E. 5·85	43·6 S.E. 4·81	54·8 S.E. 5·93
	Plus chlorothiazide.. n = 10	52·5 S.E. 4·28 0·30 > P > 0·20	31·9 S.E. 2·33 0·10 > P > 0·05	43·2 S.E. 3·36 0·20 > P > 0·10

Effect on Pulse Rate

The effect of the three drugs on the pulse rate is shown in Table XI. The mean of the supine 66, and standing 78, pulse rates on guanethidine was lower than on bethanidine—74 and 89 respectively (in both instances P<0.001); this was not due to differences in blood pressure control (Table IV). The mean pulse rate on methyldopa (supine 77, standing 93) was more rapid than on guanethidine (in both instances P<0.001). The differences between bethanidine and methyldopa were also significant in the standing position (0.05>P>0.025). The supine and standing pulse rates in the patients who received bethanidine and guanethidine appear to be slower than in those who had chlorothiazide in addition, but these differences were not significant. The supine pulses on methyldopa with or without chlorothiazide showed little difference, and there was no difference at all in the standing pulse rates on methyldopa in the presence or absence of chlorothiazide.

TABLE XI.—*Effect on Pulse Rate*

Drug		All Patients*	No Chlorothiazide	With Chlorothiazide	
Bethanidine	Supine	74 S.E. 1.56	73 S.E. 1·66	78 S.E. 3·59	0·20 > P > 0·10
	Standing	89 S.E. 1·85	87 S.E. 2·13	93 S.E. 3·54	0·30 > P > 0·20
	n =	30	22	8	
Guanethidine	Supine	66 S.E. 1·62	65 S.E. 1·98	68 S.E. 2·70	0·50 > P > 0·40
	Standing	78 S.E. 2·19	75 S.E. 2·75	83 S.E. 2·58	0·20 > P > 0·10
	n =	29	21	8	
Methyldopa	Supine	77 S.E. 1·53	76 S.E. 2·18	78 S.E. 2·15	0·70 > P > 0·60
	Standing	93 S.E. 1·87	93 S.E. 3·11	93 S.E. 1·38	—
	n =	24	14	10	

* Supine and standing pulse rates on guanethidine for all patients significantly slower than on bethanidine or methyldopa; in all instances P < 0·001. Bethanidine supine rate not significantly slower than on methyldopa, 0·20 > P > 0·10; standing rate significantly slower than on methyldopa, 0·05 > P > 0·025. Probabilities calculated as in Table IV for differences between drugs in all patients.

Results from Patients Achieving Similar Levels of Blood Pressure Control

The average blood pressure of those completing the trial (Table IV) suggests that while on bethanidine patients perhaps have a slightly greater postural drop in pressure than when on guanethidine, both of these drugs producing greater postural and exercise hypotension than methyldopa.

For reasonable comparison of these effects, and side-effects too, it is important that the blood pressure should be well controlled, and controlled to a similar level on each drug for an individual patient. Accordingly patients were assessed whose mean standing diastolic pressures on each drug over the three-month period of assessment were in the range 80 to

100 mm. Hg with no more than 10 mm. Hg between them. Though on each drug blood pressure control to the same standing diastolic level was aimed at, these more rigid criteria were satisfied in half the patients.

Out of 29 patients who received both drugs there were 17 whose blood pressure control was within this range on bethanidine and guanethidine (Fig. 2); with bethanidine and methyldopa there were 12 out of a possible 24 patients (Fig. 3); and with methyldopa and guanethidine 17 out of a possible 23 patients (Fig. 4). In Figs. 2 to 4 are plotted the per cent. ratio of the mean erect over the mean supine blood pressure (diastolic plus one-third of pulse pressure), and mean exercise over the mean supine blood pressure. The ratio is calculated from the grand mean of the average blood pressures of each patient over the three-month period of assessment. It can be seen (Fig. 2) that there is a slightly larger postural and exercise drop in blood pressure from bethanidine than from guanethidine, but this small difference is statistically significant. Figs. 3 and 4 show that while methyldopa produced some postural and exercise hypotension it was considerably less than that from bethanidine or guanethidine. In these patients the presence or absence of chlorothiazide in the regimen did not affect the differences between the three drugs. Table XIIa shows the ratios of the mean erect to mean supine blood pressure and the mean exercise to mean supine blood pressure in all the patients and in those who did not receive chlorothiazide.

