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RESULTS OF TREATMENT IN MALIGNANT HYPERTENSION

A SEVEN-YEAR EXPERIENCE IN 94 CASES

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[WITH SPECIAL PLATE]

Eight years have elapsed since the introduction of ganglion-blocking agents in the treatment of severe hypertension. Various reports have been published dealing with immediate and short-term results, and the time seems opportune for a detailed survey of the achievements over a longer period of years. The present report deals exclusively with malignant hypertension under this treatment, and the course of the treated cases is compared with a control series taken from Hammer-smith Hospital over the period 1935-56 (Kincaid-Smith, McMichael, and Murphy, 1958). Although a "double-blind" trial on alternate cases might have been more convincing, early amelioration of cardiac failure and blindness in treated patients ruled out this method on ethical grounds. The expectation of life in our control series did not differ significantly from that observed previously by Keith *et al.* (1939) and Schottstaedt and Sokolow (1953).

Material

The series comprises 82 patients with malignant hypertension. This total includes all cases seen at this hospital in the years 1951-7 inclusive in which malignant hypertension was diagnosed and in which an attempt was made to treat with ganglion-blocking drugs. The diagnosis of the malignant phase of hypertension was based on the presence of papilloedema in 81 cases. In one case, which pursued a rapidly downhill course with uraemia, post-mortem examination showed definite lesions of malignant nephrosclerosis; in this case there was a florid retinopathy with haemorrhages and soft exudates, although no papilloedema was observed during life.

In addition to the 82 cases which are the subject of this report, 12 patients were diagnosed as having malignant hypertension during the period under review but were not treated with ganglion-blocking agents. These patients were all admitted to hospital in the terminal phase of their illness, moribund or with such severe renal failure that no therapy was of any avail. They are not further considered, except to arrive at an estimate of the over-all prognosis of malignant hypertension under present conditions.

Sex and Age.—Of the 82 patients, 52 (63%) were male and 30 (37%) female. The age distribution is shown in

Text Fig. 1. Ages ranged from 9 to 76 years, the greatest incidence being in the sixth decade. This age distribution is similar to that of the control series (Kincaid-Smith, McMichael, and Murphy, 1958), but the present series shows a greater preponderance of male over female patients.

Aetiological Diagnosis

In Table 1 the cases are grouped according to aetiology so far as is possible. The diagnosis was confirmed at necropsy in 42 of the 56 fatal cases; for the remainder the clinical diagnosis is given. Where an

TEXT FIG. 1.—Age and sex distribution of the 82 cases of treated malignant hypertension.

associated renal condition, such as pyelonephritis or hydronephrosis, was found either clinically or at necropsy this has been recorded as the primary diagnosis. Only 45% of patients were considered to have essential hypertension; this figure may be further reduced in the future, since more recently the introduction of abdominal aortography and needle biopsy of the kidney has improved our capacity to recognize underlying renal lesions.

The frequency of renal arterial occlusion (8.5%) in this series is noteworthy. This diagnosis has been

TABLE I.—*Aetiological Diagnosis in 82 Cases of Malignant Hypertension*

Clinical Diagnosis	Male	Female	Total Cases		Diagnosis Confirmed P.M.
			No.	%	
Essential	24	13	37	45.0	16
Post-pregnancy	—	3	3	3.7	1
Chronic pyelonephritis . .	6	8	14	17.0	8
Renal arterial occlusion . .	6	1	7	8.5	7
Polyarteritis	3	—	3	3.7	3
Chronic glomerulonephritis type I	3	—	3	3.7	2
Chronic glomerulonephritis type II	1	1	2	2.4	—
Hydronephrosis	2	—	2	2.4	1
Disseminated lupus erythematosus	—	1	1	1.2	1
Renal vein obstruction . .	—	1	1	1.2	1
Renal amyloidosis with pyelonephritis	1	—	1	1.2	1
Renal arterial occlusion with pyelonephritis . .	1	—	1	1.2	1
Unilateral renal disease ? nature	3	1	4	4.9	—
Renal hypertension ? cause	2	1	3	3.7	—
Total	52	30	82		42

recorded only when it was proved at necropsy, and the true incidence may be higher than that shown. It is becoming increasingly clear that, when the condition is specially looked for, obstruction of the arterial supply to the kidney is a commoner association of hypertension (particularly when in the malignant phase) than has hitherto been recognized (Poutasse and Dustan, 1957).

The 7 cases classified in Table I as having renal hypertension of uncertain nature are a group in which there was a good reason to suspect the presence of an underlying primary renal disease, either from the history or from abnormal appearances on pyelography, but in which there was no ante- or post-mortem confirmation of the exact nature of the condition.

Method of Treatment

The basis of treatment in every case in this series was the administration of ganglion-blocking drugs. Initially hexamethonium was used; it was always given by subcutaneous injection, since absorption from the oral route is poor and irregular (Harrington, 1953). When pentolinium was introduced this drug was usually employed in preference to hexamethonium, owing to its slightly longer duration of action (Smirk, 1953). Pentolinium may also be absorbed irregularly from the gastro-intestinal tract, and for this reason was also always given parenterally. More recently mecamlamine has been used by the oral route, since it is fully and reliably absorbed.

