sities and in other ways. They are aware of what such teaching did for them, and I have no doubt that with a little encouragement they could open a new era in medical education in this country. They have a right to expect, and I hope would receive, support from other faculties in achieving this, the common purpose of university education.

Conclusion

The development of postgraduate education, and, in particular, the institution of the compulsory year of hospital practice under supervision before licence is granted to practise independently, have at last freed the undergraduate course to serve its essential purpose, that of training the student's mind to collect and assess data and to form a judgment on them. The fulfilment of this purpose requires, first and foremost, a change in the attitude of teachers, and, second, a reduction in content and an attempt to integrate the subject matter on which the teaching is based. To quote Karl Pearson: "The true aim of the teacher should be to impart an appreciation of method rather than a knowledge of facts," for method is remembered when facts have been forgotten.

TWO NEW GANGLION-BLOCKING AGENTS IN TREATMENT OF HYPERTENSION

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This clinical communication is based on results obtained in using, since January, 1955, the drug 356c54 and since October, 1955, the drug 139c55, two active members of a recently described group of ganglion-blocking agents (Adamson, Billingham, Green, and Locket, 1956). Chemically, 356c54 is $N^1:N^1:N^2$ -trimethyl- N^1 -(6-cyano-6:6-diphenylhexyl) ethylene-1-ammonium-2-morpholinium dichloride, and 139c55 is the 5-cyano-5:5-diphenylpentyl homologue (also called "presidal").

One very important property possessed by this new group of compounds, seen particularly when they were used in man, was the apparent dissociation between their activity as hypotensive agents and their ability to produce ocular changes and gastro-intestinal disturbances (dry mouth and delay in gastric emptying), a dissociation shown well by 139c55.

For both intravenous and subcutaneous injection we used a solution containing 20 mg. of the dichloride of either drug per ml. After discharge from hospital injections were continued by the patients at home.

Pattern of Activity in Patients after Intravenous or Subcutaneous Injections

In our hypertensive patients, using as our criterion of effectiveness a fall to or below 100 mm. Hg diastolic (measured in the sitting position), the minimal effective single intravenous dose of 356c54 was 2 mg. and the maximum dose necessary (used by us) was 12 mg., whereas the minimal effective single therapeutic dose given subcutaneously was 10 mg. and the maximum dose found necessary was 40 mg. With 139c55 the comparable doses were approximately half these, and the maximal subcutaneous dose used in treatment has been 27.5 mg. (Comparative blood-pressure readings were also always taken in the reclining and erect positions.)

The first detectable pharmacological response occurred after a delay of from 5 to 25 minutes. No immediate response occurred after an intravenous injection, irrespective of the dose given. Usually after an interval of about six minutes blurring of vision occurred. At this stage clinical examination revealed this subjective effect to be accompanied by objective changes in the eyes. Also it was often accompanied or immediately followed by a variable degree of bradycardia. A definite fall in blood pressure occurred within another 10 minutes, but the maximum fall occurred 45 to 60 minutes later. The bradycardia began about 10 to 20 minutes before the onset of any hypotensive effect. When the action of the drug was wearing off, the hypotensive effect gradually disappeared some time before the bradycardia subsided.

When the drugs were given by subcutaneous injection there was a somewhat longer delay, ranging from 10 to 60 minutes but on an average 12 to 15 minutes, before the first signs of pharmacological activity appeared. The pattern of activity was identical with that already described for the intravenous injection, but the duration of the desirable hypotensive action was much longer. With identical hypotension-producing doses the duration of hypotension given by 139c55 was longer than with 356c54—in many cases at least 50% longer and in a few even twice as long. With suitably chosen dosage—that is, that dosage which produces the longest period of hypotension below any desired maximum pressure, with the minimum of side-effects—using 139c55, this hypotension often exceeded 12 hours and on occasion 24 hours, and rarely was less than nine hours, and with 356c54 it was rarely less than seven hours and might even exceed 24 hours, though this latter duration occurred much less often with this drug than with 139c55. The maximum fall in blood pressure was reached some 60 to 120 minutes after the onset, and this level of hypotension persisted for some time before it slowly returned to its pre-treatment height.

Activity After Oral Administration

When an effective dose was given by mouth there could be a considerable delay before a fall in blood pressure began. A dose which was about 12 to 15 times the therapeutically effective subcutaneous dose was the usual effective oral dose, but it has, in an occasional patient, been as low as five times the effective subcutaneous dose and as high as 20 times this dose. The predictability of hypotension after oral administration, though certainly as good as was found in this group of patients using the other commercially available ganglion-blocking agents which could be given orally, in our opinion was not good enough, except in a very occasional case, to justify their use by mouth alone in the treatment of the severest cases. When the single oral dose

is increased to 15 to 20 times the effective subcutaneous dose there is still the same delay before the fall in blood pressure occurs. As with all other ganglion-blocking agents when given by mouth, even with this much larger dose, the degree of hypotensive response could not be accurately predicted, and might be very severe, though in some patients the response remained reasonably constant from day to day. Of the two drugs, 139c55 was far less likely to give any prolonged delay before the onset of hypotension, and it gave a higher frequency of successful responses with a more consistent oral dosage.

Ocular changes preceded the hypotension, but dry mouth was less pronounced than occurred with comparable periods of hypotension produced by subcutaneous injection. At all doses and for all comparable periods of hypotension, dry mouth occurred less often and in much less degree and less persistently with 139c55 than with 356c54. In fact, on many occasions dry mouth did not occur with 139c55 (given either by mouth or by subcutaneous injection) even though an effective degree and duration of hypotension was achieved.

