- Rasch, C. A., Cotton, E. K., Griggs, R. C., and Harris, J. W. (1958). *J. Lab. clin. Med.*, **52**, 938.
- Reynell, P. C., Spray, G. H., and Taylor, K. B. (1957). *Clin. Sci.*, **16**, 663.
- Salera, U., Tamburino, G., and Magnanelli, P. (1957). *Sci. med. ital.*, **6**, 179.
- Schiødt, E. (1938). *Acta med. scand.*, **95**, 49.
- Schwartz, M., Lous, P., and Meulengracht, E. (1958). *Lancet*, **2**, 1200.
- Sheeky, T. W., Rubini, M. E., Baco-Dapena, R., and Perez-Santiago, E. (1960). *Blood*, **15**, 761.
- Shemin, D., and Rittenberg, D. (1946). *J. biol. Chem.*, **166**, 627.
- Silverman, M., Gardiner, R. C., and Condit, P. T. (1958). *J. Nat. Cancer Inst.*, **20**, 71.
- Spray, G. H., Fourman, P., and Witts, L. J. (1951). *Brit. med. J.*, **2**, 202.
- and Witts, L. J. (1953). *Clin. Sci.*, **12**, 391.
- (1959). *Lancet*, **2**, 702.
- Stohman, F. (1959). *The Kinetics of Cellular Proliferation*, p. 318. Grune and Stratton, New York and London.
- Sturgis, C. C., and Isaacs, R. (1929). *J. Amer. med. Ass.*, **93**, 747.
- Taylor, K. B., and Morton, J. A. (1958). *Lancet*, **1**, 29.
- (1959). *J. Path. Bact.*, **77**, 117.
- Ternberg, J. L., and Eakin, R. E. (1949). *J. Amer. chem. Soc.*, **71**, 3858.
- Uotila, U. (1938). *Acta med. scand.*, **95**, 415.
- Verloop, M. C., Wolk, M. van der, and Heier, A. J. (1960). *Blood*, **15**, 791.
- Watson, G. M., and Florey, H. W. (1955). *Brit. J. exp. Path.*, **36**, 479.
- Wilkinson, J. F. (1930). *Brit. med. J.*, **1**, 236.
- (1949). *Lancet*, **1**, 249, 291, 336.
- Klein, L., and Ashford, C. A. (1938). *Quart. J. Med.*, **31**, 555.
- Witts, L. J. (1932). *Lancet*, **1**, 495.
- (1950). *Irish J. med. Sci.*, **6**, 315.
- (1956). *Anaemia and the Alimentary Tract*. Royal College of Physicians, Edinburgh.
- (1959). *Canad. med. Serv. J.*, **15**, 645.
- (1960). *Acta haemat. (Basel)*, **24**, 1.

GUANETHIDINE IN TREATMENT OF HYPERTENSION

BY

G. E. BAUER, M.R.C.P.

F. J. T. CROLL, M.R.A.C.P.

R. B. GOLDRICK, M.B., B.S.

D. JEREMY, M.R.A.C.P.

J. RAFTOS, M.R.A.C.P.

H. M. WHYTE, M.R.C.P.

AND

A. A. YOUNG, M.R.A.C.P.

From the Cardiovascular Clinic, Sydney Hospital

Effective blood-pressure control in severe hypertension was first made possible with the introduction of hexamethonium by Paton and Zaimis in 1948. The impetus to this discovery came from our surgical colleagues, who during the preceding two decades had shown that ablation of part of the sympathetic nervous system resulted, in some instances, in remarkable falls in blood-pressure. Hexamethonium, the first ganglion-blocking agent of practical value, was succeeded by pentolinium, chlorisondamine, mecamlamine, and pempidine, the introduction of each of these compounds representing an advance in therapy, particularly in respect to improved gastro-intestinal absorption, more uniform blood-pressure control, and some diminution in side-effects.

Ganglion-blocking therapy with these drugs was accompanied, when given in adequate therapeutic doses, by symptoms of parasympathetic blockade such as blurred vision, dryness of the mouth, severe gastro-intestinal disturbances, difficulty in micturition, and impotence. These pharmacological side-effects were

largely responsible for restricting treatment with these drugs to the severest types of hypertension.

Great strides were made in 1959 with the synthesis of two new compounds which for the first time made good postural blood-pressure control, with selective sympathetic inhibition and without parasympathetic inhibition, a practical proposition. Bretylium tosylate was introduced in Great Britain by Boura *et al.* (1959), and has since been evaluated in many different parts of the world. Guanethidine sulphate, the second compound and the subject of this communication, has been available for a comparable period of time and has been shown to differ from bretylium in a number of important aspects.