The malignant phase of hypertension is considered as a medical emergency, and it has been the rule to start hypotensive treatment immediately the patient is admitted to hospital. Treatment is usually begun with pentolinium subcutaneously, as it is easier by this means to bring the blood pressure rapidly under control; when a measure of control has been achieved a preparation suitable for oral use (e.g., mecamlamine, pempidine), may be introduced as maintenance treatment.

Reserpine has been shown to increase the sensitivity of hypertensive patients to a ganglion-blocking agent (Harrington, 1956); the side-effects from parasympathetic blockade are not correspondingly increased. In 31 cases in this series treatment was with a rauwolfia alkaloid in addition to ganglion-blocking drugs; at present reserpine is usually given in a dose of 0.1 mg. thrice daily, since at this level of dosage serious side-effects, including

depression, have been less troublesome. Early unconvincing experience with hydrallazine (Khan, 1953) gave us no special encouragement in its use. It was, however, given to four patients, but in only one of these was there evidence that adding this drug to the patient's regimen had any beneficial effect.

Dyspnoea and heart failure were treated with digitalis in addition to hypotensive drugs; 36 cases received either short or prolonged courses of digitalis, and six also had injections of mercurial diuretics. Except when cardiac oedema was present, sodium restriction was not enforced and a normal diet was allowed.

Two patients had been subjected to surgery at an early stage of their illness; one had a nephrectomy for hydronephrosis, and another underwent sympathectomy. Neither of these operations was effective in lowering the blood pressure adequately, and subsequent ganglioplegic treatment was necessary.

Control of Treatment

The objective in treatment was to reduce the blood pressure in the standing position to a trough approaching "normal," and to repeat the dose frequently enough to achieve this level again when the pressure began to approach the control level. Patients would seldom tolerate a dosage which kept the pressure at a "normal" level all the time. Pressure levels were thus allowed to fluctuate from troughs of 120–140 mm. Hg. systolic to 200 mm. or over. Some relief from extreme ganglion blockade during the 24 hours made life more tolerable. The systolic pressure was found to be a useful and reliable index of therapeutic efficacy, the diastolic being much more difficult to determine with accuracy when the pressure was at a low level. At night larger (often double) doses were given with the object of keeping the pressure down even in recumbency, and this often achieved some postural hypotension on rising in the morning. Elevating the head of the bed at night was seldom necessary, though patients were encouraged to sleep well propped up on pillows.

Patients were given precise (usually written) instructions to help them to cope with the problems arising during treatment. They were seen at intervals ranging from weekly at the beginning to three-monthly as they became more expert in self-care. The blood-pressure response was measured at each attendance, noting the time interval since the last dose, and adjustments to dosage were made to ensure a suitable quantitative response.

Various pharmacological aids helped with the troublesome parasympathetic paralysis. Of these the most valuable were pyridostigmine in doses of 60–180 mg. daily, which improved bowel action, and bethanechol (25 mg.), which increased the secretion of saliva. Special spectacles were prescribed for use at the time of maximum paralysis of accommodation.

Complications and Side-effects

Side-effects due to paralysis of parasympathetic ganglia were encountered in all patients. The elimination of ganglion-blocking drugs from the body is reduced in the presence of renal failure, and side-effects, particularly on the bowel, may be enhanced in uraemic patients. Five patients in this series suffered severe episodes of frank paralytic ileus even under hospital supervision, three of these when in the terminal stages of uraemia.

Toxic effects of mecamylamine on the central nervous system, as first reported by Schneckloth *et al.* (1956) and Deming *et al.* (1957), were observed in seven cases (Harington and Kincaid-Smith, 1958). The symptoms of toxicity have been tremor, affecting all limbs and the trunk, associated with slurred speech, increased muscular tone, and brisk tendon reflexes, with or without accompanying mental symptoms (confusion,

hallucinations, delirium). They occurred in patients on high doses of mecamylamine and in the presence of impairment of renal function.

The occurrence of solid oedema of the lungs in patients on hexamethonium treatment ("hexamethonium lung") is discussed below with the radiological findings.

RESULTS OF TREATMENT

I. Effect on Survival and Mortality

The length of survival in the series of 82 treated cases, calculated from the date of diagnosis of malignant hypertension, is shown in Text Fig. 2. The results in this and succeeding figures were calculated by the method of life tables (Hill, 1955). The survival rate is compared with that of the control series. These results show an over-all survival rate in the treated group of 50% at one year, 33% at two years, and 25% at four years, as compared with a 90% mortality in the first year in the untreated cases. When drawn on a logarithmic scale the curves in Text Fig. 2 are found to run nearly parallel; the results of treatment may therefore be expressed in another way by saying that the effect has been to increase the expectation of life of the treated patients by a factor of six to eight times that expected from the control series.