The means of pulse rates in these patients achieving similar blood pressure control are listed in Table XIIb. Guanethidine results in a significantly slower pulse in both the supine and the standing position than either bethanidine or methyldopa. The pulse rate on bethanidine appears slower than on methyldopa, but the differences are not significant. The same changes are seen when those patients who received chlorothiazide in addition to one or both of the drugs being compared are excluded.

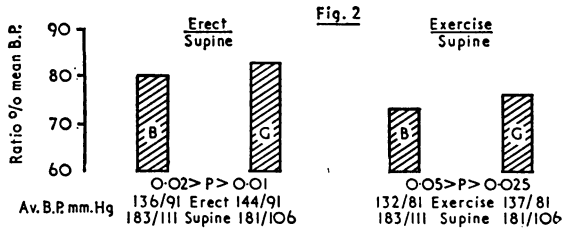

FIG. 2.—Comparison of blood pressures of 17 patients on bethanidine (B) and guanethidine (G) whose mean standing diastolic pressures in the three-month period of assessment were, on both drugs, in the range 80 to 100 mm. Hg with no more than 10 mm. Hg between them.

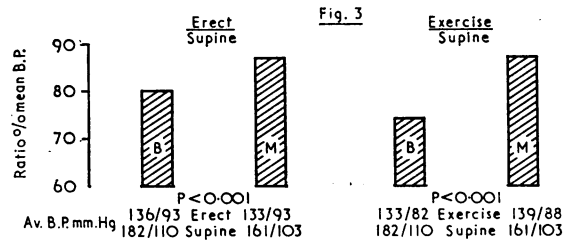

FIG. 3.—Comparison of blood pressures from 12 patients on bethanidine (B) and methyldopa (M) whose mean standing diastolic pressures in the three-month period of assessment were, on both drugs, in the range 80 to 100 mm. Hg with no more than 10 mm. Hg. between them.

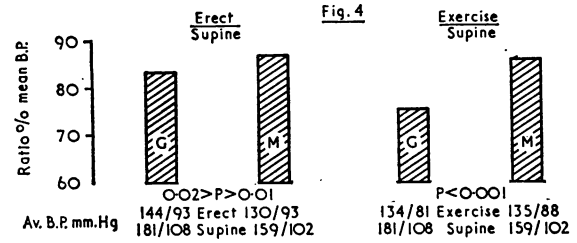

FIG. 4.—Comparison of blood pressure in 17 patients on guanethidine (G) and methyldopa (M) whose mean standing diastolic pressures in the three-month period of assessment were, on both drugs, in the range 80 to 100 mm. Hg with no more than 10 mm. Hg between them.

TABLE XIIa.—*Patients Achieving Closely Similar Levels of Blood Pressure Control. Effect of Posture and Exercise With and Without Chlorothiazide*

Comparison of	Ratio: Mean Erect / Mean Supine B.P.		Ratio: Mean Exercise / Mean Supine B.P.	
	All Patients	No Chlorothiazide	All Patients	No Chlorothiazide
Bethanidine and guanethidine	0·80 0·83 n = 17 0·02 > P > 0·01	0·81 0·84 n = 12 0·10 > P > 0·05	0·73 0·76 n = 17 0·05 > P > 0·025	0·75 0·78 n = 12 0·20 > P > 0·10
Bethanidine and methyldopa	0·80 0·87 n = 12 P < 0·001	0·82 0·89 n = 7 0·05 > P > 0·025	0·74 0·87 n = 12 P < 0·001	0·78 0·89 n = 7 P < 0·001
Guanethidine and methyldopa	0·83 0·87 n = 17 0·02 > P > 0·01	0·85 0·90 n = 10 0·005 > P > 0·001	0·75 0·86 n = 17 P < 0·001	0·77 0·89 n = 10 P < 0·001

Probabilities calculated as in Table IV.