It has been our custom at the cardiovascular clinic, Sydney Hospital, to report experiences with new ganglion-blocking agents such as pentolinium (Bauer, 1955), chlorisondamine (Bauer *et al.*, 1957), mecamlamine (Bauer *et al.*, 1959), pempidine (Croll *et al.*, 1961), and bretylium (Bauer, 1961). We now wish to record our impressions of guanethidine after treating 28 patients for a period of up to 12 months.

Pharmacology

Guanethidine sulphate is the generic name for [2-(octahydro-1-azocinyl)-ethyl]-guanethidine sulphate, which was synthesized by Maxwell *et al.* (1959).

Its discovery arose from a fortuitous observation by the same workers that experimental animals treated with a synthetic compound, hexahydro-1-azepinepropionamidoxime hydrochloride (Su-4029), several days earlier failed to respond with the usual pressor action after injection of amphetamine. Subsequently they demonstrated that this same compound, Su-4029, produced a profound and protracted antihypertensive action in renal and neurogenic hypertensive dogs. Clinical trials in human subjects were, however, disappointing. Several compounds related to Su-4029 were next studied and guanethidine sulphate proved to be the most promising. Unlike its predecessor, guanethidine sulphate elicited delayed, profound, and prolonged relaxation of the nictitating membranes in dogs and cats, giving clear indication of interference with the functioning of the sympathetic nervous system.

Pharmacological experiments with this drug may be summarized as follows. (1) Coupled with the relaxant action of the nictitating membrane, guanethidine exerts a marked and prolonged antihypertensive action in unanaesthetized renal and neurogenic hypertensive dogs. (2) Preganglionic stimulation of efferent sympathetic nerves in animals treated with guanethidine fails to elicit normal responses from smooth-muscle effectors, indicating blockade somewhere in the efferent sympathetic nerve-smooth-muscle effector complex. (3) Guanethidine does not suppress but rather augments the response of the effector organs to injected nor-adrenaline, suggesting that the blocking action is exerted within the nerve and not within the smooth muscle. Patients with hypertension due to phaeochromocytoma may develop a marked pressor response to guanethidine.

(4) Conduction along the pre- and post-ganglionic fibres and transmission across the superior cervical ganglion are only very transiently interrupted by guanethidine.

It was therefore assumed that guanethidine acts at the neuromuscular junction of the sympathetic portion of the autonomic nervous system, interfering with metabolism of a chemical transmitter substance. In addition to suppression of catecholamine release from post-ganglionic sympathetic nerve fibres, it has been shown to induce depletion of endogenous catecholamine stores in tissues such as blood-vessels and heart. Sheppard and Zimmerman (1959) demonstrated a 40% reduction of catecholamine concentration after guanethidine administration, and in this way its behaviour is comparable to that of reserpine.

Pharmacological observations on eight hypertensive human subjects were reported by Barnett *et al.* (1960). Reduced reflex sympathetic activity, as judged by the presence of exaggerated postural hypotension, impaired cardio-accelerator and pressor responses to exercise, reduced cold pressor response, and absence of sweating after indirect heating, was observed in all subjects, but in none of the human experiments were sympathetic reflexes completely blocked. No consistent effect on the parasympathetic nervous system was demonstrated; guanethidine did not seem to modify slowing of the heart rate after carotid sinus pressure, nor did it interfere with the cardio-accelerator effect of atropine.

Absorption, distribution, and excretion of the drug were studied by Dollery *et al.* (1960), using radioactive guanethidine labelled with ^{14}C in the guanidine carbon. Incomplete gastro-intestinal absorption was demonstrated by the finding of a total 24-hour urinary excretion of only 20% after an oral dose compared with

a 50% excretion after an intravenous dose. After oral treatment a considerable quantity of guanethidine was recovered from the faeces.

One of the important characteristics of guanethidine is its prolonged and cumulative effect. Urinary excretion after an oral dose was low in the first two hours, then rose to a maximum between two and four hours after ingestion, and appreciable urinary excretion was found even after 72 hours. Clinical studies demonstrated even more gradual onset of drug action and long-sustained hypotensive effect. With relatively large initial doses of guanethidine, such as 100 mg. daily, no significant blood-pressure reduction could be demonstrated in the first four days of treatment, and similarly after cessation of treatment blood-pressure rose gradually over seven days to pretreatment levels. This "hang-over" of drug-effect is particularly noticeable in the presence of impaired renal function and after prolonged periods of treatment with high doses.