Text Fig. 3 separates the severely uraemic from the others in the treated series. The considerable prognostic importance of renal function at the time of diagnosis is clearly seen: the heavy mortality during the first year falls largely in the group with grossly impaired renal function (13% survival at one year in this group, as compared with 73% survival over the same period in those with an initial blood urea level under 60 mg. per 100 ml.). The survival rate in untreated cases with initial blood urea below 60 mg. per 100 ml. is shown

TEXT FIG. 2.—Survival in the whole group of 82 cases of treated malignant hypertension, compared with the control series.

TEXT FIG. 3.—Survival in patients with treated malignant hypertension according to renal function at time of diagnosis.

TEXT FIG. 4.—Comparison of survival in treated and untreated patients with malignant hypertension and blood urea less than 60 mg. per 100 ml. at time of diagnosis.

for comparison in Text Fig. 4, which demonstrates the substantial prolongation of life by treatment in this group.

Text Fig. 5 shows the survival rate in the treated series with the patients grouped according to whether control

TEXT FIG. 5.—Survival in patients with treated malignant hypertension according to degree of blood-pressure control.

TEXT FIG. 6.—Survival in patients with treated malignant essential hypertension compared with patients in whom there was underlying renal disease.

of blood pressure was judged to be adequate or not. The standard of "adequacy" was a reduction of the standing systolic pressure to 160 mm. Hg. or less in the trough following dosage, and satisfactory maintenance of such hypotensive responses at out-patient attendances. There was no difference in survival rate between the two groups in the first year of treatment—this was accounted for by the early deaths from uraemia in each group—but after one year the adequately controlled patients had a better prognosis.

There was no difference in over-all survival between those patients with essential hypertension and those with a diagnosis of hypertension secondary to renal disease (Text Fig. 6). However, when uraemia had become established the progress of the disease was slower in those with primary renal disease than in patients with malignant essential hypertension (Text Fig. 7), a finding which had also been noted in the control series.

In Text Fig. 8 the 12 patients with malignant hypertension who were too severely ill for any hypotensive treatment are included with the 82 treated patients, in order to form a comprehensive assessment of the over-all prognosis of malignant hypertension since treatment became possible. The extreme gravity of the disorder is apparent.

Causes of Death

Death occurred in 56 cases. In 50 the cause of death is known, and these are shown in Table II, in which the relative frequency of the various causes is compared with that in the control series. The chief differences are the diminished incidence of heart failure in the treated group (particularly in uraemic patients) and the increased frequency of death from uraemia uncomplicated by heart failure.

Text Fig. 9 shows the deaths from uraemia and from cerebrovascular catastrophes according to the time of their occurrence in months after the date of diagnosis.

TEXT FIG. 7.—As in Text Fig. 6, including those cases with blood urea of 60 mg. per 100 ml. or over at time of diagnosis. Note that survival is consistently longer in the "renal" than in the "essential" malignant hypertensives.

The majority of deaths from uraemia took place within the first eight months, whereas the cerebrovascular deaths were spread out more evenly over two years.

Analysis of the 10 deaths from cerebral haemorrhage reveals that in 9 the blood pressure was not under control at the time of the terminal illness, even if it had responded satisfactorily to treatment at an earlier period. In one case cerebral haemorrhage occurred nine days after hexamethonium had been stopped on account of pulmonary complications.

II. Effect on Symptoms and Signs

Headache

A history of severe headache was present in 52 cases at the time of diagnosis of malignant hypertension. In 43 of these there was definite relief of this symptom, which was often dated from the first dose of a ganglion-blocking drug. It is of interest that in 30 cases there was no complaint of headache at any time during the illness; absence of headache was more common in the older age group, as noted in the control series.

Headaches may, however, recur during periods of inadequate blood pressure control. One patient had to raise the head of the bed in order to eliminate persistent morning headache. Another patient gave an interesting history of the relation of headache to the severity of hypertension.

A woman aged 30, who developed malignant hypertension after a pregnancy in 1951, was treated first with

hexamethonium and then with pentolinium subcutaneously. Her headaches, which had been very severe, were completely relieved at once, and the retinal changes receded over a period of six months. In 1957, after a period of six years during which her hypertension had been well controlled and she had been symptom-free, it was decided to change from a regimen of pentolinium injections to oral

TEXT FIG. 9.—Deaths from uraemia and from cerebrovascular accidents according to the date of their occurrence after starting treatment.

mecamylamine. During the time of transfer her blood pressure escaped from control and reached levels of 230/140 mm.; simultaneously she complained of a recurrence of headaches similar to those at the onset. Both the blood pressure and headache responded to an increase in dosage of mecamylamine, and she has had no complaint since.

Smirk (1957) mentions the occurrence of headaches during the acute hypotensive phase when the blood pressure is first being brought under control. This was only a rarely a complaint in our series.

Functional Capacity

An attempt was made to assess the degree of restoration to previous functional activity in those patients in whom at least three months' treatment was possible—that is, excluding those who died in less than three months from the time of diagnosis of the malignant phase. Out of 65 such patients, information is available for 62, and the results are shown in Table III.