Using special techniques, and with radio-opaque meals and repeated observations, we arrived at certain conclusions concerning the propulsion of intestinal contents in relation to these drugs. It was found that gastric emptying, small-intestine propulsion, and large-intestine propulsion behaved as three almost independent variables, and that all ganglion-blocking agents commonly used in the treatment of hypertension did not affect them all in the same degree. Whereas pentolinium and hexamethonium in therapeutic dosage caused a delay in gastric emptying and marked impairment of propulsion in both the small and the large intestine, 356c54 and 139c55 did not appreciably affect small-intestine propulsion. What was of still greater significance, however, was the observation that with identical hypotensive effects 139c55 produced much less delay in gastric emptying than did 356c54.

We suspected that gastric absorption of the drug did not occur, and this was confirmed experimentally (A. F. Green, 1955, personal communication). Here, then, was the explanation for the delay in the onset of hypotension after oral dosage and also the explanation for the greater success and more constant dosage response when 139c55 was used. By giving the drug on an empty stomach and following it immediately by a meal we obtained the greatest success, in that it enabled most of the ingested drug to enter the small intestine *en masse* and hence provide an effective hypotensive tissue-level of drug after absorption. Delay in gastric emptying was produced by initial small-intestine absorption of a minute dose of drug inadequate in that dosage to cause hypotension. Specially coated preparations that prevented gastric solution of the drug were also more successful but were not essential with 139c55. The fall in blood pressure—that is, to below 100 mm. Hg diastolic—lasted at least eight hours on every occasion that oral dosage was effective, and has lasted as long as 30 hours. The usual duration of hypotensive action of 356c54 and 139c55 when given orally was from 12 to 14 hours.

Ocular Effects

The effect on the eyes was usually (not invariably) the first clinical evidence of the action of the drug, appearing within a few minutes of intravenous or subcutaneous injections. The patient complained of blurring of near vision and an inability to read, though distance vision was not affected to any great degree (cycloplegic effect). This visual effect becomes less pronounced in many cases after the drugs have been in continuous use for a few weeks, though initial blurring of the vision within a few minutes of each injection was always noticed. Many patients, particularly older patients, showed a rapid adjustment to this ocular effect and regained their ability to read small type within 30 minutes of the injection. This recovery of vision was particularly marked in the case of 139c55. Visual disturbances could be corrected in considerable degree by

the use of 0.25% to 0.5% pilocarpine or eserine eye-drops. Most patients preferred to use pilocarpine.

Examination of the pupil usually revealed a fixed pupil in the mid-position—that is, neither grossly dilated nor constricted. Measurement has shown that both the drugs produced moderate dilatation of the pupil. Thus a pupil which was 3 to 4 mm. in diameter before the injection dilated to 5 to 6 mm. and was fixed at this diameter, not altering for light or accommodation. Neither fixation of the pupil nor any other demonstrable ocular change implied the absorption of an effective hypotensive dose. Pilocarpine and eserine eye-drops caused marked constriction of this pupil, and homatropine and atropine eye-drops caused further pupillary dilatation.

The most common order of appearance of the changes described was pupillary fixation, bradycardia, and hypotension, and the usual order of disappearance was hypotension, bradycardia, and pupillary fixation.

Effect on Gastro-intestinal Tract

With 356c54 dryness of the mouth was usually present, but varied greatly in degree. With 139c55 dryness of the mouth was often absent and for all grades of hypotension was always less pronounced than with 356c54.

The oral administration of a 15-mg. tablet of neostigmine bromide would occasionally relieve this xerostomia, but in many cases only at the expense of the production of abdominal colic.

Nausea and vomiting did not occur, nor severe constipation. Mild constipation was occasionally present. The absence of appreciable effect upon the small-intestine propulsion, even when using large oral and subcutaneous doses, has been one of the most interesting and useful features of these drugs.

Constipation, when it occurred, was easily remedied by the administration of liquid paraffin or the use of a saline—for example, magnesium oxide emulsion. It appeared to be due to a combination in varying degree of delayed gastric emptying and delayed passage along the large bowel. Oral neostigmine bromide produced more discomfort than purgation.

Fractional test meals have shown an effective cessation of free hydrochloric acid. Histamine injection during this phase of achlorhydria always elicited a free acid response lasting about 30 minutes.

Action on Cardiovascular System

Large doses of both drugs could produce postural syncope. If, one and a half hours after receiving a subcutaneous injection, standing erect and motionless caused dizziness, it was regarded by us as an indication that an effective therapeutic dose had been administered. Blood-pressure readings as usually taken—that is, sitting in a chair or lying reclining in bed—could be used as an indication of the absorption of an effective dose of drug. Standing erect always produced an additional fall of blood pressure, rarely promptly, but usually after a few minutes' delay. The return of this low blood pressure to its previous higher level on readopting the supine or sitting position also occurred only after some minutes' delay. We were always able to lower the blood pressure to below 150/100, and all the patients (except Case 6) in our series of trials had a diastolic pressure before treatment of at least 130 mm. Hg most of the time, and in several it was constantly in the range of 160–190 mm. Hg when not in receipt of treatment.

Bradycardia was present in some degree in most cases, occurring before the fall in blood pressure, and usually outlasting the hypotension. It was directly related to the heart rate before the injection of the drug. An initial rate of 90–100 a minute might fall to 70–80, and an initial rate of 70–80 might drop to 60–65. This rate never fell below 60 a minute.

