D.B.I., like the sulphonylureas, proves more effective in patients whose diabetes is of short duration.

The ultimate value of maintaining normoglycaemia in diabetics by substances whose mode of action differs from that of insulin remains undecided. There is evidence that hyperglycaemia *per se* is harmful if allowed to persist and can be responsible for the degenerative changes that occur in diabetics (Duncan *et al.*, 1958). The search for an effective non-toxic hypoglycaemic agent is justifiable on these grounds. D.B.I., although its range of action is probably wider than that of tolbutamide, is unsuitable for general use because of the high incidence of unwanted side-effects.

Summary

A new oral hypoglycaemic substance, phenethyl-diguamide (D.B.I.), was administered to 40 diabetic patients, of all grades of severity.

A significant fall of blood sugar occurred in about two-thirds of cases.

Ketosis was not rectified, and occasionally developed, in patients on D.B.I.

In five cases in which tolbutamide proved ineffective, D.B.I. produced a fall in blood sugar.

Ill effects (usually nausea, vomiting, or diarrhoea) appeared in 25 of the 40 cases, precluding the general use of D.B.I. in diabetes.

We thank the Medical Research Committee of the North-west Metropolitan Regional Hospital Board for a grant to pursue these studies, and also Dr. Simpson, of Duncan Flockhart and Co., for supplies of D.B.I. We are grateful to Dr. J. McSorley for haematological investigations, to Miss J. Savage for laboratory assistance, to Mrs. Collins for diet supervision, and to the ward sisters and nursing staff for their most helpful co-operation.

REFERENCES

- Danielson, I. S. (1933). *J. biol. Chem.*, **101**, 505.
Duncan, L. J. P., MacFarlane, A., and Robson, J. S. (1958). *Lancet*, **1**, 822.
Fiske, C. H., and Subbarow, Y. (1925). *J. biol. Chem.*, **66**, 375.
Frame, E. G., Russell, J. A., and Wilhelm, A. E. (1943). *Ibid.*, **149**, 255.
Hagedorn, H. C., and Jensen, B. N. (1923). *Biochem. Z.*, **135**, 46.
Kemsley, W. F. F. (1952). *Ann. Eugen. (Lond.)*, **16**, 316.
King, E. J. (1951). *Microanalysis in Medical Biochemistry*, 2nd ed. London.
Levine, R. (1958). *Diabetes*, **7**, 53.
Lotspeich, W. D. (1949). *J. biol. Chem.*, **179**, 175.
Luck, J. M., Morrison, G., and Wilbur, L. F. (1928). *Ibid.*, **77**, 151.
Lundbæk, K., Nielsen, K., and Rafalsen, O. J. (1958). *Lancet*, **1**, 1036.
Nielsen, R. L., Swanson, H. E., Tanner, D. C., Williams, R. H., and O'Connell, M. (1958). *A.M.A. Arch. intern. Med.*, **101**, 211.
Pomeranz, J. (1957). *J. clin. Endocr.*, **17**, 1011.
Rafalsen, O. J. (1958). *Metabolism*. In press.
Ungar, G., Freedman, L., and Shapiro, S. L. (1957). *Proc. Soc. exp. Biol. (N.Y.)*, **95**, 190.
Williams, R. H., Tanner, D. C., and Odell, W. D. (1958). *Diabetes*, **7**, 87.
— Tyberghein, J. M., Hyde, P. M., and Nielsen, R. L. (1957). *Metabolism*, **6**, 311.

The annual meeting of the Medical Sickness Annuity and Life Assurance Society, Ltd., was held in London on June 24, under the chairmanship of Mr. R. J. MCNEILL LOVE, F.R.C.S. There had been an unprecedented increase in both sickness and life business, he said, arising from the excellent results of the 1956 valuation and the reduction in premiums for sickness and accident insurance. The sickness insurance fund now stood at over £2,700,000, the annual premium income exceeding £360,000, while the life assurance and annuity fund exceeded £5m., with a premium income of over £500,000. The net new life business at practically £2½m. was nearly 40% better than the previous year. New business under the scheme to cover the risk of death under the Medical Sickness Finance Corporation's hire purchase agreements amounted to £661,000. This subsidiary, which financed the hire purchase of cars and medical and dental equipment, charged rates little more than half those current among the ordinary finance companies. The society had formed a new subsidiary company, the Permanent Sickness Insurance Co., Ltd., whose non-cancellable sickness and accident policies would be issued to those in other than the medical and dental professions and, it was hoped, also to nurses, physiotherapists, and others in the ancillary medical services.