TABLE II.—Cause of Death in 50 Cases

Cause of Death	No. of Cases	%	% Found in Control Series
Uraemia	20	40	17
Cerebral haemorrhage	10	20	20
Other cerebrovascular catastrophes	2	4	48
Uraemia and heart failure	7	14	13
Heart failure	3	6	1
Dissecting aneurysm	3	6	
Gastro-intestinal haemorrhage (with uraemia)	2	4	1
Cardiac infarction	1	2	
Ruptured mesenteric aneurysm	1	2	
Bronchopneumonia	1	2	
Cause of death not known	6		

TABLE III.—Effect of Treatment on Functional Capacity (Patients Living at Least Three Months)

	No. of Patients
Able to resume previous work or activity	30
Able to work but lighter job	4
Discharged home, unable to work	25
Died in hospital	3
	62

TEXT FIG. 8.—Survival in all cases of malignant hypertension seen in the period 1951-7. Survival rate in treated patients is included for comparison.

Visual Symptoms and Fundi

In 49 cases symptoms of visual disturbance were present at the time of diagnosis of malignant hypertension. The gravity of the visual disability was related to the degree and extent of macular involvement. Where this was more severe in one eye than the other the impairment of vision was correspondingly greater on that side. Peripheral patches of retinitis seldom interfered subjectively with vision. Improvement in visual acuity occurred in most patients and corresponded well with the clearing of macular changes. The improvement in vision was offset to some extent by the paralysis of accommodation caused by ganglion-blocking drugs, but this could usually be corrected with spectacles. In one patient a transient attack of cortical blindness due to insufficiency in the basilar arterial system was precipitated by rapid lowering of blood pressure.

The changes observed in the appearance of the fundus oculi during treatment are summarized in Table IV. It is seen that papilloedema cleared completely in 37 cases, and that this outcome was commoner in those with relatively little impairment of renal function at the start of treatment. When papilloedema receded it commonly did so early, as shown in Table V. Haemorrhages and

exudates cleared rather more slowly; it was not uncommonly six months or longer before the last traces of hard exudate had disappeared from the fundi. It was occasionally observed that papilloedema and retinitis only began to improve after an initial period of further deterioration even though treatment had been begun. The patients who went downhill and died in the early months of treatment often failed to show clearing of papilloedema. Improvement in the fundi was associated with a better prognosis (Table VI).

Table IV includes 6 cases in which papilloedema cleared, only to reappear again at a later stage. This relapse could usually be correlated with the development of a phase in which the blood pressure was difficult to control, although in yet other cases escape from pressure control was not associated with any retrogression of the fundi. One case was of interest in that papilloedema recurred and persisted in spite of strenuous efforts at reduction of blood pressure.

A woman aged 55, who had an inferior vena cava thrombosis with obstruction to the renal vein draining a solitary kidney, developed malignant hypertension in April, 1955. She was treated with pentolinium, and after two months papilloedema had cleared. She was later given mecamlamine, on which drug her blood-pressure readings were usually 200/110 mm. Hg sitting, falling to 160/100 mm. standing up. In April, 1957, papilloedema and florid retinitis recurred, and persisted until her death 18 months later, in spite of treatment with subcutaneous pentolinium, to which her blood pressure was fully sensitive.

Dyspnoea

The incidence of dyspnoea has been analysed in 73 cases (Table VII). The most remarkable effect of treatment was on paroxysmal nocturnal dyspnoea, which was relieved in every case in which it was present. It recurred terminally in 7 out of 26 cases, however; this was associated with uraemia in 3 and with "hexamethonium lung" in 2 cases. Treatment was less successful in improving effort dyspnoea, although one-third of the patients had definite relief of this symptom.

It should be emphasized that treatment in this group was not confined to the use of hypotensive agents; digitalis was used in the majority, and mercurial diuretics were added where indicated.

Angina

Ischaemic cardiac pain was recorded in only 5 cases (6%). In 3 of these a clinical attack of myocardial infarction occurred. In 3 other patients, who gave no history of anginal pain, post-mortem examination showed the presence of areas of old cardiac infarction. There was no evidence that hypotensive drugs either improved or aggravated anginal pain in this particular series, but experience in other patients suggests that they should be used with caution. The low incidence of clinical ischaemic heart disease in the malignant phase of hypertension was noted in the control series (Kincaid-Smith, McMichael, and Murphy, 1958).

Congestive Heart Failure

Congestive heart failure, as indicated by a raised jugular venous pressure and oedema, was present in 17 cases at the outset. After treatment the signs of heart failure disappeared altogether in 14 of these cases, although they recurred terminally in 4. Treatment was with digitalis and mercurial diuretics in addition to hypotensive drugs.

TABLE IV.—*Effect of Treatment on Fundi*

Grading* when Patient Last Seen	Blood Urea at Start of Treatment		Total
	< 60 mg./100 ml.	60 mg./100 ml. or Over	
I-II	20	3	23
III	6	8	14
IV improved ..	6	12	18
IV no change or worse	12	14	26
Total ..	44	37	81

* Grading according to Wagener and Keith (1939). N.B.—One patient not included (developed glaucoma).

