followed up for periods varying from three months to two years, and, although it has not been possible to obtain follow-up blood pictures, in no cases have symptoms returned.

Discussion

The fact that these cases of anaemia are labelled idiopathic indicates that their aetiology is obscure. A combination of factors has probably rendered insufficient the amount of iron available for haemoglobin synthesis. It is less likely that there was an excessive iron loss by way of chronic haemorrhage, although the possibility that this had occurred in the past cannot be ruled out. The deficiency of hydrochloric acid in the gastric secretions was probably one of the determining factors, but it cannot have been the primary cause, as four of the patients were not achlorhydric. Also, as noted by Davidson and Fullerton (1938), not all achlorhydric people are anaemic, and, whereas the incidence of achlorhydria increases with advancing years, idiopathic hypochromic anaemia in old people is rare.

The possibility that the anaemia in Case 9 was a toxic manifestation of lead has already been considered. We have also pointed out that all but one of the men had less than three months' service. Probably the amount of extra physical exertion involved in their basic training was sufficient to produce symptoms in subjects previously anaemic but hitherto symptomless. This certainly was true of Case 20, in which the gross degree of koilonychia was evidence of a long-standing anaemia, and also of Case 5, in which an anaemic state had been demonstrated twelve months previously.

There is, however, a further possible explanation. Cantarow (1947) states that 23% of the minimal iron intake is required for the manufacture of muscle haemoglobin and for use in muscle and other parenchymal cells. This iron is not available for blood haemoglobin formation, and blood haemoglobin may constitute an important source of iron necessary for growth. Davidson *et al.* (1933) have shown that persons with achlorhydria exist on an intake of iron which is very near the borderline. In most cases the first few months of the recruits' lives in the Army are accompanied by a marked increase in weight, due, in part, to enhanced development and hypertrophy of the musculature. This change is more pronounced in those previously immature and of poor physique. It may be that this abnormal demand for iron cannot be met by increased intake, on account of impaired absorption from the gut, and iron for the enhanced development is obtained at the expense of the blood haemoglobin. Thus either an anaemic state is produced or a latent anaemia is rendered obvious.

Summary

An account is given of 20 cases of idiopathic hypochromic anaemia occurring in young men.

The majority of cases showed a definite tendency to immaturity, and nail changes were present in some. The typical syndrome of hypochromic anaemia as it occurs in women was not seen.

Achlorhydria or hypochlorhydria was present in 16 of the cases. Of the remainder, normal gastric acidity was present in one and hyperchlorhydria in three.

The blood pictures rapidly improved, and in most cases became normal on treatment with adequate amounts of iron.

There was no indication that the anaemias were the result of blood loss. They were probably due to an increased demand for iron coupled with defective intestinal absorption.

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ORAL HEXAMETHONIUM BROMIDE IN ESSENTIAL HYPERTENSION

BY

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The group of compounds known for convenience as methonium halides emerged in the course of a systematic search for synthetic substitutes for curare. The pharmacological researches of Paton and Zaimis (1949) showed that compounds with carbon chains of intermediate length (five or six atoms) exert their action at ganglionic synapses rather than at neuromuscular junctions and that they are capable of influencing profoundly the functions of the autonomic nervous system. An opportunity was thus provided for a new approach to the management of diseases, such as peptic ulceration and essential hypertension, in which hyperactivity of the autonomic nervous system might be conceived to play a part.

These drugs are stable and soluble, and are apparently absorbed freely unchanged from the alimentary tract. As soon as adequate amounts became available Kay and Smith (1950), working on peptic ulcer, showed that hexamethonium bromide is pharmacologically active when given orally. We were fortunate in having direct access to Kay and Smith's work in progress. It seemed to suggest the possibility that a simple effective method might be devised of controlling by oral drug therapy the manifestations of essential hypertension. A clinical investigation along these lines was begun early in 1950. As the methonium drugs are now freely marketed we feel it appropriate that we publish our results and attempt to indicate provisional tentative conclusions.