Angina of effort ceased to occur during effective hypotensive treatment. In one patient severe angina of effort

and constant decubitus angina following two previous coronary thromboses ceased to occur whilst the patient was in receipt of this drug alone and without restriction of activity. In another, angina of effort which had been present for a year ceased to occur for the entire period of treatment (seven months) with these ganglion-blocking agents.

Episodes of severe paroxysmal nocturnal dyspnoea (in one patient these had occurred almost every night for two months with two severe episodes of pulmonary oedema) invariably ceased to occur after the use of daily injections of these drugs.

The electrocardiogram (using as a routine 12 leads—1, 2, 3, aVR, aVL, aVF, and V_1 to V_6) did not reveal any acute changes during the hypotensive phase—that is, it remained identical both before and during the hypotension. Several patients who had been receiving treatment (Cases 3, 5, 10, and 11) showed a reversion to a more normal electrocardiogram: inverted T waves in V leads became biphasic or upright, whereas previously they had been completely and persistently inverted. In one patient the duration of the QRS complex was reduced from 0.14 to 0.09–0.1 second. Three patients showed a gross reduction in the maximum transverse diameter of the heart over this trial period. In one case it was reduced by more than 2.5 cm. and in the others by at least 1.5 cm.

Action of Other Drugs

Subcutaneous injection of atropine (0.5 mg.) diminished the bradycardia, made the vision worse by dilating the pupil, and increased the dryness of the mouth, but it had no effect on the level of the hypotension. Conversely, tachycardia caused by an initial injection of atropine was always slowed within half an hour by injection of an effective dose of 356c54.

Intramuscular injection of 50 mg. of promethazine either before or during the action of 356c54 had no effect on the hypotension, merely making the patients sleepy. Occasional alcoholic drinks (sherry) did not seem to affect the hypotension. Injection of neostigmine had little effect on the bradycardia and none on the hypotension, but possibly made the mouth less dry, though abdominal colic almost invariably occurred.

Renal Function

Measurements of the para-aminohippurate and endogenous creatinine clearances before and during the fall in blood pressure, and also when the hypotension was present, revealed no gross change in any of these values. At the height of the hypotension antidiuresis was pronounced, the urine-minute volume in one case falling from 4 ml. to as low as 0.5 ml. This antidiuretic effect ceased to be noticeable clinically when twice-daily injections were persisted with. Advanced renal insufficiency did not cease to progress in spite of prolonged control of the hypertension and relief of all hypertensive phenomena—that is, incapacitating headache, vomiting, and visual deterioration (see Case 10). With increasing renal deterioration we found increasing resistance to all hypotension-inducing agents.

Tolerance

During the initial few weeks of treatment by subcutaneous injections some adjustment of the dose was necessary in most cases. Once this effective dose was achieved it did not become necessary to increase the dose by more than one-third in any patient, even with progressive renal failure (Case 10). Usually the increase was necessary in severe cases of hypertension stabilized initially on a small daily dose. In some severe cases which at first appeared to require a large daily dose it was possible, and desirable, to reduce the dose after the initial period of treatment, since we could, using this small dose, nevertheless maintain the same degree of hypotension as was initially obtained.

Case 1

A man aged 38 first attended in November, 1953, complaining of headaches and recent poor vision, and more

recently of recurrent attacks of paroxysmal dyspnoea. Examination revealed bilateral papilloedema with retinal haemorrhages. His blood pressure at the time was 220/140–160. Urine contained a small quantity of albumin. Blood urea was 30 mg. per 100 ml.; urea clearance 70% of average normal. Treatment consisted of injections of pentolinium tartrate, a salt-free diet, and digitalization. Nevertheless, left ventricular failure and paroxysmal nocturnal dyspnoea repeatedly occurred. The addition of *Veratrum viride* extract caused vomiting, with no improvement. The addition of rauwolfia alkaloids in September, 1954, did not improve the clinical picture. Early in November swelling of the ankles appeared and he also complained of recurrent episodes of light-headedness. His blood pressure was 240/130–160. In mid-November 3 mg. daily of the rauwolfia alkaloid rescinnamine was added. Morning sickness developed and bowel frequency increased to three times daily. All other treatment was stopped at this stage. After two weeks the dose of rescinnamine was reduced to 2.5 mg. daily because he complained of feeling unwell generally and restless, without being able to be more specific about the symptoms. He was sleeping poorly, his bowels were open three or four times daily, and he had severe occipital headaches. Nevertheless, the episodes of left ventricular failure and nocturnal dyspnoea had ceased and his blood pressure was now in the range of 190–205/120–125. Fundus oculi remained unchanged. His general mental and physical condition remained unsatisfactory.

On January 6, 1955, the rescinnamine was stopped and pentolinium injections were recommenced. After two weeks he was transferred to 288c53 (a ganglion-blocking agent). On March 11 he was transferred to 356c54, receiving a single daily injection of 20 mg. Treatment was accompanied by rapid improvement in his physical condition and sense of well-being. In April this injection was reduced to 17.5 mg. daily. This dose remained effective and kept his blood pressure down to 125–160/75–100 for at least eight hours daily. Early in August a recurrence of severe "bursting headaches" and increase in diastolic pressure to 140 necessitated an increase to 22.5 mg. and later to 25 mg. He remained well on this dose. In November he was changed to 15 mg. of 139c55; this was increased to 20 mg. by January, 1956, and in February was reduced to 18.5 mg. daily. This has kept his diastolic pressure below 100 for at least nine hours daily and below 85 for at least seven hours daily.