TABLE V.—*Duration of Treatment Before Papilloedema Cleared*

Months	No. of Cases
Less than 1	1
1	8
2	14
3	5
4	2
5	4
6	4
7-12	2
Over 12	2

TABLE VI.—*Length of Survival Correlated with Changes Noted in Fundi*

Papillo- oedema	Died			Surviving		
	No. of Patients	Mean Survival (Months)	Standard Deviation from Mean (Months)	No. of Patients	Mean Survival (Months)	Standard Deviation from Mean (Months)
Clearing ..	20	16	±18.7	17	42	±26.9
Unchanged or worse	22	5	±4.5	4	17	±13.5

TABLE VI.—*Effect of Treatment on Dyspnoea in 73 Cases*

Before Treatment	Improving (No. of Cases)	No Change (No. of Cases)	Worse (No. of Cases)	Worse and Nocturnal Dyspnoea (No. of Cases)
None	—	17	2	5
Effort	7	9	1	6
Nocturnal	26	—	—	*

* Nocturnal dyspnoea recurred terminally in 7 cases.

In 62 cases congestive failure was known to be absent at the time when treatment was started. In 3 of these a transient episode of heart failure was observed soon after effective hypotensive treatment had been begun, necessitating the addition of digitalis and diuretics to the regimen. This complication was associated with the development of atrial fibrillation in one case; in the other two the possibility must be considered that reduction of glomerular filtration by ganglion-blocking agents could promote fluid retention and the appearance of heart failure (Fraser and Lowe, 1954).

Ten patients, who had not had congestive failure previously, developed oedema and a raised jugular venous pressure in the terminal stages of their illness. These patients were uraemic, sometimes with severe terminal oliguria and often with marked anaemia, while their blood pressure was in many cases well under control. In one case a terminal episode of heart failure was due to myocardial infarction.

Heart Sounds

Because of the difficulty of obtaining reliable and detailed evidence on heart sounds from hospital records, only those cases which were documented personally and in which phonocardiographic recordings were made are considered here. Such observations were available on 24 patients.

All 24 patients had an atrial sound when first examined. In 12 this persisted unchanged after treatment. In the other 12 serial phonocardiography showed that treatment resulted in movement of the atrial sound closer to the first sound; in 3 cases it became incorporated into the first sound as an "atrial component." This change in the atrial sound is discussed more fully elsewhere (Kincaid-Smith and Barlow, 1959): it accompanied improvement in the clinical condition, and frequently occurred in the first few days or weeks of treatment.

A third heart sound was present in the phonocardiogram in 12 of these 24 cases. In 5 cases it disappeared after a few weeks' treatment. It persisted after treatment in 5 (one a girl of 16 in whom a third sound may well be physiological). Two patients who did not have a third sound when first examined developed this sign with congestive heart failure in the terminal stage of their illness.

Atrial Fibrillation

Atrial fibrillation was present at the time of diagnosis of the malignant phase of hypertension in 4 out of 82 patients. In one of these there was associated rheumatic mitral valve disease, proved at necropsy. The remaining 3 had essential hypertension; the blood pressure was difficult to control in all, but they lived for periods of 18, 19 (still alive), and 45 months, respectively, after diagnosis. In addition to these 4 patients, 3 developed atrial fibrillation in the terminal months or weeks of their illness. The ages of the 7 patients who had atrial fibrillation ranged from 42 to 64 with a mean of 54 years; 5 were male and 2 female.

Pulsus Alternans

Alternation of the pulse was recorded initially in 5 patients. This figure, however, almost certainly does not represent its true incidence in the series. Of the 6 patients in whom it was noted, one is still alive after 32 months; the others died after periods ranging from 2 to 14 months (mean 6 months). Records are not

sufficiently detailed to assess the effect of therapy on this physical sign, which can, on occasion, be transient even in the absence of any special treatment.

Electrocardiogram

The changes observed in the E.C.G. during treatment are summarized in Table VIII for 60 cases in which two or more records were available. The criteria for

TABLE VIII.—Changes in E.C.G. During Treatment

	E.C.G. Normal at Outset (No. of Cases)	E.C.G. Showing Left Ventricular Hypertrophy at Outset (No. of Cases)
Improvement	—	17
Temporary improvement not maintained	—	1
No change	6	24
Deterioration	1	12
Total	7	54

recording either improvement or deterioration in an E.C.G. were alterations in direction of the S-T segments and T waves in the left ventricular surface leads. It was not possible to come to any conclusions regarding changes in the voltage of the R wave over the left ventricle, as the records were not sufficiently comparable. Changes in the S-T segments and T waves due to digitalis or to variations in the serum potassium level were allowed for so far as was possible, and if there was any doubt the E.C.G. was recorded as unchanged. The effects of ischaemia might cause difficulty in interpretation of E.C.G. changes, but, as mentioned earlier, cardiac ischaemic symptoms were rare in this series, so that it seemed fair to attribute the changes observed in the E.C.G. to alterations in the degree of left ventricular hypertrophy (or "strain").

