MECAMYLAMINE AND RESERPINE IN THE MANAGEMENT OF SEVERE AND MALIGNANT HYPERTENSION IN UGANDA

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It used to be the impression of a number of clinicians that hypertensive disease was uncommon in the indigenous peoples of East Africa. This view was certainly refuted by Williams (1944) and more recently by Leather (1958), who, working in Uganda, was able to select 49 new cases of hypertension for study in a period of less than 14 months. Faced with an increasing recognition of the frequency of severe forms of hypertensive illness and at the same time appreciating the established value of ganglion-blocking compounds, alone and in combination with rauwolfia alkaloids, in the treatment of malignant and non-malignant hypertension (McMichael and Murphy, 1955; Doyle and Smirk, 1955; McQueen and Smirk, 1956), we decided, early in 1958, to embark on a regime of management of hypertension on proper clinical lines at Mulago Hospital, an African hospital in Uganda.

Experience gained elsewhere (Milne *et al.*, 1957), and generally satisfactory reports of its use at other centres (Doyle *et al.*, 1956; Smirk and McQueen, 1957; Kitchin *et al.*, 1957), resulted in the choice of mecamylamine for use at this clinic. The reports of Freis (1955), Ford *et al.* (1956) and Milne *et al.* (1957) have dealt in detail with the pharmacology of mecamylamine.

The present study describes the result of our experiences with the use of mecamylamine in combination with reserpine in the management of 29 cases of hypertensive disease treated for periods ranging from 3 months to 9 months.

Aetiology and Incidence of Hypertensive Disease

Mulago Hospital is the largest and most centrally placed hospital in Uganda. Its intake reflects a wide variety of conditions. In a single year's survey (Shaper and Shaper, 1958), hypertension constituted the largest single group, totalling 22% of all cardiovascular admissions in the medical wards of the hospital. That the greater part of cases of hypertension is due to chronic renal disease rather than essential hypertension was first noted by Williams (1944). Of the 49 cases of hypertension studied by Leather (1958), 29 were considered to be renal in origin. There were only 14 cases of essential hypertension, and in the remaining 6 cases aetiology was uncertain. It is therefore not unexpected that this treatment series includes a majority of cases with renal rather than essential hypertension.

Selection of Cases

In the selection of cases, besides generally agreed criteria, viz. high blood pressure associated with objective evidence of hypertensive retinopathy, electrocardiographic changes of left ventricular hypertrophy, or heart failure, several factors of local importance had to be taken into consideration. Some patients, who because of their simple backgrounds were unlikely to appreciate the importance of follow-up after initial improvement on treatment, proved unsuitable cases for long-term management. Others, who were migrant or returned to their homes in remote areas, also failed to attend clinic. Several patients, however, attended regularly despite distances of 40 miles or more by rural transport. Literacy and sophistication did not seem important in the selection of cases, and in practice intelligent patients with a sense of cooperation living in and around the immediate districts of Kampala were the most suitable cases for follow-up.

No patient with mild or asymptomatic hypertension was advised treatment. Nine patients had had treatment with other ganglion-blocking drugs previously. In the remainder treatment was instituted with mecamylamine. All the patients were Africans; they belonged to a variety of tribal groups found in Uganda.

Results of treatment are only considered in 24 patients. Of these, 6 were treated for 6 or more months, and 18 for 3 or more months. In 4, treatment was abandoned because of disabling side-effects of treatment. The 24 included 9 males and 15 female subjects, of ages ranging from 20 to 54 years. Five other cases were excluded from the study because of default in attendance or inadequate follow-up due to factors mentioned above.

Assessment of Cases

All the patients were admitted into hospital for initial assessment. Special investigations were directed towards detecting cases with chronic renal disease. Essential hypertension was diagnosed by exclusion.

The following factors were investigated in all cases: Urine (including culture and 24-hour collections for total proteinuria), blood urea, electrocardiograms, chest radiography and fluoroscopy, and fundal examination. In the absence of gross proteinuria, urine concentration test was performed, and in those cases where blood urea was not grossly raised, intravenous pyelography. Where a past or micturition history suggested the possibility, urethral catheterization was done to exclude urethral stricture, a not infrequent causative factor in secondary hypertension in Uganda. Renal biopsy was carried out in 11 cases.

Fundal changes were graded 1 to 4 (Keith *et al.*, 1939). The term malignant hypertension was applied to patients with grade-4 fundal changes. Electrocardiographic evidence of left ventricular hypertrophy was graded from 0 (absent) to 4, the four positive grades representing the common English adjectives of degree, slight, moderate, considerable and gross.