Since March, 1955, he has continued to work actively in his business, and this has necessitated constant journeying between Oldham and London. His papilloedema has now apparently faded. Since his transfer to 139c55 he has been able to read newspapers and books with little disability.

Case 2

A woman aged 52 was admitted to hospital with recent cerebral thrombosis. On examination gross bilateral papilloedema with exudates and haemorrhages was found. Her blood pressure on admission was more than 260/180, and remained in this region even with bed rest.

After trying various oral preparations for her hypertension without any effect, in January, 1955, she was put on to a regime necessitating the injection of ganglion-blocking agents, and on March 18 was transferred to 356c54. The initial controlling dose of 40 mg. once daily was reduced later to 30 mg. She remained fit and well on this and attended regularly as an out-patient. Owing to lack of personal cleanliness she, in August, developed infection at the sites of injection. This responded to treatment, but she then ceased to attend and received no drug for three weeks. She was readmitted in stupor due to a further cerebral catastrophe. Immediate recommencement of the drug resulted in a rapid recovery of function and she remained well until October, when she defaulted again.

In this patient 30 to 40 mg. of 356c54 produced a fall in diastolic pressure to below 100 which endured for more than 10 hours.

Early in November she was readmitted after a further acute cerebral episode and was rapidly controlled with 20 mg. of 139c55 daily. On this dose her diastolic pressure remained below 100 for at least 11 hours. She defaulted again in February, 1956, but was persuaded to attend again by her doctor, and on this occasion after two weeks without treatment her blood pressure range was 290-300+/170-190. As expected she had gross papilloedema and was physically and mentally extensively disabled. Further treatment by injection was not considered suitable.

Case 3

This patient, a woman aged 23, when first seen on January 18, 1955, was four months pregnant, and was complaining of breathlessness on effort. Her blood pressure was over 260/160. Ocular fundi, however, did not show papilloedema, nor were there exudates or haemorrhages, but thin almost invisible arteries and engorged veins. Heart examination revealed a presystolic gallop. There was an enlarged left ventricle in the skiagram. Electrocardiograms showed a "left ventricular strain" pattern, and the urine contained a small quantity of albumin. Blood urea was 43 mg. per 100 ml.

This patient, who admitted to some breathlessness on effort, was very reluctant to submit to any treatment. She was, however, persuaded to enter hospital for a rest. At rest in bed her systolic pressure varied between 220 and 300 and her diastolic between 140 and 165 but was never below 140. At this stage various ganglion-blocking agents were tried, and with these we could obtain a fall in blood pressure which lasted for five and a half hours. Routine and specialized investigation, including an aortogram, revealed a small ischaemic right kidney, and nephrectomy was undertaken at the end of February. No fall in blood pressure occurred after this nephrectomy, and histological examination revealed extensive malignant hypertensive changes in the kidneys. At the patient's request no further treatment for her hypertension was given, and she was discharged after this operation.

When seen again as an out-patient at the end of March she had not received any treatment for her hypertension since leaving hospital. She was now 26 weeks pregnant. Her blood pressure was 260/130 on this occasion.

At the end of April she was admitted urgently because of recurrent attacks of left ventricular failure, and a week later she produced a macerated foetus. Her blood pressure range (at rest in bed) was 260-300/130-170. In May treatment with 356c54 was begun. The daily dose was 35 mg. On this dose she was discharged home. She remained well, and after three months her electrocardiogram was more normal and skiagrams revealed a considerable reduction in heart size. In August the dose of drug was reduced and she felt well—so well, in fact, that in September she decided to discontinue all our treatment and receive treatment from a naturopath. We are awaiting the result of the herbalist's regime with interest. Her blood pressure without treatment when last seen by us was 270/140. The consequences of lack of any effective treatment had been fully explained to the husband on several occasions, as well as to the patient. In February, 1956, she still had the same blood pressure and felt quite well.

Case 4

This patient, a woman aged 56, was an unstable hypertensive. Her diastolic pressure varied from 110 to 150, irrespective of rest in bed. She was an emotional person. Electrocardiograms showed left axis deviation only. Because of breathlessness and recent occasional attacks of paroxysmal nocturnal dyspnoea and recurrent occipital headaches, she was admitted for treatment. Early in April she was discharged home receiving 20 mg. of 356c54 daily. On this dose her blood pressure fell from 200-260/110-150 to 120-170/70-95.

When seen on April 29 as an out-patient her blood pressure was 135/90 (sitting) and 120/70 (standing) when taken

four and a half hours after the injection. On May 6 her daughter informed us that she was not desirous of continuing injections. On May 20 her blood pressure was 210/120. She said she felt well. No treatment had been received for two weeks. She continued to attend regularly. On October 7 her blood pressure was 230/130. She was still feeling well and had received no treatment since the last visit. She was now getting occasional episodes of paroxysmal nocturnal dyspnoea, and by the end of November these were occurring every night in spite of the use of mercurials and digitalization. In March, 1956, this patient was receiving treatment from her own doctor for congestive heart failure.

Case 5

A man aged 57 was known to have had a high blood pressure and left ventricular enlargement for many years. At the time of admission he was regularly attending as an out-patient the hypertension clinic of a London teaching hospital.