Subjects

Since January, 1960, 28 patients (20 men, 8 women) suffering from hypertension have been treated with guanethidine for a period of up to 12 months (see Table). Their ages ranged from 29 to 61 years. All patients were fully investigated in order to establish a cause for their hypertension and also to determine the extent of cardiac, renal, and vascular damage. In addition to a detailed history and full physical examination, all patients had a careful ophthalmoscopic inspection, urinalysis including microscopy, estimation of blood urea nitrogen, electrocardiography, and chest x-ray examination. Further renal function tests, including intravenous pyelography and renal aorto-

Details of Cases

Case No.	Sex and Age	Diagnosis	Initial Blood-pressure (mm. Hg)	Fundi	E.C.G.	Blood urea Nitrogen (mg./100 ml.)	Complications	Treatment			Blood-pressure Control	Side-effects	Cessation of Treatment
								Daily Dose (mg.)	Duration in Months	Additional Treatment			
1	M 49	Ess.Hyp.	210/150	4	1	16		70	12	H'chlor	Good		
2	F 46	Ren.Hyp.	220/140	2	2	19		40	10		Fair	Hypo., Dep.	
3	F 48	Ess.Hyp.	240/120	1	1	17		50	9		Fair	Dia.	
4	M 57	Ren.Hyp.	240/140	4	3	16	Cardiac pain	40	8	H'chlor.	"	Hypo.	
5	F 47		230/130	1	3	17	C.V.A.	20	8	Res.	Good	Hypo.	
6	M 49	Ess.Hyp.	260/150	3	3	19		60	7	H'chlor., Res.	Poor	Dep.	Mental hospital
7	M 58	Ess.Hyp.	240/140	2	3	28	Cardiac pain	75	7	H'chlor.	Fair	Hypo., N.St., Dia.	
8	M 55	Ren.Hyp.	190/120	1	3	14		15	7	H'chlor., Res.	Good	N.St.	
9	F 61	Ess.Hyp.	200/110	1	3	21	Hyp.H.F.	50	6	H'chlor.	Fair	Bradyc., N.St.	
10	M 55	Ess.Hyp.	240/140	1	1	17		50	6	H'chlor.	Good		
11	F 50	Ren.Hyp.	230/160	3	3	46	Cardiac pain	30	6	H'chlor.	Fair	Hypo.	
12	M 52	Ren.Hyp.	210/130	1	3	19	C.V.A.	37.5	6	H'chlor.	Good	Hypo., N.St.	
13	F 52	Ess.Hyp.	260/130	1	0	11		12.5	6	H'chlor., Res.	"	N.St.	
14	M 57	Ess.Hyp.	210/110	1	2	22	"	12.5	5	H'chlor.	Fair	Dia., Dep.	
15	M 49	Ren.Hyp.	210/120	1	2	16		37.5	2	H'chlor.	"	Hypo., Dia., N.St.	Suicide
16	F 57	Ess.Hyp.	240/130	2	3	17	C.V.A.	50	4	Res.	"		
17	M 29	Ess.Hyp.	240/160	4	0	32		12.5	4	Chlor.	Good	Hypo.	
18	M 42	Ess.Hyp.	240/140	2	3	28		50	4	H'chlor.	"	Hypo., N.St.	
19	M 58	Ess.Hyp.	230/130	2	1	20	Myoc.Inf.	50	3	Chlor.	"	Hypo., Dia., F.Ej.	
20	M 48	Ess.Hyp.	200/140	3	1	18	C.V.A.	20	3		"	Dia.	
21	F 43	Tox.Hyp.	230/150	1	3	13		30	3	Chlor., Res.	"	N.St.	
22	M 61	Ess.Hyp.	190/100	2	1	15	Cardiac pain	25	3	H'chlor.	"	Hypo., N.St.	
							C.V.A.						
23	M 52	Ess.Hyp.	210/110	1	1	11		12.5	3	H'chlor.	Poor	Dep.	Overseas
24	M 40	Ren.Hyp.	220/140	2	1	14		40	2		Fair		
25	M 51	Ess.Hyp.	230/140	3	1	23	C.V.A.	20	2	Chlor., Res.	Good		
26	M 55	R.A.St.	210/150	4	2	25	Myoc.Inf.	25	2		"	Hypo.	
27	M 55	Ren.Hyp.	190/110	2	3	30	Hyp.H.F.	25	2	H'chlor., Res.	"		
28	M 47	Ess.Hyp.	170/110	1	0	22	Cardiac pain	12.5	2	H'chlor.	"		

Bradyc. = Bradycardia. Chlor. = Chlorothiazide. C.V.A. = Cerebrovascular accident. Dia. = Diarrhoea. Dep. = Depression. Ess.Hyp. = Essential hypertension. F.Ej. = Failure of ejaculation. Hypo. = Hypotension. H'chlor. = Hydrochlorothiazide. Hyp.H.F. = Hypertensive heart failure. Myoc.Inf. = Myocardial infarction. N.St. = Nasal stuffiness. R.A.St. = Renal artery stenosis. Res. = Reserpine. Ren.Hyp. = Renal hypertension (chronic glomerulonephritis, chronic pyelonephritis). Tox.Hyp. = Toxaemia hypertension.

graphy, were done when necessary, and tests to exclude pheochromocytoma or aldosterone-secreting tumour were also carried out when indicated.