TABLE XIIb.—*Patients Achieving Similar Levels of Blood Pressure Control*

		Pulse Rates		
		Bethanidine	Guanethidine	
All patients n = 17	Supine	74 S.E. 1·85	66 S.E. 2·08	P < 0·001
	Standing	86 S.E. 2·47	76 S.E. 2·67	
Excluding chlorothiazide n = 12	Supine	72 S.E. 2·21	65 S.E. 2·67	0·005 > P > 0·001
	Standing	86 S.E. 3·07	73 S.E. 3.29	P < 0·001
		Bethanidine	Methyldopa	
All patients n = 12	Supine	74 S.E. 2·58	76 S.E. 2·71	0·30 > P > 0·20
	Standing	89 S.E. 3·01	92 S.E. 3·28	0·50 > P > 0·40
Excluding chlorothiazide n = 7	Supine	71 S.E. 3·77	73 S.E. 4·00	0·50 > P > 0·40
	Standing	85 S.E. 4·32	88 S.E. 5·22	0·60 > P > 0·50
		Methyldopa	Guanethidine	
All patients n = 17	Supine	76 S.E. 1·97	65 S.E. 1·99	P < 0·001
	Standing	91 S.E. 2·34	75 S.E. 2·47	
Excluding chlorothiazide n = 10	Supine	74 S.E. 2·79	64 S.E. 2·97	P < 0·001
	Standing	90 S.E. 3·77	73 S.E. 3·75	

Probabilities calculated as in Table IV.

The side-effect scores in these patients (Table XIIc) show that there is a significant preference for bethanidine (mean 15.1) against guanethidine (mean 23.7), and for methyldopa (mean 14.4) against guanethidine (mean 20.5). There is no significant difference in the side-effect scores in patients achieving similar control of blood pressure on bethanidine (mean 12.8) and methyldopa (mean 14). A similar trend is seen when chlorothiazide is excluded from the comparison.

TABLE XIIc.—*Patients Achieving Similar Levels of Blood Pressure Control*

	Side-effect Scores (from Total Score A in Table VI)		
	Bethanidine	Guanethidine	
All patients n = 17	15·1 S.E. 2·36	23·7 S.E. 2·55	P < 0·001
Excluding chlorothiazide n = 12	14·4 S.E. 2·92	23·5 S.E. 3·16	0·005 > P > 0·001
	Bethanidine	Methyldopa	
All patients n = 12	12·8 S.E. 2·24	14·0 S.E. 2·47	0·90 > P > 0·80
Excluding chlorothiazide n = 7	8·3 S.E. 1·04	9·6 S.E. 1·59	
	Methyldopa	Guanethidine	
All patients n = 17	14·4 S.E. 1·87	20·5 S.E. 1·97	0·005 > P > 0·001
Excluding chlorothiazide n = 10	12·4 S.E. 2·18	20·9 S.E. 3·01	0·02 > P > 0·01

Probabilities calculated as in Table IV.

Weight

Patients were weighed at each visit. There was no significant difference in the average weights on bethanidine, guanethidine, and methyldopa.

Discussion

Level of Blood Pressure Control

The difficulties of comparing the effectiveness of bethanidine, guanethidine, and methyldopa have been outlined in the introduction.

The level most usually accepted as good control was 100 mm. Hg or less standing diastolic pressure. With each of the three drugs previous trials have usually shown that about half the patients achieve this level. For example, with bethanidine, Montuschi and Pickens (1962) found 44% of their 25 patients were controlled to a level of 100 mm. Hg or less; Johnston *et al.* (1964) 58% of 31 patients. In a further trial Smirk (1963b) controlled 46% of 56 patients to a level of 150/95 or less. Leishman, Matthews, and Smith (1959) treated 25 patients with guanethidine and 44% reached a level of standing diastolic of 100 mm. Hg or less. Other examples were 43% of 80 patients (Dollery, Emslie-Smith, and Milne, 1960), 64% of 28 patients (Bauer *et al.*, 1961), 40% of 75 patients (Lowther and Turner, 1963). A similar pattern is seen in many trials with methyldopa—for instance, 42% of 33 patients (Cannon, Whitlock, Morris, Angers, and Laragh, 1962), 54% of 59 patients (Dollery and Harington, 1962), 67% of 69 patients (Hamilton and Kopelman, 1963), 49% of 100 patients (Johnson, Kitchin, Lowther, and Turner, 1966). These last authors compared the fall of blood pressure in 37 patients on methyldopa with that in 66 patients of similar severity on guanethidine and found no significant difference between the drugs.