On April 10, 1955, he was admitted almost *in extremis* with acute left ventricular failure and pulmonary oedema. His blood pressure range was 210-260/170. His blood urea was 53 mg. per 100 ml. He gave a history of having had several acute episodes of paroxysmal nocturnal dyspnoea during the weeks before the present very severe episode. He had not worked for two months. He was taking hydralazine and reserpine at the time of admission. By April 12 he had had several further attacks of left ventricular failure whilst in hospital in spite of a low-salt diet and the use of mercurials. His telerradiogram showed much enlargement of the heart, mainly of the left ventricle. His lungs were considerably engorged. At the cardiac apex in the mid-axilla a presystolic gallop was easily audible. His blood pressure was 210-220/160-170. His retinae showed gross arteriosclerotic changes but without papilloedema.

On April 15 356c54 was begun, and on May 4 he was discharged home to receive 20 mg. twice daily. He has had no further attacks of nocturnal dyspnoea since April 15 in spite of cessation of a salt-free diet and mercurials, and treatment with ganglion-blocking agent only. On May 11 the doses were reduced to 17.5 mg. in the morning and 20 mg. at night, and on July 13 this was reduced to one dose daily of 20 mg.

On August 3 he felt well and was advised to return to work. On this day his blood pressure was 160-170/110-115 some four hours after one injection of 20 mg. In November he was transferred to 139c55, with a much better control of the blood pressure.

When last seen (March, 1956) he remained well, though he still complained of shortness of breath on effort. He was receiving 21 mg. of 139c55 daily subcutaneously but omitting the Sunday dose. His blood pressure four hours after the injection was 160/105 sitting and 120/40 after standing four minutes. His electrocardiogram had now reverted to a more normal appearance and his heart was much reduced in size. No further attacks of paroxysmal nocturnal dyspnoea had occurred since April 15.

Case 6

A woman aged 55, first seen on January 25, 1955, was admitted to hospital on April 25 with a long-standing history of hypertension, two past attacks of coronary thrombosis (with electrocardiographic confirmation of severe coronary damage), and angina of effort since June, 1953. The angina had steadily worsened, and now even the most moderate of efforts caused pain. Decubitus angina occurred every night and on some nights attacks of left ventricular failure. Her blood pressure was 200-220/120-130. She had a presystolic apical gallop and a resting pulse rate of 110 a minute. No improvement occurred with reserpine (1.5 mg. daily) or rauwolfia alkaloids (8 mg. daily) combined with methimazole and nitroglycerin. On May 13 356c54 was begun with 10 mg. injected night and morning. No further attacks of left ventricular failure or decubitus angina occurred. Her resting pulse rate was 76 a minute.

On May 16 the dose was increased to 12.5 mg. night and morning. She felt well and was up and about. No further attacks of angina of effort occurred during either the day or the night, nor any attacks of paroxysmal nocturnal dyspnoea. Her blood pressure was 120/60 and her pulse rate 70 a minute for most of the day.

When seen on June 16 and 23 she was well, her blood pressure remained fairly steady at 120/70, and her pulse at 64 a minute for most of the day.

On June 30 she died suddenly. Necropsy revealed a fresh and recent coronary thrombosis and myocardial infarction.

Case 7

A woman aged 58 was first admitted to the eye department in 1954 because of severe frontal headaches. Her blood pressure was 230-250/150-160. She was admitted to medical wards in January, 1955, with an acute confusional episode due either to hypertensive encephalopathy or to cerebral thrombosis. Her retinae showed numerous ecchymoses and gross arteriosclerotic retinopathy, but no papilloedema.

In May she complained of vertigo and occasional mild attacks of paroxysmal nocturnal dyspnoea. Her blood pressure range was 210-250/130-140. She had been receiving 10 mg. of rauwolfia total alkaloids daily for three and a half months, with a slight effect on her blood pressure and little on her symptoms.

On July 4 356c54 was commenced, with 15 mg. daily by subcutaneous injection. On July 25 the dose was cut to 12.5 mg. Her blood pressure on this date, taken two hours after the injection, was 140/100. This effective hypotension lasted for only four and a half hours, so the dose was increased to 15 mg. daily.

On August 8 her blood pressure was 140/90 and pulse rate 60 a minute, taken five hours after the 15-mg. injection. She continued to attend and remained well. She was transferred to 10 mg. of 139c55 in early December and remained well on this small daily dose with a more prolonged control of her blood pressure. In mid-February, at her request as she was so well, all treatment was stopped. Two weeks later she was fit and well, blood pressure 240/145. A week later she had an acute cerebral catastrophe, was admitted to hospital in coma, and died the following day, the cause being a large cerebral haemorrhage, proved at necropsy.

Case 8

This patient, a woman aged 28, was admitted on June 21, 1955. At her first pregnancy, seven years earlier, she had been told she had "blood pressure." The pregnancy went to term and she was delivered of a normal child of 8 lb. (3.6 kg.). She was kept in hospital for the last 12 weeks of this pregnancy. On May 30, 1955, she had a stillbirth at 28 weeks and was kept in hospital for 10 days. Since her discharge she had felt vaguely unwell, with no energy, weak legs, attacks of vomiting and dyspnoea, and paroxysmal nocturnal dyspnoea. Her vision was blurred and poor, and appeared to be steadily deteriorating.

On examination her blood pressure was 220-300/150-160. Her urine contained albumin, blood urea was 38 mg. per 100 ml., and her urea clearance was 110% of average normal. Her fundi showed bilateral papilloedema with numerous exudates, both "soft" and hard, and numerous haemorrhages. Her heart was enlarged and her electrocardiogram showed left axis deviation and a left ventricular strain pattern.