Table VIII shows that 7 out of 61 patients had an E.C.G. which was within normal limits at the outset. In 6 of these the E.C.G. remained normal throughout the period of observation, which lasted for four and six years in 2 patients. The exception, who showed deterioration, was a woman of 27 whose illness began with fulminating pregnancy toxæmia and in whom malignant hypertension persisted after delivery; she died in less than a month from progressive uraemia in spite of reduction of her blood pressure by treatment, and her E.C.G. showed the development of T-wave inversion within three weeks.

The majority of patients had abnormal E.C.G.s before treatment was started. Improvement in the appearance of these tracings, although not a return to normality, was seen in one-third of them (see Text Fig. 10), the others showing either no change or definite deterioration. Any improvement in the E.C.G. was usually observed in less than a year from starting treatment (average 8 months); the observation naturally depended on the timing of the second E.C.G., and 10 of the 17 patients who improved were shown to have done so within the first six months of treatment. The 23 patients who are recorded as showing no change in the E.C.G. were observed for periods of 1 to 69 months (average 16 months).

Radiological Findings

Heart Size.—The changes observed in the size of the heart, as determined radiologically, are shown in Table IX. Radiographs taken before treatment and at some later stage were available for comparison in 41 cases.

TABLE IX.—Changes in Chest Radiograph During Treatment

	No. of Cases
Heart size diminishing	9
" " no change	19
" " increasing	13
Total	41

The transverse diameter of the heart in a standard postero-anterior radiograph was measured, and differences of more than 1 cm. were regarded as significant, provided that the films had been taken in comparable phases of inspiration.

In 9 cases diminution in size of the heart was observed, at intervals varying from 1 to 30 months (average 9 months) after the start of treatment. This improvement often occurred early, and was associated with clearing of systemic venous congestion or paroxysmal dyspnoea which were present in 5 of these 9 cases at the outset. When serial films were taken, however, further reduction in heart size might be observed over a longer period. One example is shown in Special Plate Fig. 1.

In 4 out of 19 patients who showed no change in heart size (Table IX) there was initial improvement accompanying the amelioration of heart failure; in the terminal stages, however, heart failure recurred in these

patients and the final radiograph showed no overall change from the initial one.

There was good correlation between improvement in the chest radiograph and in the E.C.G. (for example, Text Fig. 10 and Special Plate Fig. 1 are from the same patient). No significant difference could be found between these two investigations as regards the time at which improvement in either was noted.

"Hexamethonium Lung."—Four patients in this series developed a syndrome of marked dyspnoea on slight exertion, associated with an irritating non-productive cough and with radiological changes consisting of bilateral soft shadows, most marked in the central zones of both lungs, but sometimes also involving the apices or bases. Three of these patients have already been described by Doniach *et al.* (1954), with necropsy findings in two. A fourth patient developed the same complication terminally, with similar findings at necropsy—namely, an organized fibrinous pulmonary oedema. All these four patients had been treated with subcutaneous hexamethonium for periods of from two to twelve months before the syndrome developed. In one case the drug was stopped, and the patient died nine days later from a cerebral haemorrhage. In the others it was continued or restarted after a short period; one patient died from progressive uraemia after two weeks; one succumbed after three months to a dissecting aortic aneurysm and cardiac infarction, the radiological appearances having virtually cleared by one month before death; the third patient is still at work five years later, his chest radiograph showing only some hard shadowing thought to represent residual fibrosis.

This clinical, radiological, and pathological picture has not been seen in this series since 1953, and has not been noted by us in any patients treated with pentolinium or mecamlamine, although one case occurring with pentolinium has been reported (Hildean *et al.*, 1958).

Renal Function

In this series renal function was assessed by measurement of the blood urea level and of the degree of albuminuria at intervals during treatment. Tests of the concentrating power of the kidney were usually performed at the outset, but were not repeated in a sufficient number of cases for the results to be of value in analysis.

Blood Urea.—The overall changes observed in the level of blood urea between the initial and final values are shown in Table X, for all except two cases in which a second estimation was not available. An alteration was regarded as significant if the later figure differed by 20% or more from the first, provided that one or other of the values was raised (over 40 mg. per 100 ml.). In addition to the 6 patients shown as having had a decreasing blood urea, an initial fall was seen in 2 others after treatment had been started, although these latter relapsed subsequently and died in uraemia. In the majority of cases in which an initially slightly raised blood urea fell to normal there was evidence of congestive heart failure at the onset of treatment, which probably played a part in the temporary impairment of renal function.

Table X shows, as might be expected, that patients with initially normal renal function most frequently showed no change in this respect during treatment, whereas those with considerable impairment (blood urea 80 mg. per 100 ml. or higher) tended to deteriorate further. No

TEXT FIG. 10.—Electrocardiogram in a woman aged 44 before and a year after starting hypotensive treatment, showing improvement in T waves and some reduction of R-wave voltage in left ventricular surface leads.