A NEW ORALLY EFFECTIVE LONG-ACTING GANGLION-BLOCKING AGENT FOR HYPERTENSION (189c56)

BY

S. LOCKET, M.B., B.S., M.R.C.P.

Senior Physician, Oldchurch Hospital, Romford, Essex

The substance 189c56, as can be seen from the formula, is a derivative of the group of ganglion-blocking sub-

stances originally described by Adamson, Billingham, Green, and Locket (1956). Careful and prolonged clinico-pharmacological investigation of these agents over a period of years has shown that systematic variations in certain chemical groupings could produce corresponding systematic and progressive alterations in pharmacological properties (Locket, 1956b; Green, 1956; Billingham, 1956). 189c56 is one of the compounds developed as a result of this investigation. Chemically it is related to pentacycnum methylsulphate ("presidal"), a ganglion-blocking agent used in the treatment of hypertension (Locket, 1956a; McKendrick and Jones, 1958).

Clinico-pharmacological Studies of 189c56

Compared with pentacycnum methylsulphate, about twice the dose of the active cation of 189c56 by subcutaneous or intravenous injection produced the same fall in blood pressure. Initial studies demonstrated that 189c56 produced hydrodynamic changes and effects on renal function comparable to those of pentacycnum.

It was possible to identify 189c56 in human urine many days after the last therapeutic dose had been injected. For this identification special biological techniques using mice were developed (A. F. Green and N. B. Ward, 1957, personal communication). Prolonged excretion could mean prolonged action with appropriate dosage, and this might be of great advantage because of longer control of the hypertension.

The hypotensive effect of 189c56 begins about two minutes after intravenous injection, but may require up to three hours before reaching its lowest level. The subcutaneous dose is two to four times larger than that necessary to produce a comparable fall in blood pressure by intravenous injection. A local reaction due to the cation may occur at the site of the subcutaneous injection, and this may be immediately apparent. The fall in blood pressure begins half an hour after subcutaneous injection, but on occasion this interval may be two hours.

Administration by Mouth

The observations of the action of the drug by mouth extend over a period of more than a year and are based on many more patients than the few "long-term" cases here reported. The small supply of drug necessitated as wide a coverage as was practicable, on a short-term basis, of severely ill hypertensive patients.

The clinical results are better than with any other member of this series so far used therapeutically, and in many ways better than those obtained in comparative trials with the other ganglion-blocking agents available for clinical use by oral administration (see Cases 2, 4, 5, 7, and 9). Within the dose range of 200* to 1,250 mg. daily by

*All dosages in this communication refer to the salt bis-methylsulphate trihydrate unless specifically stated otherwise.

mouth of the salt 189c56 bis-methylsulphate trihydrate—that is, within the range of 114 to 713 mg. of active cation—given as a single dose, we are able with ease to produce prolonged and marked hypotension in every patient. The hypotension usually begins about 25 to 45 minutes (range 20 to 150 minutes) after the oral dose, reaches its maximal effect on an average about 4 hours (range $1\frac{1}{2}$ to 8 hours) later, and lasts from 10 to 40 hours for a single dose.

Our current procedure is as follows. In any individual patient we start with a small oral dose, usually 200 mg. This is increased by 50 mg. each day until an appreciable hypotensive effect is obtained. This dose is then given daily. In a few days the patient becomes accommodated to the hypotension and it is now less marked. The dose is then increased by 25–50 mg. every few days. During these initial stages it will be necessary to stop on occasion in order to give the patient time to adjust, before proceeding to the desired degree and duration of hypotension. The degree and duration of hypotension achieved show little daily variation once a satisfactory drug level is obtained. After several weeks of daily administration of this constant dose it may occasionally be necessary to reduce it because of increased severity and duration of the fall in blood pressure. We presume this is because of a cumulative effect, as anticipated in our earlier studies.

The daily oral hypotensive dose most suitable for any individual patient is highly critical. Where the maintenance dose lies in the range 300 to 1,250 mg. a reduction of 25 to 50 mg. cuts the clinical effect quite appreciably, and an increase of 25 to 50 mg. converts a moderately severe hypotensive effect into a marked and prolonged hypotension.