Previous evidence thus indicates that bethanidine, guanethidine, and methyldopa are probably similar in their ability to control the blood pressure. The present study does not show any significant differences (Tables III and IV) provided those six patients who could not tolerate methyldopa are excluded. In addition, 10 out of 24 patients required chlorothiazide in addition to methyldopa, compared with 8 out of 29 on guanethidine, and 8 out of 30 on bethanidine. In a within-patient comparison complete in 19 patients, comparing guanethidine, methyldopa, and also pargyline, Oates, Seligmann, Clark, Rousseau, and Lee (1965) found that the three drugs produced similar average reduction of blood pressure.

The levels of blood pressure control achieved in our patients are lower on all three drugs than in some previously reported series. Our cases were not of less severity than those in many of the previous studies. It seems probable that lower blood pressure readings were obtained in this trial because the patients were thoroughly familiar with the clinic routine and were seen fortnightly by the same physician, who increased the dosage until either the desired blood pressure was reached or unacceptable side-effects occurred.

Postural and Exercise Hypotension

When a close comparison is made between the pharmacological effects of hypotensive drugs with not very dissimilar modes of action doses that produce equivalent physiological effects are best given before any comparison is made.

Consideration of those patients whose mean standing diastolic blood pressure over the three-month period was controlled to within 10 mm. Hg and was also within the range of 80 to 100 mm. Hg (Figs. 2, 3, and 4) shows: (1) that, when tolerated, methyldopa produces significantly less of a postural and exercise drop in blood pressure than guanethidine or bethanidine, or that for a given standing diastolic pressure on methyldopa the supine pressure is lower; and (2) that guanethidine produces a slightly but significantly smaller drop on posture and exercise than does bethanidine. Similar changes occur if the grand mean of all the patients is taken (Table IV).

Smirk (1963a) found that methyldopa produced less postural drop than ganglion-blocking drugs and bretylium (seven patients). He compared one group of patients treated with methyldopa with another treated with guanethidine and in addition a few patients who had received both drugs, and failed to show any conspicuous difference between methyldopa and guanethidine. Johnson *et al.* (1966) compared 37 patients treated with methyldopa with 66 patients of similar severity treated with guanethidine, and found no difference between the postural fall in blood pressure. However, Goldberg and Zimmerman (1963), reviewing the earlier work on guanethidine and methyldopa, concluded: "Methyldopa has a greater effect than guanethidine on supine pressure." In the first randomized comparison under defined conditions (a within-patient comparison) Oates *et al.* (1965) found that methyldopa produced less of a postural drop in blood pressure than guanethidine ($P<0.05$); they also found that pargyline was similar to guanethidine in this regard.

The findings of the present trial confirm this difference between methyldopa and guanethidine, and also that after erect exercise there is a larger fall of blood pressure in patients on guanethidine than on methyldopa. This difference was still seen when analysis was confined to patients whose standing diastolic pressure was controlled to similar levels. Methyldopa is thought to be converted to α-methylnoradrenaline, and this substance may then act as a false transmitter at the nerve endings, replacing noradrenaline (Day and Rand, 1963). α-Methylnoradrenaline has some stimulatory action, though much less than noradrenaline, so the effect of nerve stimulation may be inhibited without being completely blocked. This is in accord with the finding that when the supine blood pressure is reduced by methyldopa (a position where there is a low level of sympathetic nerve activity), on changing to the standing position (where a higher level of sympathetic activity is required to maintain the blood pressure) the effect of impulses is not so fully inhibited as with bethanidine or guanethidine. Hence there is not so great a postural drop in blood pressure as with many other drugs giving an equivalent degree of block at lower levels of sympathetic nerve activity.

None of the previous trials has compared methyldopa and bethanidine. Our finding that, like guanethidine, bethanidine produces greater postural and exercise hypotension than methyldopa is not surprising, as the mode of action of bethanidine (Boura and Green, 1963) has many similarities to that of guanethidine.

Likewise there has been little published evidence comparing the effect of posture and exercise in patients receiving bethanidine and guanethidine, though the statement was made by Wilson, Long, and Jagoe (1965): "In our opinion, postural hypotension is more marked with bethanidine sulphate than with bretylium or guanethidine," though no evidence was quoted. Gifford (1965) did not find any difference in "symptomatic orthostatic hypotension" between bethanidine and guanethidine. Our finding that bethanidine produces a slightly greater fall in blood pressure on standing and after erect exercise than guanethidine is statistically significant, but in view of the smallness of this difference is not of clinical importance. This difference, interestingly, was predicted by Boura and Green (1963) from animal experiments.