As a result of the above investigations nine patients were thought to suffer from chronic pyelonephritis or glomerulonephritis, one patient from post-toxaemia hypertension, and in one patient significant narrowing of a renal artery was demonstrated on aortography. In 17 patients no cause was demonstrated and they were labelled essential or primary hypertension.

Fifteen patients gave a definite family history of hypertension, or other significant vascular disease; this was almost as common in those with renal hypertension as in those with so-called essential hypertension. In 11 patients hypertension was known to have been present for over 10 years, and in a further eight patients for at least five years.

In accordance with criteria for treatment previously outlined, only the severer grades of hypertensive patients were included in this series. The pretreatment diastolic blood-pressure of all subjects, measured at the disappearance of sound, was over 100 mm. of mercury. In six the diastolic blood-pressure was very high, 150 mm. or more of mercury, and in a further 13 it was 130 mm. or more of mercury.

Eight patients had advanced ocular fundal changes with grade III and IV retinopathy (Keith *et al.*, 1939); four of these had frank bilateral papilloedema, the hallmark of malignant hypertension.

Renal function was regarded as impaired in 12 patients. In four there was significant non-protein nitrogen retention with blood urea nitrogen levels between 26 and 44 mg./100 ml., while in a further eight persistent proteinuria was taken as evidence of renal damage.

Cardiac involvement was present in most patients. Left ventricular hypertrophy, as determined by electrocardiography according to criteria previously published, was noted in all but three subjects, the changes being classified as grade III with tall R waves, S-T segment depression, and T-wave inversion in left ventricular surface leads in 12 instances. Of the three patients with normal electrocardiograms, one (Case 17) suffered from a florid malignant hypertension of relatively recent onset. Two patients had suffered from myocardial infarction, a further seven gave a history typical of ischaemic effort pain, and two had been in frank hypertensive heart failure.

Six patients had suffered from cerebrovascular accidents some time before starting guanethidine therapy.

Of the 28 patients, 23 have had prior antihypertensive therapy. Seven patients, six of whom were included in our published trial, had been given bretylium, and in each instance that drug had been stopped on account of increasing tolerance or marked side-effects. Other ganglion-blocking drugs previously used in these patients included pentolinium in seven cases, chlorisondamine in five, mecamlamine in nine, and pempidine in two. Furthermore, 16 patients had had reserpine or a similar rauwolfia preparation and 13 had had chlorothiazide or one of its derivatives, usually as an adjunct to one of the other drugs.

Patients satisfactorily stabilized on a particular regime were not changed to guanethidine unless side-effects were severe enough to make life miserable.

Compared with our previous series, there has been a subtle change in our clinical material towards a more chronic form of hypertension. The average age of our present patients is slightly higher, and there is a greater incidence of cardiac and cerebral vascular complications but a somewhat lower incidence of advanced retinal changes and renal impairment. The pharmacological properties of the drug, especially its prolonged and cumulative action, made out-patient stabilization relatively simple. This, together with the lower incidence of side-effects, has widened the scope of antihypertensive treatment, and probably explains the difference in patient-material. It is important to bear this fact in mind when comparing the results of our various trials.

Technique of Treatment

Most cases were treated as out-patients even during the initial stabilization period. All were fully informed of the essential properties of guanethidine. They were taught to recognize hypotensive symptoms and warned of the circumstances under which these were particularly likely to occur. No dietary restrictions were imposed except when indicated by the presence of obesity or heart or renal failure.

Guanethidine was made available in 10- and 25-mg. tablets. When blood-pressure reduction was not regarded as an urgent measure we began with 10 or 12.5 mg. once a day at breakfast-time. Out-patients were seen at weekly intervals at the cardio-vascular clinic, when the blood-pressure was measured several times during the morning in the standing position and at least once lying down. Owing to the prolonged and cumulative drug action much less diurnal variation was found when compared with previous ganglion-blocking agents and with bretylium. Adequacy of a given dose of guanethidine could thus be estimated with fewer blood-pressure readings, and this made out-patient supervision easier.