Side-effects

Dryness of the mouth is noticeable with the larger doses, as with all other commercially available ganglion-blocking agents. Gastric emptying is hardly affected.

Disturbance of bowel motility is of little importance in this small series. As a rule, passage through the small intestine does not appear to be delayed, but when delay does occur it seems to be due to slowing down in the passage of gut content through the colon. Constipation is seldom complained of, and our information on this disturbance is elicited in most cases by leading questions. When present it is controlled by any mild aperient. Ileus does not occur.

No disturbance of bladder function occurred, nor was it complained of by any patient; yet with mecamlamine and little effective hypotension two of our small “long-term” group (Cases 5 and 9) developed severe retention of urine.

Disturbance of the vision occurs, as with other ganglion-blocking agents. This visual disturbance is in many cases of little significance, and the patient rapidly adjusts to it. On other occasions the use of 0.25–0.5% pilocarpine or physostigmine eye-drops will control the visual disturbance for several hours.

Effect of Renal Damage on Clinical Response

Using this drug, given only by mouth, we are able to control hypertension in malignant hypertensive patients. The severity of the hypertension at all ages, as judged purely by the height of the diastolic pressure, did not affect dosage in the small but severe group reported in this paper. We find that the larger doses, both per kilogram of body weight and per patient, are required by the younger patients. The presence of renal insufficiency may necessitate larger doses. Four patients in this group showed evidence of renal insufficiency, and in two cases this was severe. One patient (Case 2), who when first seen had a very considerable degree of renal impairment, showed a marked improvement in his condition, and his renal function as shown by renal-function tests rapidly improved. He has returned to work. The second patient (Case 9), though his blood pressure was adequately controlled and the retinal changes regressed, died of uraemia. Of the other two cases (Nos. 8 and 10) with

moderate impairment of renal function at the onset, one (Case 8) has shown a progressive deterioration in renal function in spite of an initial marked improvement in general condition and regression of ocular changes, and the other (Case 10) has improved, the blood urea falling steadily from 80 to less than 30 mg. per 100 ml.

It is a curious observation that with an effective reduction in blood pressure these cases and others have shown a reversion of retinal changes to normal, alterations in the electrocardiogram to a more normal picture, reduction in heart size, and amelioration of many disturbing symptoms (paroxysmal nocturnal dyspnoea and angina of effort); and these improvements seem to occur independently of and without necessarily any improvement in renal function. Nevertheless adequate control by the same drugs of the most severe hypertension, which, when treatment begins, is without apparent renal damage, is not followed by the occurrence of renal damage or progressive renal functional impairment.

Effect of Diet on Severity and Duration of Hypotension

No significant effect was elicited upon the duration of action of the orally administered drug, the size of dose, the time of onset of symptoms, or the hypotension, by a very considerable variation in the constitution of the diet. It was found, however, that to produce any specific length of effect the dose of drug necessary in any patient is smaller when given by mouth before breakfast than when given at night before going to bed, even if followed by a meal. For most patients giving the drug before breakfast is the recommended procedure. In some cases, by giving the drug at night and following it with a meal, it is possible to obtain prolonged hypotension, with the maximum hypotensive action whilst the patient is in bed. The less-disturbing later hypotensive effect (amplified by posture and activity) is present when the patient is up and about the next day. In other cases, and particularly when large doses are necessary, a more satisfactory scheme seems to be to give a large dose at night and a small “topping up” dose before breakfast.

Effect of Posture and Activity

Physical activity, when any degree of drug effect is demonstrable, is found to produce a fall in blood pressure. Posture has an appreciable hypotensive effect, the erect position invariably producing a far greater fall in blood pressure than the supine. The drug 189c56, however, produces an easily demonstrable hypotension in the patient reclining in bed during the first 5 to 10 hours of its action.

Action in Combination with Other Drugs

In view of the statement that chlorothiazide will augment the hypotensive effect of many hypotensive agents (including mecamlamine, pentolinium tartrate, chlorisondamine chloride, and reserpine) (Freis and Wilson, 1957; Hollander and Wilkins, 1957; Tapia *et al.*, 1957), some of our patients were given chlorothiazide additionally. We were unable in this brief trial to demonstrate any significant hypotensive action attributable to the combined use of chlorothiazide and 189c56 which in any way differed in intensity or duration from that given by the same dose of 189c56 without chlorothiazide. Nevertheless chlorothiazide produced its diuresis when the blood pressure had fallen in response to administration of 189c56.