Guanethidine preferentially abolished the response to low frequency of sympathetic nerve stimulation to the cat's nictitating membrane but did not alter the slope of the curve relating frequency of sympathetic nerve stimulation to the resultant contraction of the cat nictitating membrane (Boura and Green, 1962). Bethanidine, however, depressed the slope—that is, relatively greater blockade at higher rates of stimulation than guanethidine, with responses to a low rate of stimulation inhibited relatively less (Boura and Green, 1963). In the standing position, because of gravity, increased sympathetic activity—that is, a high rate of stimulation—is required to maintain the blood pressure. If drugs are given in a dosage to produce equivalent effects at higher rates of sympathetic stimulation—that is, in the standing position, as was done in this study—a

drug with a relatively greater inhibition at low frequencies of stimulation as pertains in the supine position (for example, guanethidine) would be expected to produce a lower supine blood pressure than one with less inhibition at low frequencies —for example, bethanidine.

Pulse Rate

There seems little doubt that guanethidine produces a greater reduction in pulse rate than bethanidine or methyldopa (Table XI), this difference not being due to differences in blood pressure control (Table IV). This same difference is also seen when the standing diastolic pressure is controlled to similar levels in each patient (Table XIIb). It is also possible that bethanidine produces greater slowing than methyldopa ; the difference is significant when all patients are considered in the standing position (Table XI), but this difference did not reach accepted levels of significance in those patients achieving similar levels of blood pressure control (Table XIIb). The reason for these findings is not clear, but it is suggestive that there are differences in the relative effects of these drugs on the sympathetic supply to blood vessels, arteries, and/or veins from that to the heart.

Chlorothiazide

Those patients who received chlorothiazide in addition to their primary drug achieved blood pressure control similar to that of patients not receiving chlorothiazide (Table IX). There seems to be a tendency for patients whose blood pressure is controlled with chlorothiazide in addition to bethanidine, guanethidine, or methyldopa to have a lower pulse pressure than those not having chlorothiazide in addition (Table X). It is well known that the treatment of hypertension with chlorothiazide (Freis, Wanko, Wilson, and Parrish, 1958) and other diuretics (Cranston, Juel-Jensen, Semmence, Handfield Jones, Forbes, and Mutch, 1963) often produces a greater reduction in systolic than in diastolic pressure, though this might be largely ascribed to an effect of general lowering of the blood pressure. This cannot be the explanation when the pulse pressure in patients receiving chlorothiazide is lower than in those not having chlorothiazide when blood pressure is controlled to a similar level in both groups. Long-term administration of chlorothiazide reduces peripheral resistance and does not reduce the cardiac output (Conway and Lauwers, 1960) ; a lowered peripheral resistance might be contributory to the reduced pulse pressure.

Though the differences were not significant, there was a tendency for the pulse rate to be faster in those who received chlorothiazide in addition to bethanidine or guanethidine (Table XI) ; this could at least account for some of the reduced pulse pressure on chlorothiazide. However, while the standing pulse on methyldopa was the same with and without chlorothiazide, the differences in the pulse pressure (Table X) approached the 5% level of significance.

A within-patient study with and without chlorothiazide is needed to confirm these points and to eliminate the possibility that the differences in those patients receiving chlorothiazide were not due to chlorothiazide but to whatever factors that caused us to administer chlorothiazide to facilitate control of the blood pressure.

Side-effects : Overall Assessment

Table V lists side-effects which were given an arbitrary score in an effort to present some composite picture of the comparative effect of the drugs. As is well known, direct questions elicit many more side-effects, so it seemed reasonable to score an additional 2 for a side-effect if it was mentioned spontaneously. The effect of variation between patients was reduced by the within-patient design, and randomization of order of administration of the drugs reduced the effect of diminishing side-effects as the trial progressed. There was no appreciable difference in the comparative scores, whether the total side-effect score (score A, Table VI)—that is, including dizziness, headaches, and the overall feeling of the patient—was considered, or the side-effects excluding dizziness, headaches, and overall feeling (score B, Table VI). As can be seen from Table VI, bethanidine and methyldopa were not significantly different, while both these drugs produced significantly fewer side-effects than guanethidine. However, this does not take into account that six patients could not tolerate methyldopa, against only one on guanethidine and none on bethanidine.