On July 7 treatment with 30 mg. of 356c54 was begun. This was later increased to 32.5 mg. Her blood pressure range of 220-260/140-160 fell, so that six hours after an injection the readings were 180/130 (measured sitting) and 120/90-100 (standing). The patient characteristically always showed a marked postural fall in blood pressure on standing and only a moderate fall in the reclining or sitting position, and practically none in the supine position.

On July 18, with a marked fall in blood pressure on standing that lasted more than eight hours, she was allowed

home. Occasional postural syncope occurred on standing upright and motionless for more than a few minutes.

A week later she was feeling well. No fainting attacks had occurred since her last visit, and she was doing her housework.

On August 9 her blood pressure was 230/170-180 (sitting) and 110/85 (standing) three hours after injection had been given. In December she was transferred to 139c55 and has remained on 20 mg. of this drug daily. When last seen (March, 1956) she was working; her vision was still poor, and her blood pressure four hours after the injection was 180/120-130 (sitting) and 160/<100 (standing).

Case 9

This patient, a woman aged 59, was admitted on July 26, 1955. We had known her as an old severe hypertensive for more than five years. Rauwolfia alkaloids caused a fall of 10 to 20 mm. in diastolic pressure only. She had gross cerebral damage (two past cerebral thromboses) and also was practically blind from recurrent vitreous and retinal haemorrhages. She showed a mild organic dementia.

On August 8 20 mg. of 356c54 was given subcutaneously. Her blood pressure range was 210-260/130-140 before injection, and one and a half hours after injection it was 150/110 and remained at the level of 150-170/100-105 for 18 hours. On August 9 a further 20 mg. was given subcutaneously. Her blood pressure fell to 120/80 in one and a half hours and remained—in bed—below 140/90 for seven and a half hours; it returned to pre-injection level at 11 hours. She was readmitted in November and was transferred to 139c55, 11 mg. This produced a fall in systolic pressure to below 120 for longer than 12 hours. In this patient 100 mg. of 139c55 by mouth produced hypotension for more than 14 hours with a systolic pressure below 140.

Case 10

A man aged 32 was admitted to hospital on August 9, 1955, with a three-months history of headaches. Two months before admission the headaches became intensely severe and would awaken him at night. For the two weeks before admission they were accompanied by episodes of vomiting. These attacks were particularly severe on awakening in the morning. For two weeks his vision had been poor.

He was admitted to the neurological service because of bilateral papilloedema, exudates, and haemorrhage. His blood pressure was in excess of 260/150-160. Blood urea was 65 mg. per 100 ml. and his urine showed albumin (6 parts of albumin per 1,000 parts of urine) and casts. He was transferred to the medical service on August 20 in view of increasing severity of symptoms. The diagnosis was "probably malignant hypertension, possibly secondary to chronic nephritis." Treatment with 356c54 was begun immediately, the dose being 27.5 mg. twice daily. There was an immediate amelioration of symptoms. Later the dose was reduced to 27.5 mg. a day, and on October 29 he was discharged home. The retinal changes were considerably improved and the electrocardiogram showed upright T waves in leads V₄, V₅, and V₆ (previously T inverted in these leads). However, the renal function has ceased to improve, and the blood urea has remained steadily between 90 and 110 mg. per 100 ml.; urea clearance, 9 ml.; creatinine clearance, 11 to 12 ml. (serum creatinine 6 to 6.4 mg. per 100 ml.); P.A.H. clearance, 40 to 50 ml.

During the next months his condition remained static. At the end of November haemoptysis, cough, and a small area of pulmonary consolidation necessitated his readmission. He was then transferred to 139c55. Originally controlled by 15 mg., the dose was steadily increased to 20 mg. daily by the end of December. At this time his blood urea had risen to 120-140 mg. per 100 ml. and his serum creatinine to 10 to 12 mg. per 100 ml. His hypertension was now not causing any symptoms and his papilloedema appeared to have subsided. At this time 200 to 250 mg. of 139c55 given by mouth produced 12 to 14 hours' hypotension one day in

three. He was discharged home on this dose, but steady deterioration of renal function and the onset of gross oedema of his lower limbs and abdomen (not due to congestive failure) necessitated his readmission in January, 1956. His blood urea was in the region of 200 to 230 mg. per 100 ml., his urea clearance below 5% of average normal, his serum creatinine 16 mg. per 100 ml., and his creatinine clearance about 8 ml. At this time he required 27.5 mg. of 139c55 subcutaneously to produce hypotension for six hours with a blood pressure below 150/100.

Incidentally, during this period 50 mg. of mecamlamine by mouth had no effect on his hypotension but caused vomiting and intractable constipation, and injections of up to 70 mg. of pentolinium had no hypotensive effect. In view of the intractability of his disease all hypotensive agents were stopped. Dietetic measures and treatment directed specifically for his oedema and less hopefully directed towards his heart were without any success, and his attacks of left ventricular failure necessitated liberal use of morphine. He died towards the end of March. Necropsy revealed evidence suggestive of chronic nephritis with superimposed changes of malignant hypertension.

Case 11

A man aged 51 was admitted to hospital on September 8, 1955, having collapsed at work. The left side of his body was flaccid, the left great toe upgoing, and he was cyanosed and frothing at the mouth. His blood pressure was in excess of 260/140. His fundi showed bilateral papilloedema and recent haemorrhages. Blood urea was 41 mg. per 100 ml.; urea clearance, 50–75% of standard clearance; creatinine clearance, 58 ml. a minute; trace only of albumin in urine. He gave a past history of increasing shortness of breath for 12 months and had been receiving treatment for angina of effort during this period. Treatment with 356c54 was begun and he was discharged home on October 29, receiving 20 mg. twice daily.