After the initial pharmacological investigations all our patients given 189c56 for long-term control of their hypertension receive in addition 2 mg. of “rauwilloid” (a preparation of total active rauwolfia alkaloids) nightly.

Case 1

A girl aged 18½ (weight, 50 kg.) had malignant hypertension. She was a known hypertensive of nine months' duration when she first came under our care more than a year ago. There were visual disturbances, recurrent severe headaches, and vomiting. Nephrectomy for a unilateral

fibrotic kidney had no effect on her blood pressure. Her mother died of malignant hypertension, aged 52.

On examination her B.P. was 260+ / 170-180; blood urea 30 mg. per 100 ml.; renal function normal; urine normal; fundi—papilloedema, numerous haemorrhages, some very large, hard and soft exudates; x-ray examination of chest showed moderate cardiomegaly; E.C.G.—left axis deviation and left ventricular strain patterns.

Treatment with daily subcutaneous injections of 189c56 resulted in a complete relief of symptoms and a return of her fundi to normal. One year ago she was transferred to oral 189c56. Originally she required 1,250 mg. daily; but later was adequately controlled by 750 mg. nightly—this produced hypotension for 16+ hours. She has been back at work for six months and is more comfortably controlled by 650 mg. at night and 150 mg. before breakfast. In addition she receives 2 mg. of rauwiloid nightly. Chlorothiazide, 1 g. daily for four days each week, had no effect on hypotensive response. No gastro-intestinal disturbance. Some dryness of mouth and occasional blurring of vision. Postural symptoms not incapacitating.

Case 2

A youth of 17½ (weight, 60 kg.) had malignant hypertension superimposed on a long-standing renal lesion. He attended the medical out-patient department for six years with albuminuria and low clearance, but no hypertension until 1½ years ago, when his B.P. was 160/100. He was admitted to hospital in September, 1957, with a six-weeks history of vomiting and incapacitating headache.

Examination showed B.P. 260+ / 170, blood urea 180 mg. per 100 ml., albuminuria, bilateral papilloedema with exudates and haemorrhages.

Treatment was started with oral 189c56. The result was dramatic. 800 mg. daily before breakfast produced hypotension lasting 20+ hours. Headaches and vomiting ceased, papilloedema receded, and blood urea fell steadily to 40 mg. per 100 ml. Albuminuria diminished but persisted. In this patient the later trial of mecamlamine, 15 mg. daily before breakfast, produced little effect on blood pressure, which after three hours was 240/150, but vomiting, constipation, abdominal discomfort, and malaise were present; 17.5 mg. of mecamlamine produced moderate hypotension lasting six to eight hours, persistent vomiting, severe abdominal pain, ileus, and intractable constipation. With oral 189c56 this lad was able to return to work as a hospital orderly, but when put on to mecamlamine he became so ill that he was unable to work. No constipation with 189c56. The pre-breakfast dose was changed to 1,200 mg. at night with nearly as good a hypotensive effect (16+ hours), but more comfortable control is given by 1,000 mg. at night (9 p.m.) and 300 mg. before breakfast. He also receives rauwiloid, 2 mg. nightly. Chlorothiazide, 1 g. for four days each week, had no detectable effect on the hypotension.

Case 3

A man aged 56 (weight, 80 kg.) had severe essential hypertension with gross arteriosclerosis.

Examination revealed long-standing hypertension and marked vascular arteriosclerosis. Hemiplegia from stroke 14 months ago; gross retinal arteriosclerotic changes; no papilloedema. Uncontrolled B.P. 260-290/150-170; 450 mg. 189c56 daily before breakfast produced hypotension to 147-170/70-95 for 8-16 hours. No undue side-effects, according to this patient.

Case 4

A man aged 62 (weight, 64 kg.), with severe hypertension with papilloedema and gross arteriosclerosis, was admitted to hospital 10 months ago after a stroke; B.P. 260+ / 150; gross vascular arteriosclerosis; papilloedema, haemorrhages, and exudates. B.P. below 150/100 for 14 hours on 450 mg. 189c56; objectively, physical condition remained unchanged and in general poor; fundi now showed no papilloedema, only occasional haemorrhages and hard exudates; on

mecamlamine 10 mg. twice daily deteriorating mentally and physically, with aphasia and constipation, but no demonstrable effect on blood pressure. All hypotensive treatment with ganglion-blocking agents stopped; rauwiloid, 2 mg. nightly, continued—present condition unchanged. B.P. fairly static at 220/110.