Dosage was increased by 12.5-mg. increments at weekly intervals until an adequate response, judged by standing blood-pressure readings, was obtained. This stage was usually accompanied by the appearance of hypotensive symptoms, especially early in the morning.

More difficulty was experienced in some patients whose treatment began in hospital. Attempts to increase the drug more often than once, or at the most twice a week, when approaching a therapeutic dose, almost invariably led to severe and prolonged hypotensive symptoms necessitating interruption in treatment. It is one of the striking characteristics of guanethidine, as compared with previous available potent hypotensive drugs, that it is more suitable for gradual out-patient stabilization and is hardly to be recommended when blood-pressure reduction is urgent.

The hypotensive effect of guanethidine is greatly potentiated by saluretic agents. The majority of patients in this series were given chlorothiazide 500 mg. twice a day or, more recently, hydrochlorothiazide 25 mg. twice a day. Other hypotensive agents occasionally prescribed included reserpine or a similar rauwolfia preparation. This was advised for those showing a very marked postural difference in blood-pressure in an attempt to obtain some control also in the lying-down position. Except in a few instances the dose of reserpine was kept below or not greater than 0.5 mg. a day.

Results

Blood-pressure Control

Of the 28 patients started on guanethidine, 25 are continuing with treatment. One patient committed suicide while taking the drug, one is at present in a mental hospital being treated for depression, and one interrupted treatment before being adequately stabilized on account of an overseas trip.

Blood-pressure reduction has been achieved in all patients at present under treatment. In 18 blood-pressure control was regarded as good, with standing figures of below 150 mm. Hg systolic and 100 mm. Hg diastolic during a large part of the day. In the remaining seven blood-pressure control was regarded as only fair, which meant a significant reduction but not reaching the figures of 150 and 100 mm.

The dosage of guanethidine which we have found necessary to obtain these results has on the whole been smaller than reported in the literature. Sixteen of our patients were stabilized on 25 to 50 mg. of guanethidine a day, the maximum dose used in this series being 75 mg. a day. We should have no hesitation in exceeding this dosage, but so far have not had need to.

Five patients obtained adequate blood-pressure reduction with 12.5 mg. a day. Four of these were relatively mild cases with grade I or II retinopathy and normal renal function; they all received additional hydrochlorothiazide and two of them also reserpine. The fifth patient (Case 17) suffered from severe malignant hypertension and renal damage. He was initially stabilized in hospital on a daily dose of 50 mg. After discharge from hospital he developed severe morning hypotension and gradually the dose of guanethidine was reduced to 12.5 mg. with good blood-pressure control. He has now continued on this regime for over three months with excellent clearing of papilloedema, and has been able to resume his normal work.

Twenty-three patients received some additional hypotensive treatment. Sixteen were given hydrochlorothiazide and four chlorothiazide in dosage mentioned above. Ten patients were also given reserpine or a similar rauwolfia preparation, often in conjunction with a saluretic agent.

Hypotensive Symptoms

Hypotensive symptoms were mentioned by 13 patients, most of them receiving larger doses of guanethidine. Nine of the 13 were taking 37.5 mg. a day or more, but one complained of hypotensive symptoms on as little as 20 mg. guanethidine a day.

Hypotensive symptoms appeared mainly under four sets of circumstances. On occasion more than one factor was evidently contributory. First of all there was the well-known postural hypotension, patients feeling giddy and somewhat nauseated when standing still for any length of time or when suddenly getting up from the reclining posture. Secondly, there was the hypotension associated with augmented drug-action caused by hot weather, excessive perspiration, marked diuresis, gastro-enteritis, and other forms of sodium loss. The third form of hypotension is confined to the early hours of the morning, and appears to be peculiar to guanethidine and its prolonged and cumulative effect. This morning hypotension takes the form of marked fatigue and tiredness, lack of energy, and muscle weakness, and lasts an hour or two after awakening. It occurs before the day's dose of guanethidine is taken,

and thus results from a cumulative effect of the previous day. Attempts to modify and reduce the incidence and severity of this morning hypotension by dividing the daily dose of guanethidine or by administering the drug at some later time during the day have been unsuccessful. Unless it is possible to encourage a patient to accept it as a reasonable price for adequate blood-pressure control, the only remedy is reduction in the dose of guanethidine, and thus risking loss of good control.

A fourth type of hypotension is that following exertion which takes the form of fatigue and dyspnoea, especially during morning hours. It has previously been noted with bretylium and occasionally reported with older ganglion-blocking agents. Dollery *et al.* have issued the warning that it is inadvisable to dismiss as neurotic patients' complaints of faintness and weakness, even in the face of high-standing blood-pressures, without measuring the blood-pressure immediately after exercise. We have repeatedly observed the tendency for the blood-pressure to be much lower after a brisk walk or climbing stairs in patients receiving adequate doses of guanethidine.