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FIG. 1.—Serial chest radiographs from same patient as in Text Fig. 10: (a) before treatment; (b) at 4 months; (c) at 12 months, showing progressive reduction in heart size.

FIG. 2.—Interlobular renal artery from case of untreated malignant hypertension showing cellular proliferation of intima. (Haematoxylin and eosin. $\times 176$.)

FIG. 3.—Interlobular renal artery from case of treated malignant hypertension showing a double internal elastic lamina. The outer elastic layer marks the site of the original lumen. The lumen is narrowed by a layer of collagen fibres and a new internal elastic lamina has formed. The vessel differs from that in the case of untreated malignant hypertension (Fig. 2) in the replacement of cellular connective tissue by mature collagen. (Weigert's elastic, haematoxylin, and Van Gieson's stains. $\times 176$.)

FIG. 4.—Renal arteriole from case of treated malignant hypertension showing hyaline replacement of wall and breaks in elastic lamina. (Weigert's elastic, haematoxylin, and Van Gieson's stains. $\times 240$.)

FIG. 5.—Renal arteriole from case of benign hypertension showing layer of subendothelial hyaline. (Weigert's elastic, haematoxylin, and Van Gieson's stains. $\times 300$.)

FIG. 7.—Glomerulus from case of treated malignant hypertension showing fibrous replacement of half the glomerular tuft resulting from "healing" of previous fibrinoid degeneration. (Haematoxylin and eosin. $\times 220$.)

FIG. 8.—Glomerulus from case of treated malignant hypertension showing laying down of reticulin fibres in one half of glomerular tuft. No reticulin fibres are present in normal glomeruli impregnated in this way. (Silver reticulin impregnation. $\times 165$.)

FIG. 6.—Renal arteriole from case of treated malignant hypertension showing double internal elastic lamina similar to that described above in interlobular arteries (Fig. 3). (Weigert's elastic, haematoxylin, and Van Gieson's stains. $\times 360$.)

FIG. 9.—Glomerulus from case of treated malignant hypertension showing fibrous tissue staining with aniline blue replacing half the glomerular tuft. (Mallory's azo-carmin. $\times 167$.)

The erythrocyte sedimentation rate (E.S.R.) was measured by the Westergren method in 68 cases, and

the findings are shown in Table XII. The E.S.R. may be elevated in the malignant phase of hypertension to a degree which cannot be accounted for by anaemia or any other underlying condition, but is not of much value in diagnosis or prognosis (Kincaid-Smith,

intimal tissue seen in untreated cases. In the older age group, where untreated cases may show fibrous intimal thickening in interlobular arteries, it is difficult to assess the modifications produced by therapy.

TABLE XII.—*Erythrocyte Sedimentation Rate*

E.S.R. (mm. in 1 Hour)	No. of Cases	Essential Hypertension	Renal Hypertension
Under 20	32	17	15
20-40	19	10	9
41-60	6	—	6
61-100	8	3	5
Over 100	3	—	3
Total	68	30	38

McMichael, and Murphy, 1958). Later observations of the E.S.R. after a period of treatment were made in 33 cases; in 11 there had been a significant fall (>50), in 18 there had been no change, and in 4 the E.S.R. had risen. These changes, however, could not be correlated with any differences in survival; a fall in E.S.R. was as likely to be associated with a bad prognosis as an increase.

Pregnancy

One patient in this series, a woman aged 37, had a successful pregnancy four years after malignant hypertension had been diagnosed. She had been treated with ganglion-blocking drugs and reserpine, and this regimen was continued throughout the pregnancy, which terminated in spontaneous premature labour at the thirtieth week with the birth of a healthy infant. This case has already been reported in detail (Kincaid-Smith, Somers, and Browne, 1958). Occasional other cases of successful pregnancy have been reported following the treatment of malignant hypertension by nephrectomy (Rosenheim, 1954) and sympathectomy and ganglion-blocking drugs (Ross and Wright, 1958).

III. Pathology of Treated Malignant Hypertension

A total of 42 patients came to necropsy after treatment with hypotensive drugs over periods varying from one week to two years. A comparison of the histological lesions in the kidneys of this group with those described in untreated malignant hypertension (Kincaid-Smith, McMichael, and Murphy, 1958) revealed certain modifications of the pathological picture in the treated group.

Interlobular Arteries

These vessels in untreated malignant hypertension, particularly in the younger age group, show a loosely arranged cellular hyperplasia of the intima (Special Plate, Fig. 2) in which no collagen or elastic fibres are present. Older patients with malignant hypertension may show fibroelastic intimal thickening in interlobular arteries resembling that seen in benign hypertension, although the degree of narrowing of the lumen is greater in the malignant group. In young patients treated with hypotensive drugs the intimal lesions lose their cellular appearance and develop mature collagen fibres. The lesions may now be indistinguishable from those in benign hypertension. Usually, however, they show a difference in that the lumen is significantly narrowed and a broad layer of collagen is present within the original internal elastic lamina; a newly formed internal elastic lamina often separates the new collagen layer from the lumen (Special Plate, Fig. 3). This appearance almost certainly results from fibrosis of the cellular