Case 5

A man aged 61 (weight, 72.5 kg.), with severe hypertension and papilloedema, was admitted to hospital with hemiplegia and aphasia of recent onset and rapidly improving.

Examination showed B.P. 300/170; fundi, papilloedema, occasional exudates, and haemorrhages. 500 mg. 189c56—hypotension 14+ hours—upset by dryness of mouth and postural vertigo. Nevertheless incapacitated by giddiness when not receiving treatment. Mecamlamine, 17.5 mg. before breakfast, produced slight temporary hypotension and marked constipation, dryness of mouth, and visual disturbance. Mecamlamine, 20 mg., caused retention of urine, nocturnal frequency, strangury, constipation, though the blood pressure was as high as ever 4½ hours after this drug. Chlorothiazide, 1 g. daily for four days each week, did not augment hypotensive effect of 189c56. Not keen on taking any ganglion blocker in spite of knowing consequences of untreated hypertension.

Case 6

A man aged 61 (weight, 63 kg.), with severe hypertension and papilloedema, was admitted to hospital after mild cerebral catastrophe (cerebral thrombosis) with practically complete recovery. Fundi—papilloedema, exudates, and haemorrhages; B.P. 240/160. 500 mg. 189c56 gave 15+ hours of hypotension. Postural vertigo a nuisance; dryness of mouth slight. B.P. 4½ hours after 10 mg. of mecamlamine 270/140. Increased to 12.5 mg. with no appreciable hypotensive effect beyond constipation. Accepts treatment under duress. Has been under treatment for eight months.

Case 7

A man aged 63 (weight, 81 kg.) had essential hypertension with recurrent left ventricular failure. He was a known hypertensive of more than 20 years' duration, cardiomegaly and gross E.C.G. changes (left bundle-branch block). Recurrent attacks of left ventricular failure. B.P. 240/140; B.P. controlled for 12+ hours below 150-170/90-110 by 350 mg. of 189c56 daily and rauwiloid, 2 mg. at night. Chlorothiazide, 0.5 g. daily for four days each week, did not apparently augment hypotensive effect of 189c56, but produced an appreciable diuresis. He has been under treatment for six months.

Case 8

A woman aged 42 (weight, 56 kg.), with malignant hypertension, had a history of medical attention for preceding two years for severe recurrent headaches, vomiting, anorexia, vertigo, and gross emotional disturbance. Two weeks before admission she developed haematuria and was referred to the genito-urinary surgeon, who referred her to us.

On examination she was well covered; B.P. 260+ / 180; blood urea 55-60 mg. per 100 ml.; urine—much albumin, occasional R.B.C.s and granular casts; I.V.P. normal; cystoscopy normal; E.C.G.—L.A.D. and L.V. strain patterns; x-ray chest—L.V. ++; fundi—papilloedema and numerous exudates and haemorrhages; profound emotional disturbance.

She was controlled satisfactorily on 500 mg. before breakfast, which gives hypotension below 150-160/100 for 18+ hours, and 2 mg. of rauwiloid at night. In hospital felt well, no headaches, no vomiting, bowels regular, slight dryness of mouth, good appetite, slept well, fundi practically normal, but blood urea remained up (last figure 72 mg. per 100 ml., and serum creatinine 3 mg. per 100 ml.). Said she felt better than she had felt for many years. Urine still contained 0.1% protein and some R.B.C. Under treatment for three months. Discharged home to attend out-patient departments. She took drug erratically—said it was because

she felt giddy. Emotional symptoms and vomiting recurred (? due to reappearance of hypertension). Stopped taking tablets. Vomiting and hypertension persisted. Readmitted with hypertension uncontrolled; blood urea, 220 mg. per 100 ml.; oliguria and albuminuria: papilloedema; and B.P. 240+/160 mm. Hg.

Case 9

A man aged 47 (weight, 75 kg.), with malignant hypertension, was a known hypertensive under care of a London teaching hospital for two years, first being treated with oral pentolinium and reserpine with no effective hypertensive control; was then transferred to mecamlamine and reserpine. Admitted to us as an emergency whilst receiving treatment with mecamlamine 10 mg. four times a day. Mecamlamine dose had apparently been halved some few months earlier owing to intolerable and incapacitating side-effects. History of recurrent episodes of severe dyspnoea for at least preceding nine weeks. Constant "asthma" for past nine days. Bowels not open. Contiguous nocturnal and diurnal frequency of many months' duration.