Our material consists of 15 cases of essential hypertension under treatment for periods varying from ten months to one month. The latter short period refers to one case of malignant hypertension (Case 15) which did not yield to methonium drugs. The patient was submitted to surgery and died. Most of the others (cases of severe hypertension in the benign phase) have come under treatment because of disabling symptoms. Apart from such brief periods in hospital as were necessary for investigation and assessment, these have been treated on an out-patient basis, and the aim has been to keep them not less active than they were before treatment began. Particulars of age, sex, and duration of treatment are listed in Table I. In addition, for convenience, an indication is given in this table of the general results achieved.

TABLE I.—List of Cases and General Assessment of Results

Case No.	Age	Sex	Duration of Therapy	Result
1	29	F	10 months	Improved
2	50	F	9 "	I.S.Q.
3	51	F	8 "	Worse
4	35	M	8 "	Improved
5	62	F	7 "	"
6	57	M	7 "	I.S.Q.
7	34	M	7 "	Improved
8	43	M	7 "	Worse
9	44	F	7 "	Improved
10	47	M	7 "	I.S.Q.
11	49	F	6 "	"
12	65	F	3 "	"*
13	27	F	3 "	"
14	45	F	2 "	"
15	27	F	1 month	Worse†

* Refused to persist owing to lack of subjective improvement.

† Malignant hypertension uncontrolled by C6 therapy; operation; death after second-stage total thoracic sympathectomy and splanchnicectomy.

Preliminary Investigations

Of the fifteen cases studied, thirteen were admitted to hospital for initial assessment. Some in fact had been under medical in-patient treatment for many weeks without response and were transferred to our care as potential subjects for surgery. The investigations carried out were those appropriate for cases of essential hypertension, and need not be fully detailed here. They included a thorough cardiovascular survey, assessment of renal function, and recording of fundal pathology. Lability tests were carried out with "sodium amylal," and in a few cases of violent and variable hypertension piperoxane tests were done to shed light on the possibility of the existence of pheochromocytoma. Particular attention was naturally paid to estimation and recording of blood pressure, multiple readings being taken with the patient both erect and recumbent. In Tables II and III we have endeavoured to indicate a comprehensive clinical assessment by means of the groupings suggested by Palmer, Loofbourow, and Doering (1948). Changes in fundi, heart, and kidneys are graded 1-4. Fundal standards are those of Wagener and Keith (1939). Each case is given a P.L.D.* number representing the highest grade of damage found under any of the three headings.

Institution of Therapy

For short non-significant periods at the beginning of treatment of the earliest cases, pentamethonium (C5) was used alternately with hexamethonium (C6) (largely because the former drug was more readily available at that time) in an attempt to determine their comparative

merits. These rather inadequate observations favoured C6, and the use of C5 was discontinued, especially because we quickly found that results in individual patients showed so much diurnal variability that intentional introduction of variables would render them insusceptible of analysis. The routine, therefore, has been to begin with test doses of C6 intramuscularly, the initial dose being 25 mg. If this proved ineffective, subsequent doses of 50 or even 100 mg. were given. This routine was designed to screen the cases for unusual sensitivity to the drug. It is in fact rather doubtful whether it is of value. The usual effect of intramuscular C6 is well known (Burt and Graham, 1950; Turner, 1950; Restall and Smirk, 1950). There is a sharp drop in blood pressure, maximal in about half an hour, with recovery over a period of 6 to 8 hours, the postural element in the hypotension persisting longest.

Following the test doses administered parenterally, oral therapy was begun. We found it most convenient to use tablets of 0.25 g. administered crushed, with water, before meals. At the same time the patients were made fully ambulant, and in most cases were discharged to the follow-up clinic within a few days. The commencing dose was 0.25 g. three times a day, before meals, and this was raised to a dosage adequate to lower blood pressure or, alternatively, to the maximum tolerable dose. In an "average" case the dosage stabilized at approximately 0.5 g. thrice daily, before meals.

Longer-term Assessment.—After discharge the patients were seen at regular intervals: Cases 1 and 9, for example, have been seen weekly without interruption for ten and seven months respectively. On each occasion they have spent the entire day at the hospital, where frequent blood pressure readings have been taken, renal status has been assessed, eye grounds have been examined, and, in addition, their general clinical condition has been objectively and subjectively evaluated. The other cases have been seen every few weeks.