Side-effects

A number of side-effects other than hypotension were noted during the follow-up period. Most of them appeared to be the result of sympathetic inhibition and unopposed parasympathetic action, and resembled those observed with bretylium and to a minor extent with reserpine. Effects of parasympathetic blockade, for so long the bugbear of ganglion-blocking therapy, were conspicuous only by their absence.

A tendency to diarrhoea was reported by seven patients. This largely took the form of a sudden urge to defaecate, usually in the morning hours, perhaps repeated once or twice, rather than true diarrhoea with very frequent watery motions. This "intestinal hurry" was uncommon in patients taking a small dose of guanethidine and was observed only once, in a transient form, in patients taking 25 mg. or less. The severer forms of this disturbance are usually controllable by a belladonna or bismuth and opium mixture or by one of the synthetic parasympathetic inhibitors such as propantheline bromide. A small dose of ganglion-blocking agent such as mecamlamine or pempidine should also control this side-effect.

Nasal stuffiness was noted by nine patients. It was rarely of great consequence, and often was elicited only by specific questioning. Nose-drops proved of little symptomatic help. Some patients complained of soreness of the eyes associated with conjunctival injection, Parotid-pain, a common side-effect with bretylium, was not complained of by any patient in this series although it has been reported by other authors. The effect on sexual function in the male was similar to that observed with bretylium and comparable to that after lumbar sympathectomy. In contrast with ganglion-blocking drugs there was no interference with potency; erection and orgasm occurred normally but seminal ejaculation was absent or much reduced. Occasionally frequency of micturition was observed by patients.

Guanethidine frequently slowed the heart rate. One patient (Case 9), who had suffered from hypertensive heart failure and had been treated with digitalis and diuretics for years, was noted, six months after the beginning of guanethidine therapy, to have a slow

irregular pulse of 35 beats a minute. Electrocardiograms confirmed that the arrhythmia was due to sinus bradycardia with nodal escape. The bradycardic effect of guanethidine is particularly pronounced in patients receiving digitalis and diuretics, and extra care in supervision is advisable under these circumstances.

Four patients developed depressive symptoms during the period of observation. One patient (Case 15) with cyclothymic temperament committed suicide. He had previously developed reserpine depression and was under psychiatric supervision throughout. Ten weeks after the starting of guanethidine treatment and while taking 37.5 mg. of this drug daily in conjunction with hydrochlorothiazide, he was found dead in his factory. A definite worsening of his depression had been noted when last seen a week before his death, and after consultation with the psychiatrist he was urged to accept institutional treatment, which he refused.

Another patient (Case 6) who had previously been treated with electric convulsion therapy for depression is at present receiving psychiatric in-patient treatment. He had proved a difficult patient, unable to be satisfactorily controlled with bretylium and other hypotensive agents. At the time of his admission to the mental hospital he was taking 60 mg. of guanethidine and 0.25 mg. of reserpine a day. It is difficult to estimate to what extent either or both these drugs contributed to his present depressive state.

Two other patients (Cases 2 and 23) complained of depressive symptoms. The latter, a highly intelligent business executive, while taking as little as 12.5 mg. of guanethidine, complained that he had lost his sense of humour, had become irritable and intolerant both in his business and at home. Hypotensive treatment was interrupted shortly thereafter on account of a proposed overseas trip. Forty-eight hours after cessation of guanethidine treatment the depressive symptoms disappeared, described by the patient as "the lifting of a heavy cloud." In retrospect this patient volunteered the statement that these guanethidine side-effects were rather similar to those experienced when taking reserpine some years earlier.

Discussion

Favourable clinical reports on the use of guanethidine in the treatment of hypertension have been published by Page and Dustan (1959), Richardson and Wyso (1959), Frohlich and Freis (1959), Leishman *et al.* (1959), Jaquerod and Spühler (1960), Dollery *et al.* (1960), and others. The first preliminary Australian report, including some pharmacological observations, came from Barnett *et al.* (1960). All of these stressed that this drug constituted a definite advance in the management of severe hypertension and underlined the fact that it is free from the parasympathetic blocking effects which had made treatment with hexamethonium, pentolinium, chlorisondamine, mecamlamine, and pempidine often difficult.

Our experiences during the past 12 months have largely confirmed these early impressions. We have found guanethidine a very suitable drug for the long-term treatment of a large proportion of hypertensive patients in whom blood-pressure reduction has been thought advisable. The slow and cumulative effects of this compound have raised some new problems, but on the whole have made long-term treatment and supervision easier than with most other potent hypotensive agents.