A diagnosis of chronic pyelonephritis was made on consideration of the following grounds: A history of acute pyelonephritis, untreated gonorrhoea or urethral stricture; pyuria and bacteriuria; loss of urinary concentrating power, with blood-urea levels within normal limits (Raaschou, 1943). Chronic glomerulonephritis was diagnosed on the presence of persistent proteinuria, with the passage of large numbers of casts. No reliable history of acute glomerulonephritis was forthcoming. Even on applying these simple

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clinical criteria, chronic pyelonephritis and chronic glomerulonephritis might readily have been overlooked.

In the 11 cases in whom renal biopsy was carried out an accurate diagnosis was possible.

CLINICAL FINDINGS

Certain important features emerge in the series. There were 13 cases which presented with congestive heart failure and 3 with left ventricular failure. All but one case of congestive heart failure showed grade-3 or grade-4 electrocardiographic changes of left ventricular hypertrophy. Five of these were cases of malignant hypertension, of whom 3 showed evidence of renal failure in that blood-urea levels at the time of diagnosis of the malignant phase persistently exceeded 100 mg. per 100 ml.

There were only 5 patients who presented with headache as the only clinically important symptom, and one of these had malignant hypertension. No cases of major cerebrovascular accidents were selected for treatment. One patient with malignant hypertension presented with loss of vision.

Three patients were diagnosed during pregnancy, 2 with toxaemia and one with recurrent left ventricular failure in the last trimester.

Aetiologically, 11 cases were considered to be due to chronic pyelonephritis, 2 to chronic glomerulonephritis, and 3 to pregnancy toxaemia. There were 8 cases of essential hypertension and one doubtful essential. One patient (case 21), also had mitral and tricuspid incompetence, which was considered to be due to endomyocardial fibrosis, a common cause of valvular disease described from Uganda (Ball *et al.*, 1954; Davies and Ball, 1955).

For reasons explained, the series represents a highly selected group of cases of severe hypertensive disease with undoubted indications for treatment; the proportions of aetiological types are therefore not necessarily representative of the general incidence in Uganda.

The important clinical facts relating to each case are given in Table I.

Measurement of blood pressure. In the ward, blood-pressure readings were taken for several days to obtain basal levels before treatment. The exceptions were cases of malignant hypertension in whom treatment was started on an emergency basis. Once treatment was commenced, blood pressure was recorded with the patient first supine and then erect.

After discharge from hospital, patients were seen first at a week's interval and thereafter fortnightly or monthly as indicated by requirements of treatment and the patient's convenience.

ADMINISTRATION OF MECAMYLAMINE

As the duration of action of mecamylamine is long—more than 12 hours—it was decided to treat patients with two doses a day.

The initial dose was usually 2·5 mg. and it was increased by 2·5 mg. every other day until the blood pressure was adequately lowered. If the blood pressure remained high, the dose was increased by 5-10 mg. every other day. Dosage increments were more cautious in patients with chronic uraemia, as it is known that excretion of mecamylamine is delayed in patients with chronic renal failure (Milne *et al.*, 1957).

Initial stabilization was done in hospital. The dose was further adjusted at subsequent visits to the clinic.

Postural hypotension after administration of mecamylamine. The occurrence of postural hypotension after the administration of ganglion-blocking drugs has been referred to on many occasions. Whilst the extent of postural hypotension varied from patient to patient, our experience was similar to that of Kitchin *et al.* (1957) in that the benefit obtained by posture was often slight. Nevertheless, patients were advised to avoid the horizontal position as much as possible during the day and to raise the head of the bed at night.

Sensitivity and tolerance. The dose required to achieve a satisfactory fall of blood pressure varied widely from patient to patient. Many patients developed a material degree of tolerance in the early stages, necessitating periodic adjustments in dosage. The development of tolerance emphasized the need for regular supervision of treatment. The final stabilizing dose ranged from 5 mg. to 80 mg. (average 30·1 mg.) per day. Some patients were highly resistant and, in a few, resistance increased as dose was increased. Doses were increased gradually to avoid undue side-effects.

Use of reserpine in conjunction with mecamylamine. Advantage was taken of the beneficial effect of a combination of mecamylamine with reserpine. The dose of reserpine prescribed was 0·25 mg. twice daily.