Examination on admission: B.P. 300+/195; pulmonary oedema; fundi—gross papilloedema, numerous exudates, and haemorrhages; E.C.G.—L.A.D. and L.V. strain patterns; chest x-ray examination showed gross left ventricular enlargement, pulmonary oedema patterns; blood urea 180 mg. per 100 ml. Urine—albumin and R.B.C.

Given subcutaneous pentacynium methylsulphate, 10 mg. thrice daily for 24 hours, and then oral 189c56. Controlled with 800 mg. daily. Blood pressure below 160/100 for 16–22+ hours daily on this dose, with rauwiloid 2 mg. nightly. Chlorothiazide, 1 g. daily for four days each week, produced initial diuresis, but no apparent effect on degree or duration of hypotension. On admission he was found to have marked retention of urine. After catheterization on admission, and again in 12 hours, retention of urine cleared, and whilst having 189c56 with marked hypotension no residual urine could be demonstrated, and strangury and frequency did not occur. Bowels, previously intractably constive, opened regularly. Retention of urine due to mecamlamine. Renal insufficiency persisted, and renal function continued to deteriorate in spite of a vast improvement in his mental and physical condition, a controlled low B.P., absence of pulmonary oedema, and no retention of urine. He developed pericarditis and died two months after admission.

Necropsy: Cardiomegaly and pericarditis. No other macroscopic changes. Histology of kidneys showed evidence of malignant hypertensive changes, healed, much fine fibrosis in parenchyma, and a large renal cyst.

Case 10

A man aged 55 (weight, 74 kg.) had malignant hypertension and recurrent attacks of left ventricular failure. He had a four-months history of increasing dyspnoea and recurrent paroxysmal nocturnal dyspnoea.

Examination showed: B.P. 260+/150–170; fundi—occasional exudates and haemorrhages, early papilloedema; urine—albuminuria; blood urea, 82 mg. per 100 ml.; cardiomegaly; E.C.G.—L.A.D. and L.V. strain patterns. Adequately controlled by 600 mg. of 189c56 orally before breakfast; B.P. below 140/95 for 16+ hours. Steady improvement: no constipation; no dyspnoea. Blood urea falling over period of six weeks—last figures less than 30 mg. per 100 ml. At home, well controlled and feeling fit on 600 mg. of 189c56 before breakfast.

Case 11

A man aged 43 (weight, 83.5 kg.), with malignant hypertension, was a known malignant hypertensive of five years' duration, controlled on injections of pentacynium and daily rauwiloid. Now adequately controlled on 500 mg. of 189c56 daily before breakfast and rauwiloid 2 mg. nightly. Without treatment, B.P. 240–260/150–160; with treatment, B.P. below 150/100 for 20+ hours.

Conclusion

In patients with very severe hypertension, compared with all other ganglion-blocking (or presumed ganglion-blocking) agents commercially available for oral use, at comparable levels of induced hypotension, 189c56 has a longer duration of action, a far greater hypotensive action on the supine blood-pressure level, much less effect on the intestinal motility, and no effect on bladder function. It is our impression, too, that the general discomfort associated with the induced hypotension is less disabling than that associated with similar falls of blood pressure caused by these other ganglion-blocking agents.

Two features of the action of 189c56 which seem worthy of comment are: (1) A constant daily effect with predictable results is achieved with oral dosage, though the effective dose by mouth is far higher than either the effective intravenous or subcutaneous dose. (2) The separation in some degree of hypotensive action from effects on gastro-intestinal motility. The evidence suggests that the small intestine and bladder effects are due to high local luminal concentration of active ganglion-blocking agent (Lockett, 1951), also with mecamlamine a direct effect on smooth muscle (Bennett, Tyler, and Zaimis, 1957). Salivary gland and visual effects appear to be due to systemic blood levels and not dependent upon high concentration of drug in the gut. However, ganglion-blocking hypotension too is related to blood levels of active drug. If the drug is given by mouth in an inactive or less active form, activated during or after absorption, we could avoid appreciable gut effect (but not eye or salivary gland effect). Similarly, prolonged excretion at low concentration, excretion of inactivated drug, or destruction of drug in the body would avoid any effects on bladder and ureteral motility. This mechanism might explain the demonstrable absence of ileus and retention of urine after the use of ganglion-blocking drugs by injection. It could also explain the minimal gut effects and the absence of bladder effects with oral 189c56.