Guanethidine is the first of the ganglion-blocking and adrenergic-blocking agents suitable for out-patient stabilization. We have found it preferable to begin with a small dose of guanethidine, such as 12.5 mg. given in one single daily dose, and gradually increase the dose at weekly intervals until an adequate response, as judged by a satisfactory fall in the standing blood-pressure or the appearance of hypotensive symptoms, is obtained. Used in conjunction with saluretic agents, chlorothiazide or hydrochlorothiazide, the effective dose of guanethidine was between 12.5 and 75 mg. a day.

On account of the slow action we do not regard the drug as very suitable for the control of hypertensive crises such as acute left ventricular failure with pulmonary oedema or encephalopathy. Under those circumstances we would prefer to use parenteral pentolinium or, better still, parenteral chlorisondamine, which lower blood-pressure within minutes.

The cumulative effect of guanethidine may lead to the appearance of prolonged hypertensive symptoms even after apparently satisfactory control without change in dosage. We have observed several times that patients discharged from hospital on a daily dose of 50 mg. develop severe giddiness and weakness, especially in the morning hours on resuming normal activities, and are eventually well stabilized on no more than 12.5 mg. We think it important to be particularly cautious in three groups of patients in whom prolonged and excessive lowering of blood-pressure may well be detrimental: (1) those with incipient and frank renal failure; (2) those with a history of recent cardiac infarction or recent cerebrovascular accident; and (3) elderly patients with advanced atheroma. If treatment with guanethidine is begun under those circumstances closest supervision is obviously essential.

Although only a quarter of our patients were completely free from side-effects, these, with few exceptions, were not very troublesome. Apart from hypotensive symptoms, diarrhoea and nasal blockage were the commonest causes of complaint and were alleviated by the passage of time or by simple symptomatic measures.

Our main concern was the appearance or aggravation of depressive symptoms in four patients during guanethidine therapy leading to suicide in one and readmission to a mental hospital in another. Although it is fairly certain that at least three of these patients were of psychopathic personality and that their psychiatric disability may well have been independent of any hypotensive therapy, it is difficult at this early stage in our experience to exonerate guanethidine completely as at least a precipitating or contributing factor. This suspicion is strengthened by a similar observation of Dollery *et al.* (1960), who reported that two of their patients developed severe depressive states with suicidal thoughts during guanethidine treatment. Awareness of this possibility, thus creating a need for continued supervision, may prevent a repetition of the unfortunate consequences of overenthusiastic and indiscriminate reserpine therapy. Other features support this analogy between guanethidine and reserpine: both drugs interfere with the catecholamine metabolism at sympathetic nerve endings, the clinical use of both is characterized by similar side-effects such as nasal stuffiness, mild diarrhoea, and a tendency to retain water and salt in the body; and now it appears that both may induce or at least aggravate depressive states.

Two favourable aspects of guanethidine remain to be stressed. First, the absence of any significant development of drug tolerance, one of the major disappointments of bretylium tosylate therapy; and, secondly, the absence of any toxic drug effects on liver, kidney, or haemopoietic organs.

Comparison of guanethidine with the specific sympathetic blocker and other anti-adrenergic substance, bretylium tosylate, becomes unavoidable. Although in their main pharmacological action these two drugs appear to be essentially similar, there are certain differences which have an important bearing on their practical use in clinical medicine.

1. Each drug has been shown to have its own peculiar side-effects. Bretylium commonly causes parotid pain and muscle weakness, while guanethidine is more likely to induce diarrhoea and seems to be associated in some patients with the appearance of depressive symptoms.

2. Drug tolerance is a frequent problem with bretylium; with increasing length of observation it has become obvious that many patients require increasing quantities of the drug. This unfortunately necessitates frequent visits to the clinic or the physician's consulting-room, resulting in increased loss of time from work and domestic duties and leading to excessive economic burdens, as well as placing a great strain on the medical staff. So far, tolerance has not been a problem with guanethidine, although minor adjustments in drug dosage may occasionally be necessary.

3. The prolonged action of guanethidine makes it possible not only to administer the drug in a single daily dose but also to estimate its effectiveness with fewer blood-pressure readings. Bretylium has a shorter duration of action and is given in three divided doses a day. It is therefore essential to take several blood-pressure readings at various intervals after administration of the drug to assess its effectiveness.

4. Although neither drug is fully absorbed from the gastro-intestinal system, guanethidine is somewhat superior and gives more constant day-by-day blood-pressure reduction. The incomplete and irregular absorption of bretylium is partly responsible for the unpredictable hypotensive effects, not unlike those seen in the early days of oral hexamethonium treatment.