Towards the end of November he was transferred to 12.5 mg. of 139c55. His blood pressure was controlled all the waking day with this dose, and postural symptoms were usually present for the second and third hours after the injection. Dyspnoea had practically disappeared, and angina of effort did not occur. Urea clearance has remained normal. His fundi have improved considerably. Papilloedema has subsided and haemorrhages were rarely seen. ST depression and T-wave inversion in chest leads were less pronounced, the T wave being biphasic or upright. The heart size had been considerably reduced. In March, 1956, his blood pressure four hours after his injection was 105/55 (sitting).

Case 12

A man aged 57 was admitted to hospital on February 10, 1956, with a history of incapacitating headaches for 10 weeks, steadily increasing visual deterioration for eight weeks, and frequent vomiting, particularly on awakening in the morning, for three weeks.

On clinical examination his blood pressure was 210–270/135–160. His fundi showed gross bilateral papilloedema and numerous exudates and haemorrhages. Extensive macular haemorrhages appeared to be the main cause of his visual impairment. His urine contained albumin. His blood urea was 40 mg. per 100 ml.; urea clearance in excess of 80% average normal; and creatinine clearance 90–100 ml. a minute. Treatment with 139c55 was begun and he was stabilized on a daily dose of 12.5 mg. and discharged home. When last seen (April 4) his blood pressure, sitting in a chair seven hours after a subcutaneous injection of 12.5 mg. of 139c55, was 90–110/50–80, his papilloedema had subsided considerably, no retinal haemorrhages could be seen but numerous exudates, and his vision remained very poor. He was feeling quite well.

Case 13

A woman aged 55 was admitted to hospital on February 18, 1956, complaining of recurrent attacks of paroxysmal

nocturnal dyspnoea and severe shortness of breath. She had been attending as an out-patient regularly since 1950. Her blood pressure since that date has varied between 210 and 300 systolic and 140 and 180 diastolic during most of this period. On the occasion of this admission her diastolic pressure was 170 mm. Hg (± 15 mm. Hg). Her urine contained 1+ albumin, and renal-function tests were normal. Her fundi showed bilateral papilloedema with a few small haemorrhages and exudates. She was put on to 139c55, a daily injection of 15 mg. consistently producing a fall of blood pressure for more than 10 hours, during which period the diastolic pressure remained below 90. When last seen as an out-patient (March 29) her condition was excellent.

Case 14

This patient, a woman aged 49, was admitted on August 14, 1955, with a history of sudden onset of severe pain in her neck and behind her right eye. The onset of the pain was accompanied by vomiting.

Clinical examination confirmed the presence of a sub-arachnoid haemorrhage, but neurosurgical examination did not reveal the presence of an aneurysm. Her blood pressure was 200–240/130–145. Her condition improved quite satisfactorily and it was found that 200 mg. of 356c54 by mouth produced a considerable degree of hypotension, the systolic pressure being below 110 for more than 14 hours. During her stay in hospital she had several epileptiform fits which were associated with hypertensive episodes. Piperoxan and phentolamine tests were negative. She was treated with mixed rauwolfia alkaloids and was discharged.

Her condition as an out-patient remained most unsatisfactory. Her hypertension and epileptiform fits were not controlled. She was readmitted on December 12. Her hypertension was found to be adequately controlled by a single injection of 139c55, 10 mg. of which gave at least 12 hours of hypotension, and she was discharged. When last seen (April 4) her condition was very satisfactory, her blood pressure three and a half hours after the injection being 140/90.

Case 15

A woman aged 54 was referred for treatment of her hypertension from the ophthalmic department, which she attended because of visual deterioration, and where she was found to have numerous retinal and macular haemorrhages.

On admission her blood pressure range was 190–250/130–160. Renal-function tests were normal. Her retinae showed gross arteriosclerotic changes but no papilloedema. She was adequately controlled by 10 mg. of 139c55, which produced hypotension for more than 12 hours with a diastolic pressure below 100.

Discussion

This report is concerned with the clinical results of the trials of drugs 356c54 and 139c55 when used in the treatment of severe hypertension. These drugs differ in many of their detailed actions from those of the methonium group. I would emphasize here the gradual though reasonably quick appearance of activity, the easily demonstrable prolonged effect when given by the intravenous or subcutaneous routes, as well as the fall in blood pressure in the reclining and sitting positions, their relative lack of depression of small-intestine propulsion, their ability to slow the heart rate, and the slower appearance of postural symptoms on assuming the erect posture.

Experience with other members of this group of compounds has revealed that some members have a differential action on ganglia concerned with different activities though situated in the same autonomic group. Thus hypotensive ability does not appear to run parallel to ocular, oral, and gastro-intestinal activity. This is well shown in a comparison between 356c54 and 139c55. From results to date we think that there is a reasonable chance of evolving a compound showing considerable dissociation of hypotensive power from the other activities not required in dealing with hypertension.