Effects of Therapy

The pharmacological action of the methonium compounds is to diminish synaptic conduction throughout the autonomic nervous system and at adequate dosage to produce "synaptic blockade." The clinical effects of the operation of this mechanism must obviously be widespread, complex, and profound. There has been an understandable tendency to classify these effects in relation to the therapeutic objective of the investigator as primary effects and side-effects. Thus, if the investigation concerns peptic ulceration, lowering of blood pressure is a side-effect, while if hypertension is under consideration lowering of blood pressure becomes a primary effect and modification of the digestive processes is classified as a side-effect. We believe this differentiation to be unjustified. All the effects of methonium therapy seem to be predictable manifestations of the physiological action of the drugs. If the term "side-effect" is to be retained it can be only as a convenient abbreviation for effects inconvenient to patient and investigator.

Undesirable Effects

In the management of a case of essential hypertension the object of treatment is to lower the blood pressure and so to diminish strain on heart and blood vessels, especially the arterioles. It is probable that this can always be achieved by adequate amounts of the

*P.L.D. is used in the text and tables as a convenient abbreviation for Palmer, Loofbourow, and Doering.

methonium compounds. In addition, however, undesirable effects may be produced as a result of the actions of the drugs on either (a) the sympathetic, or (b) the parasympathetic.

(a) *Related to Sympathetic*.—Excessive lowering of blood pressure. It is common to have the patient complain of a certain amount of giddiness and lassitude. In effective dosage methonium drugs produce marked postural hypotension. In moderation this is therapeutically beneficial. When excessive, it may be completely incapacitating and result in the patient requiring to spend a day in bed. We have found patients to complain of dimness of vision at times when blood pressure is excessively low, apparently a pre-syncopal phenomenon. Marked postural tachycardia has not been observed. Our findings in this respect do not coincide with those of Restall and Smirk (1950). The hypotension produced by methonium therapy seems to differ strikingly from that following bilateral "Smithwick splanchnicectomy" and the comparison favours methonium. The absence of tachycardia may be explained by depression of the synapses of the cardiac ganglia.

(b) *Related to Parasympathetic*.—The effects on gastric secretion and motility are well known (Kay and Smith, 1950). In addition, all patients on effective dosage have relatively dry mouths and are constipated. In some there is progressive impairment of appetite culminating in anorexia. These modifications of alimentary function introduce difficulties in regulation of dosage, discussed more fully below. Almost all patients state that methonium therapy weakens the power of accommodation so that it may be difficult, for example, to read a newspaper. Two patients complained of dryness of skin and scalp.

Results

There is no doubt that in a condition such as essential hypertension final evaluation of any new method can be made only after many years of continuous work and careful recording of observations. We propose, therefore, to present our interim "results" only in quite general terms, and also to endeavour to analyse these in relation to a few of the more important elements in the clinical pathology of the condition.

As will be seen from Table I, five of our fifteen cases have been classified as improved, while the remaining ten are unchanged or worse. The improved cases are shown in synopsis in Table II. In this group the subjective satisfaction of the patients based upon relief of disabilities and complaints corresponds with recordable objective improvement, especially in the matter of reduction of blood pressure. In only one case has the P.L.D. grouping been lowered, by significant improvement in cardiac status resulting presumably from lowering of the blood pressure. The group is too small to permit classification in terms of age and sex. It is to be noted, however, that four of the five were comparatively young and that three of these four were cases of very severe hypertension, verging, as indicated by exudative phenomena in eye grounds or cerebrum, on the malignant phase. In Cases 1 and 9 these exudative phenomena slowly diminished under treatment, but not to a degree justifying lowering of P.L.D. group.

Therapeutic failures are outlined in Table III. There is no attribute which constantly differentiates these cases from those in Table II. The only general feature of the unsuccessful group is that dosage sufficient to affect the blood pressure produced disablement. Differences in tolerable dosage are rather striking. In Case 10, for

TABLE II.—Synopsis of Improved Cases

No.	Age and Sex	P.L.D. Group	Principal Complaint	Duration of Treatment	Final Maintenance Dose	Final P.L.D. Group	Subjective Change	Objective Change
1*	29 F	2	Headache, palpitation, and dyspnoea; retinal oedema	10 mths	0.75 g. t.i.d.	2	Improved	B.P. lowered
4†	35 M	3	Headache; encephalopathy	8 "	0.25 g. t.i.d.	3	Complaints relieved	B.P. lowered
5	62 F	3	Dyspnoea, headache, dizziness	7 "	0.75 g. t.i.d.	2	Complaints improved	B.P. lowered. Cardiac status improved
7	34 M	2	Headache, dizziness	7 "	0.75 g. t.i.d.	2	Complaints improved	B.P. lowered
9	44 F	4	Headache, dyspnoea, depression, papilloedema	7 "	0.5 g. t.i.d.	4	Complaints relieved	B.P. lowered. Retinopathy diminished

* Reported *in extenso*.