5. The number of tablets required is less with guanethidine than with bretylium; and this, in our opinion, is a definite advantage. The largest dose of guanethidine prescribed by us was 75 mg. a day—three 25-mg. tablets. With bretylium we have given up to 3,000 mg. a day, or 15 200-mg. tablets, and to many of our patients this has been a definite psychological hardship, quite apart from the bitter taste and large bulk of the tablets.

In summary it is felt that guanethidine is a more suitable drug for routine clinical use.

Summary

Guanethidine sulphate, a new potent oral hypotensive agent, was administered to 28 patients for a period of up to 12 months. This drug selectively blocks adrenergic nerve transmission, leading to sympathetic inhibition with marked postural falls in blood-pressure without any parasympathetic blocking effects such as blurred vision, dryness of mouth, constipation, and bladder atony. Its prolonged action makes it suitable for long-term out-patient treatment provided certain precautions

are taken. It is best given in conjunction with saluretic agents such as chlorothiazide or hydrochlorothiazide. Drug tolerance has not been a problem, and side-effects have been slight except for the appearance of depressive symptoms in four patients. Guanethidine has been compared with another adrenergic blocking agent and has been found to be a more suitable drug for routine clinical use.

We are grateful to Dr. V. G. Balmer and Dr. H. H. Knop, of Ciba Company Pty. Ltd., for a generous supply of guanethidine sulphate ("ismelin") and up-to-date information concerning the drug. We thank the members of the nursing staff of the cardiovascular clinic and the clinical research department, Sydney Hospital, for their kind help. This work was undertaken with the aid of a grant from the Post-Graduate Medical Foundation, which we are happy to acknowledge.

REFERENCES

- Barnett, A. J., Kincaid-Smith, P., and Simpson, F. O. (1960). *Med. J. Aust.*, **2**, 617.
 Bauer, G. E. (1955). *Ibid.*, **2**, 727.
 — (1961). *Jap. Circulat. J.*, **25**, 49.
 — Edwards, A. W. T., Ritchie, F. L., and Whyte, H. M. (1959). *Med. J. Aust.*, **2**, 33.
 — Ritchie, F. L., and Whyte, H. M. (1957). *Ibid.*, **2**, 427.
 Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., and Rosenheim, M. L. (1959). *Lancet*, **2**, 17.
 Croll, F. J. T., Bauer, G. E., Raftos, J., Goldrick, R. B., and Young, A. A. (1961). *Med. J. Aust.*, **2**, 98.
 Dollery, C. T., Emslie-Smith, D., and Milne, M. D. (1960). *Lancet*, **2**, 381.
 Frohlich, E. D., and Freis, E. D. (1959). *Med. Ann. D.C.*, **28**, 419.
 Jaquerod, R., and Spühler, O. (1960). *Schweiz. med. Wschr.*, **90**, 113.
 Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, **197**, 332.
 Leishman, A. W. D., Matthews, H. L., and Smith, A. J. (1959). *Lancet*, **2**, 1044.
 Maxwell, R. A., Mull, R. P., and Plummer, A. J. (1959). *Experientia (Basel)*, **15**, 267.
 Page, I. H., and Dustan, H. P. (1959). *J. Amer. med. Ass.*, **170**, 1265.
 Paton, W. D. M., and Zaimis, E. J. (1948). *Nature (Lond.)*, **162**, 810.
 Richardson, D. W., and Wyso, E. M. (1959). *Virginia med. Mon.*, **86**, 377.
 Sheppard, H., and Zimmerman, J. (1959). *Pharmacologist*, **1**, 69.

METHOSERPIDINE

A NON-DEPRESSANT ISOMER OF RESERPINE

BY

MARY C. HOLT, M.D., M.R.C.P.

Physician, Royal Eye Hospital, London

In the treatment of moderate hypertension reserpine is often the drug of choice, particularly in the older patient in whom a precipitate fall in blood-pressure, such as can occur during administration of the ganglion-blocking and adrenergic blocking agents, may lead to coronary or cerebral thrombosis. Unfortunately, its usefulness may be limited by side-effects, which can be severe. Platt and Sears (1956), for example, were forced to discontinue treatment because of mental depression in 10 out of 54 cases, and found that over half the patients complained of drowsiness and nasal stuffiness. Palmer (1961) has pointed out that rauwolfia alkaloids may cause mild suppression of mental alertness and diminished intellectual capacity, which can be serious in brain workers. He believes this to be far more common, and therefore more important, than the occasional instances of serious mental depression and of the other well-known side-effects. Animal experiments and early clinical studies have suggested that the synthetic isomer of reserpine, methoserpidine