RESULTS OF TREATMENT

Because of the somewhat exacting nature of the regime, therapy was limited to selected hypertensives whose illness was complicated by burdensome headache and dizziness, heart failure, or malignant hypertension. In the remaining majority, it was felt that prognosis had become sufficiently poor to strongly justify a regime that demanded intelligent cooperation by the patient and set in train side-effects creating at times difficult management problems. In general, a fall in blood pressure could not be regarded as the important criterion of successful treatment unless it was followed by the relief of complications. As with other hypotensive agents, however, satisfactory control of blood pressure often resulted in the alleviation of symptoms, regression of hypertensive retinopathy or the electrocardiographic pattern of left ventricular hypertrophy, and the relief of cardiac failure, in some cases permitting the elimination of maintenance digitalis. One patient (case 19) with toxaemia of pregnancy was successfully taken to term on treatment. Because of the short time for which most patients in this series were treated, greater reference will be made to the control of blood pressure and relief of disablement from heart failure and the malignant phase of hypertension. That moderate uraemia does not rule out successful management and in fact may regress on treatment, is indicated by the following history:

Case 2, B.K., a male tailor, Ganda, aged 26, was first seen in September 1958. There was a history of venereal infection—? nature in 1950. In 1956 he developed headaches. In January 1958 headaches had increased in severity and were soon followed by blurring of vision and vomiting. Recurrent vomiting and hiccoughs had been present for 2 days before admission.

On examination. Grade 4 retinopathy. Blood pressure 250/170 mm. Hg. Atrial gallop, left ventricular hypertrophy, raised jugular venous pressure, peripheral oedema. Blood urea 208 mg. per 100 ml. Urine: Albumen +++, many red cells and pus cells in deposit.

TABLE I. CLINICAL DATA AND RESULTS OF TREATMENT OF 24 PATIENTS TREATED WITH MECAMYLAMINE AND RESERPINE

Case No.	Sex	Age	Aetiology of hypertension	Major symptomatology	Fundi	ECG	Average blood pressure (mm. Hg)		Daily dose mecamylamine (mg.)	Total follow-up (mths.)	General result	Remarks
							Before treatment	After stabilization*				
1	F	47	Essential	Headache, dizziness	1	N	210/110	130/90	15	5	Good	Headache ceased
2	M	26	Chronic pyelonephritis	Congestive heart failure, renal failure	4	LVH (4)	250/170	130/110	10	4	Good	Regression of malignant phase and renal failure; no recurrence of heart failure
3	F	28	Chronic pyelonephritis	Headache	2	LVH (1)	190/130	110/90	7·5	6	Good	Headache ceased
4	M	49	Essential	Congestive heart failure	1	LVH (3)	250/150	140/90	50	5	Poor	Mecamylamine tremor. Treatment abandoned
5	F	25	? Essential	Left ventricular failure	2	LVH (2)	220/130	150/100	40	4	Good	No further LVF
6	F	38	Chronic glomerulonephritis	Congestive heart failure	1	NT	240/160	148/80	45	4	Good	Headache ceased; heart failure regressed
7	F	31	Pregnancy toxaemia	Headache, dizziness	N	LVH (1)	250/150	150/130	25	5	Poor	Tolerance; marked curare-like effects. Treatment abandoned
8	M	54	Essential	Left ventricular failure	1	LVH (4)	250/130	140/80	20	4	Good	No further LVF
9	F	41	Essential	Headache	4	N	230/140	150/100	15	8	Good	Regression of malignant phase. Tolerance; curare-like effects
10	F	50	Essential	Congestive heart failure	1	LVH (4)	210/140	130/90	60	4	Good	Heart failure regressed
11	M	35	Chronic pyelonephritis	Congestive heart failure	4	LVH (3)	230/130	130/100	20	4	Good	Regression of malignant phase; Parkinsonism due to reserpine
12	F	30	Pregnancy toxaemia	Congestive heart failure; recurrent abortions	1	LVH (4)	220/135	140/110	10	3	Good	Pregnant 24/52, condition satisfactory
13	F	25	Pregnancy toxaemia	Recurrent left ventricular failure in pregnancy	1	LVH (4)	190/130	140/100	80	8	Poor	No further LVF but marked tolerance. Treatment abandoned
14	F	44	Chronic pyelonephritis	Toxaemia of pregnancy	1	LVH (1)	180/130	120/90	5	3	Good	Headache ceased
15	F	50	Essential	Headache, dizziness	1	N	180/125	130/80	5	3	Good	Headache ceased
16	M	20	Chronic pyelonephritis	Visual	4	LVH (3)	240/185	110/80	60	9	Poor	Regression of malignant phase. Tolerance; marked curare-like effects. Treatment abandoned
17	M	21	Chronic pyelonephritis	Congestive heart failure	4	LVH (3)	260/140	150/100	5	4	Good	Regression of malignant phase
18	M	52	Essential	Congestive heart failure	N	LVH (4)	190/140	140/110	10	5	Good	Heart failure regressed
19	F	24	Chronic glomerulonephritis	Toxaemia of pregnancy	N	LVH (1)	210/135	130/70	15	9	Good	Second pregnancy taken successfully to term
20	M	36	Chronic pyelonephritis	Congestive heart failure	1	LVH (4)	175/130	140/90	50	3	Good	Heart failure regressed
21	F	43	Chronic pyelonephritis	Congestive heart failure	2	LVH (3)	195/125	150/110	35	8	Good	Heart failure regressed. Patient also has endomyocardial fibrosis
22	F	25	Chronic pyelonephritis	Congestive heart failure, renal failure	4	LVH (3)	220/170	110/80	15	3	Good	Regression of malignant phase and renal failure. No recurrence of heart failure
23	F	35	Chronic pyelonephritis	Congestive heart failure, renal failure	4	LVH (4)	200/140	120/80	15	3	Good	Regression of malignant phase; heart failure controlled
24	M	24	Chronic pyelonephritis	Left ventricular failure	1	LVH (4)	200/110	120/80	10	3	Good	Regression of LVF