Though arbitrary, it was thought that those side-effects scored as 2 instead of 1 were worthy of such a weighting. Scoring diarrhoea as 2—present in two-thirds of patients on guanethidine—might be thought to weigh against this drug. However, even if scored as 1 there remains a significant difference in the score reached by the drugs. Side-effects can be fairly assessed only in patients whose blood pressure is controlled to a similar level by the drugs being compared. Patients achieving similar blood pressure control show the same variation in side-effects as seen with the patients as a whole (Table XIIc). The difference between the drugs is also shown in patients who were not receiving chlorothiazide (Table XIIc).

The patients were asked to state their preference at the end of the trial. As might be expected they showed a tendency to prefer the most recently administered drug (Table VIIIc), and a similar improvement was seen in side-effect scores (Table VIIIb) as the trial progressed. This did not appear to be related to changes in blood pressure control (Table VIIIa). The randomization resulted in approximately equal numbers receiving the drugs in each possible order. As is seen in Table VII, the patient's preference mirrors the side-effect scores in that there is little difference between methyldopa and bethanidine but fewer patients prefer guanethidine.

In the only other close comparison of any of the three drugs Oates *et al.* (1965) listed the side-effects on guanethidine and methyldopa (and also pargyline) but made no further attempt at comparison.

Individual Side-effects : Dizziness

Table V summarizes the side-effects experienced by patients able to tolerate the drugs. The incidence of spontaneous complaints is more comparable to previous reports. Most previous trials did not ask direct questions, neither did patients keep a record of dizziness and headaches, so that the incidence of side-effects of the present trial was likely to be higher.

The incidence of dizziness on guanethidine and bethanidine is about the same, though there was a slightly higher incidence of symptoms of exertional hypotension with bethanidine. Postural and exercise hypotensive symptoms are fewer with methyldopa. These findings correlate with the postural and exercise changes of blood pressure. The occurrence of dizziness broadly agrees with previous trials. Oates *et al.* (1965) reported postural faintness in 36% on guanethidine and in 18% on methyldopa ; in our series the incidence was higher at 48% and 29% respectively for morning dizziness. Other non-comparative trials confirm this finding of greater postural and exercise symptoms on guanethidine than on methyldopa. For instance, in a larger series (75 patients) Lowther and Turner (1963) found an incidence of postural symptoms in 81% and exercise hypotension in 40% on guanethidine, whereas on methyldopa Johnson *et al.* (1966) found postural dizziness in 7 out of 100 patients and non-postural dizziness in 9%. Some trials of methyldopa in discussing side-effects do not mention dizziness (Smirk, 1963a ; Lauwers, Verstraete, and Joossens, 1963). The few previous trials of bethanidine do not provide sufficient evidence for comparison, but Gifford (1965), as cited above, suggests an incidence similar to that of guanethidine.

Headaches

There was no significant difference in the incidence of headaches with the three drugs. For patients who had an average of one or more headaches a week the figures were 27%, 14%, and 29% on bethanidine, guanethidine, and methyldopa respectively. Lowther and Turner (1963) reported headaches in 30% of their 70 patients on guanethidine, but a large number of trials do not mention the occurrence of headaches—for example, Oates *et al.* (1965) in their comparative study. Smirk (1963b) makes the comment that headaches are seen more often on bethanidine than on other hypotensive drugs, but figures are not quoted.

Bowels

Fifty-two per cent. of our patients tolerating the drug complained of diarrhoea spontaneously while on guanethidine; with direct questioning the incidence was 66%. For bethanidine the incidence was 7% and 10% respectively, and for methyldopa 8% and 13%. In addition, one patient could not tolerate guanethidine because of diarrhoea; as happened to two with methyldopa, one withdrawing from the trial for this reason. Other trials confirm the very high incidence of diarrhoea on guanethidine—for example, 61% of patients (Lowther and Turner, 1963); the low frequency on methyldopa—for example, 4% (Johnson *et al.*, 1966); while one previous trial recorded one patient who had diarrhoea with bethanidine (Johnston *et al.*, 1964).