The trial group of patients (5 male, 10 female) were selected only because of their severity, and were in fact consecutive admissions. They happen also to give a reasonable selection of the various disorders associated and often attributable to hypertension. Cases 1, 10, 11, and 12 (male), and 2, 3, 8, and 13 (female) were probably cases of malignant hypertension. Cases 2, 9, and 13 (female), and 11 (male) had cerebral thromboses, Cases 3, 4, 5, 6, 7, 8, 9, 10, 11, and 13 had recurrent attacks of left ventricular failure. Case 11 had angina of effort for at least a year, Case 6 had severe angina of effort and decubitus angina, and Cases 1, 2, 8, 9, 10, 11, 12, 13, and 14 had severe incapacitating occipital headaches often accompanied by vomiting and made worse by reclining. Gross vascular arteriosclerosis in peripheral vessels was easily demonstrable in Cases 2, 4, 5, 6, 7, 8, 9, 11, 13, and 15. The ages of the patients were 23, 28, 32, 38, 49, 51, 52, 54, 55 (two patients), 56, 57 (two patients), 58, and 59 years, and all except the 23-year-old woman and the 32-year-old man were known to have had severe hypertension for more than two years, and in some cases (Nos. 5, 6, 7, 8, 9, and 13) for more than seven years. Every patient in this series was fully investigated for phaeochromocytoma (phenolamine and piperoxan in every case) and had full radiological investigation, including intravenous pyelography and often aortograms—for example, Case 3.

In no case were any of the hypertensive signs and symptoms made worse by treatment. In every case in which a change occurred it was for the better. In every case attacks of left ventricular failure stopped when treatment began, breathlessness was relieved, and angina of effort ceased to occur. When electrocardiographic changes occurred they were towards normal, and heart size was reduced. It was believed that the papilloedema in Cases 1, 2, 8, 10, 11, 12, and 13 was subsiding or has subsided. Only one patient (Case 10) in this group had grossly impaired renal function. There was no evidence to suggest an increased liability to thrombosis in arteriosclerotic vessels; in fact, the evidence in these patients and many others was to the contrary. Those headaches which were hypertensive in origin were immediately ameliorated, but they recurred when treatment was inadequate to maintain the lowered blood pressure.

In conclusion, there can be no doubt, from our experience with this group of patients, that the ability to maintain a sustained hypotension with the drug 356c54 and, better still, with 139c55 resulted in a rapid relief of symptoms and a reversion to normal of many of the changes known to be associated with persistent severe hypertension.

Summary

This paper is a report on the use during the past year and a half of two of a new group of ganglion-blocking agents (compounds 356c54 and 139c55) in the treatment of 15 severe cases of hypertension. These compounds were given subcutaneously, and the results so far have been most satisfactory. The advantages of the compounds, particularly 139c55, in the treatment of hypertension lie in the more gradual onset of activity, the greater duration of action, which makes treatment possible with a single or at most two daily injections, the slowing effect on the heart rate, and the relative lack of action on the small intestine.

I am indebted to a number of lay, technical, and medical helpers, too numerous to mention. I am grateful to my scientific collaborators, Dr. D. W. Adamson, Mr. J. W. Billingham, and Mr. A. F. Green, without whose close chemical and pharmacological association this work would never have been accomplished. I am indebted to Dr. F. Prescott, from whose original suggestion this entire investigation arose, and to the Wellcome Foundation for supplies of ganglion-blocking agents and for help in many other ways. I wish to acknowledge the careful and ungrudging work of Mr. H. Williams, Mr. A. Richardson, and the other staff of the Oldchurch Hospital pharmacy; and Mr. D. Stephenson, of the Wellcome Chemical Works. I am grateful to Dr. J. Stewart and the technical staff of the radiological department of

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INFECTED SUBDURAL EFFUSIONS

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The striking improvement in the results of treatment of purulent meningitis in recent years has led to the increasing recognition of the relative frequency with which subdural effusions complicate convalescence in such cases in childhood. Partly responsible also is the present awareness in paediatric circles of subdural collections of fluid of various kinds in infancy.

The condition has long been recognized and cases have been described; thus Schwartz (1916), in a paper on the aetiology of pachymeningitis haemorrhagica interna in infants, describes a fatal case of meningitis with bilateral subdural effusions. The pathological findings were described by Spitz, Pollak, and Angrist (1945). Only two cases were encountered in a series of post-mortem examinations of 95 consecutive deaths from meningitis in a total of almost 5,000 necropsies. One was an elderly man, the other a child of 3 years. Spitz *et al.* concluded that "subdural suppuration is a rare complication of purulent meningitis, although a higher incidence will undoubtedly be revealed as a result of more complete necropsy studies."

The contrast in recent American experience is expressed by McKay *et al.* (1953), who state that 60% of all infants under 1 year of age suffering from meningitis due to *H. influenzae*, pneumococci, and meningococci develop subdural effusions. Likewise Smith *et al.* (1951), in a period of 11 months, found 20 cases of subdural effusion in 43 infants under 2 years admitted with proved meningitis. The role of *H. influenzae* (Pfeiffer's bacillus) as the causative organism in meningitis associated with subdural effusion is impressive, appearing in at least 50% of the American cases, the pneumococcus and meningococcus accounting for the remainder. *H. influenzae* was the fourth commonest cause of meningitis; but in infants it was the most frequent, with the highest incidence in the second six months of life. It is possible, however, that subdural effusions may be peculiar to the age of the patients rather than to the causative organisms.

The case-fatality rate of *H. influenzae* meningitis was reported by Mutch (1941) as being between 90 and 100%. The very significant change in mortality which has occurred was recorded by Bloor, Grant, and Tabris (1950). Their 44 cases showed a mortality of 22.7%; but when divided into cases above or below 9 months of age the mortality was 8% and 42% respectively. These authors make no mention of the presence of sub-