† Two months before institution of C6 therapy this patient had first-stage (right-sided) "Smithwick splanchnicectomy."

TABLE III.—Synopsis of Unimproved Cases

No.	P.L.D. Group	Principal Complaint	Duration of Treatment	Final Maintenance Dose	Final P.L.D. Group	Subjective Change	Objective Change
2	2	Headaches, dyspnoea	9 mths	0.5 g. t.i.d.	2	None	None with tolerable dose
3	3	Headaches, dizziness, slight dyspnoea	8 "	0.5 g. t.i.d.	3	Dyspnoea worse. Onset of angina	Development of cardiac failure
6	4	Headaches, recent episode of congestive failure	7 "	0.75 g. t.i.d.	4	Headaches less. Dyspnoea troublesome	Remains on verge of congestive failure
8	3	Headaches, angina, dyspnoea	7 "	0.5 g. t.i.d.	4	Headaches less. Angina less	C-V status I.S.Q. or worse. Early retinopathy
10	1	Lassitude, giddiness	7 "	0.125 g. t.i.d.	1	Lassitude increased	None with tolerable dose
11	2	Symptomless hypertension	6 "	0.25 g. t.i.d.	2	None	None
12	2	Giddiness, focal cerebral damage	3 "	0.5 g. t.i.d.	2	"	Slight fall in B.P.
13	2	Slight dyspnoea, slight angina	3 "	1.0 g. t.i.d.	2	Slight amelioration of symptoms	B.P. I.S.Q. E.C.G. slight improvement
14	2	Headaches, giddiness, dyspnoea	2 "	0.75 g. t.i.d.	2	Headaches and giddiness relieved. Slight dyspnoea persists	B.P. less*
15	4	Severe dyspnoea. Fundi Grade IV (K. & W.)	1 month	0.5 g. t.i.d.	4	None	Capricious effect on B.P.

* This case is recorded as unimproved, but the trend of her illness during C6 therapy appears to be in the direction of improvement.

TABLE IV.—A Series of Sample Blood Pressures in 9 of the 15 Cases, Showing the Variable Effect

Case No.	Average* B.P. Before Treatment		Lowest Single† B.P. Before Treatment		Lowest Single† B.P. on C6 Treatment‡		Highest Dose	Average‡ B.P. in Last Month of Treatment		Final Dose
	Upright	Recumbent	Upright	Recumbent	Upright	Recumbent		Upright	Recumbent	
1	—	230/140	—	200/120	130/80	145/75	1,000 mg. t.i.d.	170/97	185/85	2,000 mg. per day
3	—	214/118	190/105	200/110	200/130	185/100	750	248/138	235/125	500 mg. t.i.d.
5	—	225/115	—	180/100	178/84	190/95	750 " "	161/95	186/103	750 " "
6	—	208/132	—	190/125	160/100	160/105	750 " "	227/139	229/143	750 " "
7	—	184/134	165/135	160/130	145/95	150/105	750 " "	163/125	165/125	750 " "
8	—	220/136	220/150	225/125	150/110	205/130	750 " "	201/142	230/139	500 " "
12	—	194/92	188/90	156/74	106/70	102/70	750 " "	166/105	177/103	500 " "
13	215/133	228/132	189/132	204/132	158/106	175/118	750 " "	186/135	193/135	1,000 " "
14	241/141	235/140	210/133	206/125	105/75	168/108	3,250 mg. per day	187/123	190/128	2,500 mg. per day

* These figures are the average of many recordings taken in the month before treatment and most closely represent the average level of the individual's blood pressure under standard conditions.

† These figures are the lowest blood pressure recorded before or during treatment and represent the lowest levels to which the pressures fell at any one time under these conditions.