* On mecamylamine and reserpine.

LVF = left ventricular failure. LVH = left ventricular hypertrophy. N = normal. NT = not taken.

Chest X-ray: Moderate left ventricular enlargement. ECG: LVH (4).

Mecamylamine was started on 5 September and gradually increased to 10 mg. daily. He has been on this dose ever since. Within 2 months his papilloedema had gone and a recent examination revealed only grade-2 fundus changes. His headaches have been completely relieved and apart from slight puffiness around the eyes he has no symptoms. Monthly blood ureas since were 125, 71, 87, 56 mg. per 100 ml.

Comment. This was a case of gross uraemia at the time of recognition of a malignant phase and treatment has been successful in relieving it.

Table I shows, in addition to a summary of initial clinical data, basal blood-pressure levels both before treatment and after stabilization on mecamylamine.

In all cases reserpine was given with mecamylamine from the beginning, and therefore the results reported are based on the degree of control achieved with both agents. Toxic effects with the dose of reserpine used were unusual, apart from occasional nasal stuffiness and in one case (case 11), Parkinsonian tremors.

In 4 cases (4, 7, 13 and 16) a good result was not achieved; the reasons for the failure were considered to be as follows:

Case 13 rapidly developed tolerance to the hypotensive action of mecamylamine. The dose reached was the highest in the series, 80 mg., and in view of the extreme rapidity of development of tolerance it was considered unwise to increase her dose further. In cases 7 and 16, one (case 16) with malignant hypertension, tolerance was associated with disabling muscular weakness due to curare-like effects of mecamylamine (Stone *et al.*, 1956) which interfered with the patients' occupations. Case 4 developed mecamylamine tremor (Harington and Kincaid-Smith, 1958). His history was as follows:

Case 4, a male Ganda cultivator aged 49, was first seen in August 1957, when he was admitted in congestive heart failure.

On examination. Blood pressure 250/150 mm. Hg. Atrial gallop rhythm; left ventricular hypertrophy; fundi grade 1. Urine contained a trace of albumen. Blood urea 30 mg. per 100 ml.

Treatment. Benign essential hypertension having been diagnosed he was treated with oral pentolinium, to which reserpine 0·25 mg. twice daily was later added. This regime reduced his blood pressure, and his heart failure regressed.

Mecamylamine therapy. In May 1958 mecamylamine was substituted for the pentolinium, 50 mg. daily being necessary to keep the blood pressure down to 140/90 mm. Hg. with the patient in the erect position for the greater part of the day. This dosage, however, caused troublesome side-effects at first principally constipation and abdominal distention, dry mouth, and blurred vision, but later micturition difficulty as well.