Our clinical experience with the drug 189c56 in the treatment of hypertension extends to more than 18 months. During the past year we have used it only by mouth.

Owing to our very limited initial supply we have had to restrict its long-term use to a small group of the most severe hypertensives. We have no reliable experience of the extent of its long-term value in the less severe cases.

Summary

The valuable features of 189c56 would seem to be: (1) It is invariably effective when given by mouth. (2) When given daily, before breakfast and followed by this meal, it consistently produces the expected degree of hypotension. (3) Duration of action is such that single daily dose control of hypertension in some patients becomes possible for the first time. (4) Dosage is highly critical. A small alteration in the controlling dose of the order of 5–12% causes a marked effect on the extent and duration of the hypotension. (5) Constipation is absent or minimal, even with large doses. Ileus does not occur. (6) Disturbances of bladder-emptying do not occur.

Brief case reports are given and may help to amplify some of these points.

I am grateful to Burroughs Wellcome and Co. (Wellcome Foundation Ltd.) for a continuous supply of the hypotensive agents in this group. I wish to thank Dr. F. Prescott, Dr. P. O. Jones, Mr. J. W. Billingham, Mr. A. F. Green, of the Wellcome Research Laboratories, for their unstinted help and advice, and Mr. D. Stevenson, of the Wellcome Chemical Works, for his help with the pharmaceutical preparation of 189c56. I am grateful to Riker Laboratories Ltd., Mr. J. Lumley, and Mr. R. W. Richards for a continuous supply of the "alseroxylon" preparation of rauwolfia known as "rauwiloid." I am also grateful for the help of my housemen and registrars over a

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REFERENCES

- Adamson, D. W., Billingham, J. W., Green, A. F., and Locket, S. (1956). *Nature (Lond.)*, 177, 523.
 Bennett, G., Tyler, C., and Zaimis, E. (1957). *Lancet*, 2, 218.
 Billingham, J. W. (1956). In M. Harington's *Hypotensive Drugs*, p. 35. Pergamon Press, London.
 Freis, E. D., and Wilson, I. M. (1957). *Med. Ann. D.C.*, 26, 468.
 Green, A. F. (1956). In M. Harington's *Hypotensive Drugs*, p. 95. Pergamon Press, London.
 Hollander, W., and Wilkins, R. W. (1957). *Boston med. Quart.*, 8, 69.
 Locket, S. (1951). *Brit. med. J.*, 1, 1331.
 — (1956a). *Ibid.*, 2, 116.
 — (1956b). In M. Harington's *Hypotensive Drugs*, p. 142. Pergamon Press, London.
 McKendrick, C. S., and Jones, P. O. (1958). *Lancet*, 1, 340.
 Tapia, F. A., Dustan, H. P., Schneckloth, R. A., Corcoran, A. C., and Page, I. H. (1957). *Ibid.*, 2, 831.

EFFECTS OF PENTACYNIIUM METHYL-SULPHATE ON RENAL CIRCULATION IN HYPERTENSION

BY

J. R. COX, M.B., Ch.B.

Senior House Officer

AND

J. J. DALY, M.R.C.P.

Research Assistant

The Medical Professorial Unit, Sheffield Royal Hospital

One of the disadvantages of some of the ganglion-blocking drugs used in the treatment of hypertension is the fall in renal blood flow that follows their systemic administration. Reports of the new ganglion-blocking drug pentacynium methylsulphate (139c55; "presidal") claim (Locket, 1956) that it is not associated with gross changes in renal blood flow or glomerular filtration rate and produces a prolonged fall in blood pressure with few side-effects. We have therefore studied the effect of pentacynium on the renal circulation in a number of patients with hypertension.