‡ The figures in this column are those most nearly comparable to those in columns two and three.

example, it was never possible to give more than 0.125 g. of C6 thrice daily. The patient (a business man with no knowledge of the action of the drug he was taking) described himself as "completely knocked out" by this small dose, extremely weak, giddy, and almost unable to read. These effects are the more difficult to explain since the effect on his blood pressure was negligible. Case 13, on the other hand, received 3 g. a day with little effect on blood pressure and few added disabilities. In Case 15 the attempt to control malignant hypertension

with C6 was abandoned after one month. The dosage used, at this early stage of our investigations, was not large (0.5 g. thrice daily), and the effects obtained on blood pressure were irregular. Operative treatment was followed by death from unexplained air embolism.

More Detailed Consideration of Effects of C6 Therapy

We have endeavoured to assess the results of C6 therapy in our small group of cases in terms of certain of the major manifestations of hypertensive disease.

Blood Pressure

The blood pressure of a hypertensive subject receiving C6 tends to show considerable variations in level, even in the course of a single day. The variations in systolic pressure tend to be much greater than those in the diastolic. A further element of variability is introduced by the effects of posture. Effective dosage with C6 produces a moderate reduction in the blood pressure in recumbency but a much more striking lowering of blood pressure taken in the erect posture. It is difficult to indicate in graphic or tabular form the effect of this therapy continued over a period of months. With these reservations, however, we have endeavoured to illustrate typical results by Table IV (Figs. 1a, 1b, and 2).

A conservative assessment of the effects of C6 therapy on blood pressure shows that a reasonably maintained lowering without clinical disablement has been achieved in eight of the fifteen cases. In the remainder the effect has

FIG. 1a (Case 3)

FIG. 1b (Case 8)

FIGS. 1a and 1b.—Showing upright (between solid lines) and recumbent blood pressures taken under relatively standardized conditions at intervals throughout treatment in two cases adjudged as failures on C6 therapy.

FIG. 2.—Case 5. Showing upright (between solid lines) and recumbent blood pressures taken under relatively standardized conditions at intervals throughout treatment in a case adjudged to be a success on C6 therapy. The second course of treatment (months 7-9) had a much more pronounced effect on blood pressure than the first.

either been negligible or been accompanied by so much disability as to make continuance of effective dosage impracticable. As has been indicated, patients in whom the blood pressure is lowered by methonium therapy manifest, in addition, a certain degree of postural hypotension. Without doubt, as in the post-splanchnicectomy state, this postural hypotension makes its contribution to the clinical improvement of the patient. We have found that the margin between an adequate and an excessive dose is small. Moreover, cases apparently stabilized satisfactorily are liable to suffer from time to time from critical hypotension which may disable them for an entire day. There is reason to believe that the irregularities of therapeutic effect may be associated with variation in absorption of the drug. We have found hypotension to occur, for example, in the presence of constipation or of anorexia.

Headaches

Of our fifteen cases twelve complained of headaches. Of these, eleven were relieved or substantially improved. The failure was Case 15, in which patient drug treatment may have been inadequate. The only useful com-

ment would appear to be that of all the manifestations of hypertension headache is the most easily relieved.

Cardiac Status

We have used this term as a convenient abbreviation. It represents our general assessment of cardiac efficiency as indicated by clinical signs and symptoms, together with radiological and electrocardiographic findings. Of our fifteen cases, nine showed evidence of cardiac damage. We record three of these as improved. All three were relieved of dyspnoea. Before treatment this had been incapacitating and had been a primary reason for admission to hospital. After the establishment of C6 therapy, dyspnoea was relieved and normal activity became possible. In one case there seemed to be diminution of the electrocardiographic signs of left-ventricular preponderance in heart strain and in another the cardio-thoracic ratio showed progressive reduction. In general, the effect of C6 therapy on the severer manifestations of hypertensive cardiac disease has not been striking.

Renal Function

We are not in a position, in respect of the present series of cases, to discuss in detail this aspect of hypertensive disease. In general we have found no striking change in renal function under C6 therapy. We have found, however, that it is possible to lower blood pressure over a period of many months (ten, Case 1; seven, Case 9) without deterioration of renal efficiency. In the single case (No. 8) in which renal function has deteriorated, this has been associated with evolution of the malignant phase despite C6 therapy.