Readmission. In September 1958 he developed tremor of the hands and 3 days later his condition deteriorated. On readmission on 29 September he had a coarse generalized shaking affecting the whole body, present at rest and accentuated on attempting voluntary movement. His speech was slurred and jerky. There was a general increase of muscular tone, and in the deep reflexes the plantars remained flexor. His mental state, however, was clear, but he was extremely restless, nervous and agitated. His mouth was extremely dry. Blood urea was 27 mg. per 100 ml. This striking clinical picture persisted for over a week and gradually subsided with the withdrawal of mecamylamine. By early October, 10 days after mecamylamine had been stopped, his condition had returned to normal. During this period he had been treated with pempidine because his blood pressure had risen after the cessation of hypotensive treatment. He was discharged from hospital on 10 October 1958 on a combination of pempidine and reserpine and when last seen had remained well.

Comment. This patient undoubtedly suffered from a syndrome well recognized as an occasional complication of treatment with mecamylamine.

In summary we consider that treatment was ineffective in 4 of the 24 patients because of undesirable side-effects attributable to mecamylamine.

Side-effects after Administration of Mecamylamine

The side-effects discussed here are those which were due to mecamylamine alone. Doubtless, the use of reserpine with the mecamylamine enabled a smaller mecamylamine dosage to be given to obtain the same hypotensive effects. Thus fewer side-effects were evident than would have been the case with the use of mecamylamine alone. All the side-effects which may follow the administration of a ganglion-blocking drug occurred in the series. The side-effects observed (Table II) were as follows:

TABLE II. SIDE-EFFECTS OF MECAMYLAMINE IN 24 PATIENTS

		No. of cases
Alimentary	Dry Mouth	6
	Constipation and abdominal distension	19
	Diarrhoea	1
Genito-urinary	Dysuria	2
	Impotence	2*
Neurological	Blurred vision	7†
	Fatigability	4
	Tremor	1

* Present before treatment in one case.

† One case of secondary optic atrophy following malignant phase.

Dryness of the mouth was not common and was severe in only 2 cases.

Constipation was often troublesome and required constant vigilance. A regular aperient was usually prescribed and patients were encouraged to take whichever aperient suited them best, e.g. vegetable laxative tablets, salts, liquid paraffin. None of our patients on treatment developed paralytic ileus. Distention was frequently associated with constipation but did not seem to be particularly distressing.

Diarrhoea. Contrary to the experience of Kitchin *et al.* (1957) only one patient (case 16) in this series developed diarrhoea. The explanation may lie in the smaller doses required for stabilization of our cases, or there may be a dietetic factor. The staple diet of most of our patients is cooked unripe banana, which is a bulky item of diet and its digestion is probably slow.

Dysuria. Difficulty in micturition developed in 2 patients but was not serious.

Impotence. In 2 patients impotence was of sufficient degree for the complaint to be raised spontaneously. In one, however, the complaint had been present before treatment with mecamylamine had been begun. No patients were questioned specifically on this side-effect.

Blurring of vision from impairment of accommodation was complained of by 7 patients. Many of our patients were illiterate and perhaps might have complained more had they been great readers. One patient, a nun (case 3), benefited from a change of spectacles.

Fatigability. As in the experience of Smirk and McQueen (1957) and Kitchin *et al.* (1957), we also noted that some patients complained of a vague and general feeling of malaise and fatigue. These and other curare-like effects were so disabling to 2 patients that (as mentioned earlier) treatment had to be abandoned.

Mecamylamine tremor. Two patients developed tremor. In one only (case 4, see above) could it be ascribed to mecamylamine, on cessation of which the tremor disappeared. In the other case (case 11) tremor started 3 weeks after commencement of therapy, while the patient was on 20 mg. of mecamylamine and 0·5 mg. of reserpine daily. The tremor was of a Parkinsonian quality and characterized by 'pill-rolling', mask-like face, slowness of movements, and shuffling gait. The syndrome did not reverse when mecamylamine was withdrawn and as it persisted as long as reserpine was continued, it was probably due to the reserpine. A similar syndrome has been described, as due to reserpine, by Kline (1954) and Stead and Wing (1955).

SUMMARY

29 African patients with severe hypertensive disease were considered suitable for long-term treatment with ganglion-blocking drugs. Treatment regime consisted of mecamylamine in combination with reserpine. 24 cases were followed up for periods up to 9 months.

The majority of patients were cases of renal rather than essential hypertension.

The results were good or excellent in 20 cases and poor in 4 cases. Failure to achieve a good result was due to resistance to mecamylamine and intolerance of side-effects. Side-effects occurred in most cases but were rarely disabling. Constipation and abdominal distention were the most frequent side-effects.

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