Present Investigation

Nine patients (seven women and two men), whose ages ranged between 50 and 70 years, were studied (Table I). The minimum basal blood-pressure reading was 230/130, and all showed clinical and electrocardiographic evidence of left ventricular hypertrophy. Cases 6 and 7 had been in heart failure some months previously but had responded

to digitalis and diuretics and were free of this complication at the time of study. Hypertensive retinopathy of varying degree was present in all cases; six showed retinal haemorrhages, and exudates and papilloedema were present in Case 8. In six cases there was a trace of albumin in the urine, but with the exception of Case 8 there were no red cells or casts in the urinary deposits. The blood urea, in the absence of vomiting and heart failure, was above 40 mg. per 100 ml. in seven subjects. Seven patients had been treated for between 6 and 18 months with either pentolinium tartrate or hexamethonium bromide in combination with one of the reserpine alkaloids. Treatment was stopped because with the increasing dosage necessary to control blood pressure side-effects became intolerable. Case 8 presented with malignant hypertension and Case 3 had not been previously treated.

Methods

Each subject lay at rest in bed with the head raised to 30 degrees. Renal blood flow and glomerular filtration rate were measured by a technique previously described (Smith *et al.*, 1938) and inulin and para-aminohippuric acid (P.A.H.) were estimated, using a method as reported by Dick and Davies (1949). Mean blood pressure was calculated as the diastolic plus one-third of the pulse pressure.

Renal-clearance periods lasted 20 minutes. Each value for effective renal blood flow (E.R.B.F.) and glomerular filtration rate (G.F.R.) in Table II is the average of two consecutive measurements. Following the drug two clearance periods were estimated during the period of falling blood pressure. Two further estimations were carried out in six subjects when their blood pressure had remained at or near normal levels for an average of 30 minutes. Percentage changes of blood pressure E.R.B.F. and G.F.R. in Table II are related in all cases to control values. Blood pressures were recorded every two minutes during the study and then six-hourly for 24 hours in both lying and standing positions. Pentacynium was given subcutaneously; Cases 8 and 9 received 12.5 mg. and the remainder 25 mg.

Results

Blood Pressure.—A fall in blood pressure occurred in all subjects between 9 and 20 minutes after the drug. In six the figure was approximately 120/80 by 30 minutes. The diastolic pressure fell to 100 mm. Hg in Cases 1 and 9 by 50 minutes, while Case 4 showed little change in blood pressures at this stage. The average reduction in mean blood pressure for the whole group was 49% at 50 minutes. Diastolic blood-pressure readings in all patients had reached levels below 100 mm. Hg by 120 minutes and remained so for a further 16 to 24 hours.

E.R.B.F.—A mean reduction in E.R.B.F. of 53% occurred by 50 minutes, and the individual changes were closely related in time and magnitude to the alteration in blood pressure. Subsequent clearance values obtained between 30 and 110 minutes in Cases 2, 5, 6, 7, 8, and 9 reveal a mean percentage increase in E.R.B.F. of 28 above mean control value. This figure is largely accounted for by a rise in renal blood flow to above control levels in Cases 8 and 9. The remaining four cases show a rising E.R.B.F., but individually these were still well below control values.

G.F.R.—Changes in G.F.R. showed a similar trend to those of E.R.B.F. but were proportionately greater in amount, producing a fall in the filtration fraction. The reduction in G.F.R. occurred *pari passu* with the fall in blood pressure. Case 4 showed little initial change in blood pressure and a correspondingly small alteration in G.F.R. The initial mean reduction in G.F.R. for the nine patients occurred between 10 and 30 minutes, and was approximately 71%. Subsequent values for G.F.R. obtained between 30 and 110 minutes in six subjects reveal a mean rise of 9%. As with E.R.B.F., this striking rise in G.F.R. for the group is produced largely by the increase in Cases 8 and 9 to above control values. Cases 2, 5, 6, and 7

TABLE I

Case No.	Age and Sex	Basal B.P.	Retino-pathy Grade	Left Ventricular Hypertrophy	Blood Urea mg./100ml.	Previous Therapy
1	50 F	250/160	I	+	41	Pentolinium
2	51 F	260/160	I	+	42	Hexamethonium bromide
3	58 F	270/150	III	+	55	Nil
4	51 M	230/130	II	+	180	Hexamethonium bromide
5	52 M	240/130	I	+	62	Pentolinium
6	52 F	260/140	III	+ with heart failure	31	Hexamethonium bromide
7	70 F	300/140	II	+ with heart failure	35	" "
8	51 F	260/150	IV	+	200	Nil
9	53 F	250/140	III	+	49	Hexamethonium bromide, pentolinium, and mecamlamine