Eye Grounds

The changes in the eye grounds in hypertension are of two types: (1) Narrowing, hardening, and tortuosity of the arteries, alteration in A/V ratio. It is unlikely that these changes will be affected by any form of treatment. (2) Exudative phenomena—oedema, haemorrhages, exudates. Theoretically, these may be absorbed if their cause be removed. Of our fifteen cases, five showed exudative phenomena initially. Two (Cases 1 and 9) have shown over a period of many months slow improvement in oedema of retina and nerve heads respectively. One (Case 8) has entered the malignant phase and has developed papilloedema, haemorrhages, and exudates despite treatment. In general, C6 therapy has not produced striking changes in eye grounds. It is, of course, obvious that prolonged study of many cases will be necessary before conclusions can be drawn regarding the degree and duration of hypotension necessary to reverse retinopathy.

Summary and Conclusions

Our study represents a tentative exploration of the possibility of long-term management of essential hypertension by oral administration of drugs. The drug used has been hexamethonium bromide (C6), and for all practical purposes it has been the sole therapeutic weapon employed in the 15 cases presented. These cases have been accepted as they offered, without any attempt at selection. It is our impression that methonium therapy is not subject to the extremely restrictive criteria which govern surgical "treatment" of hypertension. Some of our cases have been under treatment for nearly a year, the majority for more than six months. So far as we have seen, the drug exerts no specifically harmful effects over such periods, and it may well be that indefinitely prolonged treatment will prove tolerable. We agree, of course, with Campbell and Robertson (1950) that the exact place of methonium compounds in the treatment

of hypertension has yet to be defined. Nothing suggestive of "cure" by a course of treatment of limited duration, as described by these authors, has occurred in our series. It may be that our cases have been of more chronic and fixed type. Even in a proportion of these, however, we have found it possible to exercise a useful measure of control.

The advantages of this new method of management of hypertension are obvious. The principal disadvantages appear to be two. First, the daily dosage of the drug necessary to produce a useful effect varies greatly from patient to patient. Secondly, the effective dose is separated from the disabling dose by an increment which is only fractional. Indeed, we have found it impossible in some of our cases to reduce blood pressure without producing disablement.

We feel justified in regarding 5 of our 15 patients as significantly benefited by methonium therapy. In brief, the benefit has consisted in reduction of blood pressure and relief of symptoms. We have no evidence that the unknown underlying lesion has been reversed, or even modified.

Our thanks are due to junior colleagues too numerous to mention individually for much assistance in the recording of blood pressures; to Professor W. J. B. Riddell and his staff for sustained interest in the retinal findings in certain cases treated at the Western Infirmary, Glasgow; and to Professor C. F. W. Illingworth and Dr. E. G. Oastler for facilities and helpful advice freely given. Messrs. May and Baker provided generous supplies of hexamethonium bromide and, in addition, much technical information.

APPENDIX

A Successful Case

This patient (Case 1 of the series), a married woman aged 29, had eclampsia in 1946 during her only pregnancy, which terminated in a stillbirth. High blood pressure and albuminuria have persisted since then. Recently she had headache, palpitation, and dyspnoea. Her mother was hypertensive; her father died young of heart disease.

She was admitted on January 6, 1950, to the medical service of Dr. W. R. Snodgrass. While under treatment for five weeks by rest in bed and sedation her blood pressure was maintained at a very high level, varying between 240/135 and 260/140. On February 10 it was decided to investigate the therapeutic effect of C6 and C5.

Injection intravenously of 22 mg. of C6 produced a sharp hypotensive response, the blood pressure falling from 260/140 to 155/105. The effect was maximal in one hour and passed off slowly over a period of six to nine hours.

Tests carried out on seven consecutive days had roughly comparable results, and attempts were made to achieve continued hypotensive effects by injections given three or four times daily. These met with a varying degree of success, but in general the shape of the blood pressure graph, with its dramatic initial fall and slow rise, indicated that therapeutic success was not to be expected with parenteral administration, which in any case was too inconvenient to be practicable as a long-term policy.