While there is no doubt about the incidence of diarrhoea with guanethidine, it seems probable that methyldopa produces more diarrhoea than does bethanidine, and it can be troublesome enough to warrant withdrawal of the drug.

Constipation occurred in four (13%) of our patients on bethanidine, one on guanethidine, none on methyldopa. Examination of previous trials indicates that constipation is most unusual with methyldopa or guanethidine. Wilson *et al.* (1965) report one patient out of 43 on bethanidine, while Smirk (1963b) records instances of mild constipation. It seems probable that bethanidine is more likely to produce constipation than are the other drugs.

C.N.S. Side-effects

Seventy-five per cent. of patients spontaneously complained of various degrees of tiredness on methyldopa, as against 10% on bethanidine and 17% on guanethidine. Direct questioning elicited this symptom in 83%, 50%, and 52% respectively. In addition, one patient could not tolerate methyldopa at all because of tiredness. Oates *et al.* (1965) report drowsiness in 47% of their patients on methyldopa, but in none of those on guanethidine. Tiredness from use of bethanidine has been reported by Gifford (1965) in 2 out of 23 patients, but other authors have not found it (Montuschi and Pickens, 1962; Smirk, 1963b; Johnston *et al.*, 1964; Wilson *et al.*, 1965). It is unusual with guanethidine; was not seen in the trials of Page and Dustan (1959), Leishman *et al.* (1959), Bauer *et al.* (1961), or Lowther and Turner (1963); but was described as common by Dollery *et al.* (1960). In contrast, a relatively high incidence of tiredness, temporary or permanent, has been seen in trials with methyldopa—for example, 41% (Johnson *et al.*, 1966) and "most" (Hamilton and Kopelman, 1963).

Dreams were complained of spontaneously in four (17%) patients on methyldopa; with direct questioning the incidence was 38%. No patient mentioned dreams spontaneously on bethanidine or guanethidine, though the incidence was 10% and 14% with direct questioning. Dreams were reported by Johnson *et al.* (1966) in 4 of their 100 patients on methyldopa and Smirk (1963a) in one patient.

Marked depression necessitating immediate withdrawal of the drug occurred in two patients on methyldopa; in both it quickly subsided after treatment was stopped. Mild depression was elicited on direct questioning of two patients (7%) on bethanidine, six (21%) on guanethidine, and three (13%) on methyldopa. This confirms previous trials which show that depression is more troublesome with methyldopa (4 out of 100 patients (Johnson *et al.*, 1966), 3 out of 69 patients (Hamilton and Kopelman, 1963), 5 out of 47 (Smirk, 1963a), 2 out of 59 (Dollery and Harington, 1962)) than with guanethidine (4 out of 28 with one suicide (Bauer *et al.*, 1961), 2 out of 80 (Dollery *et al.*, 1960), none out of 75 (Lowther and Turner, 1963), none out of 25 (Leishman *et al.*, 1959)). Previous trials of bethanidine have not reported any cases attributed to the drug, though Gifford (1965) mentions two incidental instances.

Side-effects of Sympathetic Blockade

The greater incidence of symptoms attributable to excessive hypotension has been discussed above. Other side-effects attributable to sympathetic neurone block also show a lower incidence with methyldopa. This can be seen in Table V from the relative incidence of nasal obstruction or failure of ejaculation. The reports quoted above confirm this differential incidence. There was also less nocturia on methyldopa.

Other Side-effects

The incidence of shortness of breath was similar on all three drugs, and the weights of the patients were not affected by the drugs. However, ankle swelling was a complaint of one patient while on methyldopa, and with direct questions a second patient reported it. Ankle swelling has been reported with methyldopa (Dollery and Harington, 1962; Hamilton and Kopelman, 1963; Johnson *et al.*, 1966); it is uncommon with guanethidine; and has not yet been reported on bethanidine.

Conclusions and Summary

In those patients who tolerated the drugs the control of the blood pressure on each drug was very similar (Tables III and IV).

If a patient is able to tolerate methyldopa control of the blood pressure is more physiological, there being less postural and exercise hypotension on that drug (Tables IV and IX; Figs. 3 and 4). However, 6 of the 30 patients could not tolerate methyldopa, and one additional patient withdrew from the trial because of diarrhoea. The acceptability to the 24 patients tolerating methyldopa was the same as for all 30 patients on bethanidine, as judged by side-effect scores; and by patients' preference (Table VII) differences in favour of bethanidine were not significant (Tables VI and XIb). Tiredness is the most characteristic and troublesome side-effect with methyldopa, patients often not realizing how tired they are until they change to a different regimen.