After a day without methonium therapy during which blood pressure rose to its former level, C5 was administered in doses of 22 mg. thrice daily on February 18 and 19. The results achieved were similar in nature to those with C6, but less in degree, and on the morning of February 20 the patient had a hypertensive crisis with violent headache, vomiting, nystagmus, and deafness in the left ear. The blood pressure was unregistrable on the ward equipment, the systolic pressure being in excess of 260 mm. Hg and the diastolic 150 mm. Hg. After an injection of 22 mg. of C6 the pressure fell in two hours to 190/110 mm. Hg and symptoms disappeared, leaving the patient exhausted. It was decided, following this emergency, to persist with C6 rather than C5.

On February 20, in view of the possibility that the hypertensive crisis might indicate the presence of a phaeochromo-

cytoma, a piperoxane test was carried out, with negative result.

On February 22 a scheme of oral therapy with C6 was begun, and continued up to the time of writing. The initial dosage was based on that employed at that time by Kay and Smith (1950) in their work on cases of peptic ulceration, 0.5 g. being administered thrice daily before meals, in capsules, tablets, or solution. There was no significant difference in the results obtained by these different methods of administration, but the tablets proved the least disagreeable to take.

With this dosage it was possible to maintain the patient symptom-free and fully ambulant, with a blood pressure markedly lower than previously. Pressures recumbent averaged 230/130, while those standing were lower, averaging 205/120.

As the course went on there were at times signs of developing tolerance for the drug. For example, the degree of postural hypotension steadily diminished and the blood pressure tended to rise slowly. On June 7, therefore, the dose was raised to 0.75 g. t.i.d. and on June 15 to 1 g. t.i.d.

This dosage was completely effective in controlling the blood pressure, but "side-effects" were disabling, and after two weeks it was clearly necessary to reduce the amount of the drug.

With some difficulty a dose at once effective and tolerable was devised—namely, 1.75 g. daily, 1 g. being given at noon and 0.75 g. at 8 p.m. On this dosage the blood pressure was of the order of 160/100 mm. Hg and side-effects were minimal.

On June 29 C6 therapy was discontinued. The blood pressure rose steadily. On July 2 it was 230/140 and on July 11 260/134.

C6 was restarted at a dosage level of 0.5 g. t.i.d., and was continued up to the time of writing.

On September 14 the patient had difficulty in making her way to hospital, feeling extremely weak, tired, light-headed, shivery, and cold. Her blood pressure was unusually low—145/95 lying and 132/97 standing—and pulse 80 a minute in either position. These findings seemed to indicate development of increased sensitivity to the drug, but the capsules which she was taking at that time were found to contain 0.65 g. of C6 instead of 0.5 g. as intended. She had been taking three of these capsules daily before meals. The dosage was adjusted once more to 0.5 g. t.i.d. The blood pressure rose once more to its former average levels.

On September 28 the blood pressure was found to vary during the period of observation between 250/150 lying and, in the latter part of the day, 175/105 standing.

As we have pointed out, it is extremely difficult to devise a means of registering variations of blood pressure over a period of many months, and if the averages of a considerable number of readings at intervals are taken it may in the end be difficult to establish any general picture of the effect of the drug. In this case, however, such averages taken regularly during the 10 months, throughout which the patient was completely ambulant and performing normal household duties, under treatment with C6 were significantly lower than those constantly obtained during a period of five weeks' rest

Comparison of Status Before and After Treatment

	Before Treatment	After Treatment
Symptoms ..	Headache, palpitation, dyspnoea	Nil, apart from drug effect
Blood pressure ..	240/135 to 260/140	Average lying 220/135 and standing 190/120
Urine ..	Albuminuria	Albumin disappeared early in course of treatment and has not been recorded since
Fishberg ..	1000–1014	1002–1012
Blood urea ..	52 mg./100 ml.	52 mg./100 ml.
E.C.G. ..	Left ventricular preponderance	Left ventricular preponderance less severe

in bed with sedation. The average lying blood pressure was of the order of 220/135 and the standing figure 190/120. The pulse rate remained fairly constantly in the region of 80 a minute whether standing or lying.

Attempts were made to assess renal function on very many occasions during the course of this treatment. In general, the findings of the urea-clearance test were extremely erratic, and the impression is that technical errors were of such magnitude as to render the results worthless. The blood-urea figures were:

January 10	52 mg./100 ml.
" 31	57 "
February 22	Sustained course of oral C6 begun.
March 4	71 mg./100 ml.
" 14	61 "
" 17	52 "
" 25	54 "
May 19	46 "
June 30	45 "
July 11	50 "
October 6	59 "
November 24	50 "

Lowering of blood pressure was not associated with diminution of renal efficiency.