Bethanidine and guanethidine are qualitatively similar in their side-effects with the exception of the very high incidence of diarrhoea on guanethidine. As shown by side-effect scores (Tables VI and XIIc) or patients' preference (Table VII), guanethidine was much less popular with patients than the other two drugs. Bethanidine also differs from guanethidine in having a much shorter duration of action (Johnston *et al.*, 1964). Guanethidine does produce less postural and exercise hypotension, but this difference is slight (Tables IV and XIIa; Fig. 2) and might not be regarded as of much clinical importance, though it achieves high statistical significance. It might be felt that the higher incidence of side-effects from guanethidine outweighs this advantage.

In summary, methyldopa, provided it is tolerated, produces the best all-round blood pressure control of these three drugs, but 20% of our patients could not tolerate it. Bethanidine was tolerated by all patients, but brought slightly greater postural and exercise hypotension than guanethidine, which, however, produced the largest number of side-effects.

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Congenital Abnormalities of Anus and Rectum: Mortality and Function

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When the results of the surgical treatment of any congenital abnormality which threatens survival are reviewed two aspects seem to be of particular importance: firstly, how many children survive their surgical treatment, and, secondly, the quality of the functional result eventually achieved. This report reviews the mortality and function in 133 patients with anorectal anomalies who were treated in the professorial surgical unit at the Hospital for Sick Children between September 1958 and June 1967.

Anatomical Classification and Method of Treatment

The anorectal lesions have been classified anatomically (Table I) according to a modification (Wilkinson, 1963) of the scheme originally proposed by Ladd and Gross (1934). In this classification stenosis at or just above the anus is due to fibrosis in the wall of the anal canal ; this can be relieved simply by repeated dilatation, preferably under general analgesia. In covered anus the orifice of the anus is covered over completely or almost completely by a lid of skin. In both these types the rest of the anorectal region is normal, and when the stenosis has been fully dilated or the skin lid has been excised from a covered anus subsequent bowel and sphincter function will usually be good. With the exception of a very small group, which includes examples of cloaca and other complicated anomalies such as vesicointestinal fissure, the remaining anorectal anomalies are regarded as variants of rectal atresia. In this the rectum ends blindly in the pelvis above the levator ani muscles but in most cases communicates through a fistula with the urethra, the vagina, or the perineum.

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In all cases with a low fistula to the vagina or perineum this passes forwards from the blind stump of the rectum between the limbs of the puborectalis part of the levator ani. In the high fistulas to the prostatic or membranous urethra or to the posterior fornix of the vagina the fistula is above the levator muscles.

TABLE I.—*Anatomical Classification*

Primary Lesion	Male	Female	Total Cases No.	Total Cases %	Deaths No.	Deaths %
Anorectal stenosis ..	8	6	14	10·5	2	14
Covered anus ..	22	5	27	20·3	2	7
Rectal atresia ..	47	43	90	67·7	23	25
Perineal fistula ..	4	8	12	9	1	8
Low vaginal fistula	—	28	28	21	7	25
High vaginal fistula	—	6	6	4·6	1	16
Rectourethral fistula	29	—	29	21·8	5	17
No fistula ..	14	1	15	11·3	9	60
Rectal atresia middle third of rectum ..	1	1	2	1·5	—	—
Total ..	78	55	133	100	27	20

The object of treatment was to mobilize the rectum and bring it down to the perineum through the limbs of an intact puborectalis sling so as to ensure continence. This so-called "pull-through" operation, which involves a laparotomy and often the division of some of the blood supply of the rectum to gain sufficient mobility, was delayed until the child was a year old or weighed 9.1 kg. (20 lb.). The partial or complete intestinal obstruction associated with rectal atresia at birth was usually relieved by a transverse colostomy in the first few days of life. The exception to this was atresia with a rectoperineal fistula in which dilatation of the fistula alone was employed ; this is possible because since the fistula passes through the levator sling the child will be continent, and in girls the opening of the fistula is usually far enough from the vagina for the