Ophthalmoscopic Findings

The eye grounds were examined on numerous occasions by Professor W. J. B. Riddell and Dr. R. Leishman. In general, they showed no striking change. Reports at the beginning and the end of the course of treatment are as follows:

February 25.—"The optic disks show fibrous veils of congenital origin. The A/V ratio is 1:2, accounted for by diminution of calibre in the arteries, which are of copper-wire appearance and show marked calibre variation. There is concealment of the veins at A/V crossings. There is no oedema of the disks, but there is oedema of the retina along the course of the main vessels. There are no haemorrhages or exudates and no pigment disturbance. In the left eye, about 2 p.d. above and temporal to the disk, there is an area of collateral vessel formation, probably the result of previous branch thrombosis in a venule. The appearances are those of hypertension in the retinal vessels."

October 7.—"O.E. Right: The disk is normal in colour. The physiological depression is present. Fibrous tissues of congenital origin are seen on the disk surface. The disk margins are well seen. The A/V ratio varies between 1:2 and 2:3. The arteries show a colour change. Light reflex is broad and dull. There is well-marked concealment of the veins at A/V crossings. The arteries show calibre variation. There is a slight degree of oedema of the retina along the course of the main vessels. O.E. Left: The findings are similar. These appearances suggest hypertension in retinal vessels which are affected by arteriosclerosis. There is no evidence of significant vascular breakdown."

Side-effects

The most constant side-effect was constipation, which gave trouble throughout treatment. On dosage near the upper limit of comfortable tolerance, visual disturbance with failure of accommodation was troublesome. On the heaviest dosage of 3 g. daily the patient was almost incapacitated, with marked weakness and giddiness, especially on rising in the morning. Appetite was poor, and she was troubled with smarting and watering of the eyes and running of the nose. On occasion she was compelled to remain in bed most of the day. In general, however, side-effects were not a serious inconvenience, and for the greater part of the time that she was on oral C6 therapy she was able to do all her own housework in comfort and to travel from the country to hospital once a week to spend a whole day in the wards for continuous observations on blood pressure and pulse rate.

In late September, 1950, the patient began to complain of extreme dryness of the scalp and falling of the hair. At the same time she noticed that she tended to perspire much less than formerly. This disturbance of the hair and scalp responded to simple measures. It may or may not have been a direct result of methonium therapy.

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A CLINICAL STUDY OF THE EARLY POST-GASTRECTOMY SYNDROME

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The description of the syndrome which follows is based on the records of cases studied in a follow-up clinic at Bristol Royal Infirmary and Southmead Hospital, Bristol.

When the routine study of post-gastrectomy cases was begun it was soon obvious that patients who exhibited symptoms after meals fell into two major groups, as described by Adlersberg and Hammerschlag (1947). These were as follows:

Group 1.—Cases in which symptoms occurred towards the end of a meal or within a few minutes of its completion. This group corresponds to the "dumping syndrome" of most authors, but we prefer the term "early or immediate post-gastrectomy syndrome."

Group 2.—Cases in which the symptoms occurred during the second or third hours after meals—to be referred to as the "late or delayed post-gastrectomy syndrome."

Early or Immediate Post-gastrectomy Syndrome

This variety of the post-gastrectomy syndrome is rather more common than the delayed type. It occurred in 79 of the 660 cases reviewed (11.97%). In our opinion it constitutes the major problem, as it accounts for the most severe cases. Typically, there is quite a sudden onset, the patient often "bracing himself up" in his chair as the syndrome starts. There is a feeling of fullness and distension in the epigastrium, associated with nausea and lassitude. Vomiting is rare, but should it occur it affords considerable relief, the patient often going on to resume and enjoy a full meal. The epigastric sensation is sometimes described as "painful," and may radiate to the back. The onset of the abdominal symptoms is associated with a spreading sense of warmth or cold, and accompanied by perspiration, as a rule most marked on forehead and face. There is usually definite pallor, and frequently a "goose-flesh" appearance of the skin. The patient complains of palpitations and occasional throbbing in the head and neck, and often expresses a desire "to get to an open window or out