Arterioles

Hyaline arteriolar change has not been commonly observed in cases of untreated malignant hypertension. In cases treated with hypotensive drugs, however, hyaline material is often present in arterioles. This hyaline change may affect the whole arteriolar wall (Special Plate, Fig. 4), in contrast to the type seen in benign hypertension, where it is usually subendothelial in situation and has a clearly defined muscular layer and internal elastic lamina external to it (Special Plate, Fig. 5). Breaks in the elastic lamina (Special Plate, Fig. 4) frequently accompany the hyaline arteriolar changes, and in many vessels the elastic lamina may be entirely absent. Fibrosis of arterioles with collagen replacement of arteriolar muscle and elastica is also observed in treated cases. Both hyalinization and fibrosis of arteriolar walls probably represent "healing" of the fibrinoid arteriolar lesions of untreated malignant hypertension. Another change very similar to that occurring in interlobular arteries, and probably due to the same process, is the presence of a ring of collagen internal to the original elastic lamina and with a newly formed elastic lamina separating it from the lumen (Special Plate, Fig. 6). As in the arteries, this change probably results from fibrosis of the cellular intimal proliferation seen in untreated cases.

Glomeruli

In untreated cases of malignant hypertension a hyaline or fibrous segment in a glomerular tuft is rare. In cases treated with hypotensive drugs this type of glomerular change is almost invariably present and may be very frequent (Special Plate, Fig. 7). It may be seen after a few weeks of treatment. This appearance almost certainly results from an alteration in glomerular fibrinoid which often involves only a portion of a glomerular tuft. In treated cases such an area of fibrinoid first loses its specific staining reactions and resembles hyaline material. At this stage it may still show nuclear debris confirming the recent necrotic process. Subsequently reticulin (Special Plate, Fig. 8) and aniline-blue-stainable fibres (Special Plate, Fig. 9) appear in the "healed" segment of the glomerular tuft, and finally van-Gieson-positive collagen fibres are stainable. The alteration occurs without any obvious migration of fibroblasts into the tuft. Where a portion of a glomerulus shows this type of lesion the remainder of the tuft may contain blood within apparently healthy capillary loops (Special Plate, Fig. 7).

Thus the histologically detectable effects of hypotensive therapy in malignant hypertension are a conversion of cellular intimal hyperplasia to fibrous intimal thickening and a "healing" of fibrinoid degeneration to hyaline and fibrous tissue. Although the histological picture comes to resemble that of benign hypertension, it is usually possible to distinguish the two.

In four cases a rapid deterioration to renal failure occurred in spite of a normal or only slightly elevated blood urea at the beginning of treatment. All four cases showed a striking degree of narrowing of interlobular arteries with consequent incomplete infarction of almost the entire renal parenchyma. This group contrasts

strongly with those in which fairly good renal function was maintained on hypotensive drugs over periods from six months to two years. In the latter the interlobular arteries showed little narrowing and parenchymal damage was slight, death being due to causes other than renal failure.

These findings suggest that where hypotensive treatment is begun before an appreciable narrowing of interlobular arteries occurs renal damage does not progress and the prognosis is good. Where, however, widespread marked narrowing of interlobular arteries is present at the start of treatment progression to renal failure is inevitable. A correlation with the clinical findings suggests that a blood urea of over 100 mg. per 100 ml. indicates considerable narrowing of interlobular arteries, and that in such cases death is likely to occur from progressive renal failure within a few months in spite of treatment.

DISCUSSION

The present report represents an extension of observations published previously (McMichael and Murphy, 1955). The number of patients now studied has been more than doubled, and the pattern and prospect of survival are now more clearly apparent. Smirk (1957) reports a 37% five-year survival in patients "whose renal function is good or but moderately impaired," but indicates that the prognosis may be even better when rauwolfia alkaloids are combined with ganglion blockade. Results of the latter method of treatment have, however, been published only for the last two years. Barnett (1956) also reported particularly satisfactory results in treatment of malignant hypertension, 23 out of 32 patients surviving more than one year, and 12 for more than two years. The death rate in his series seemed to flatten out after the second year. The Cleveland Clinic series (Dustan *et al.*, 1958) deals with 84 cases, but only includes patients who survived three months or more from the start of treatment; 30 patients were surviving and 52 had died at the time of their report. Congestive heart failure, as in our series, was notably reduced as a cause of death. Perry and Schroeder (1958) reported their results with oral methonium and hydrallazine. In 82 cases of malignant hypertension there was a 50% four-year mortality. They also noticed an improved prospect in co-operative patients. It is clear, however, that the patients selected for treatment included fewer with severe uraemia than were treated in the present series.

The therapeutic regimens in these varied series are not identical. Schroeder was alone in using oral methonium combined with hydrallazine, while the present series was possibly treated with less effort at reducing the blood pressure to normal than may have been adopted by Smirk's group. It is striking, however, that the over-all results appear to be remarkably similar. Any improvement in mortality is probably the result of blood-pressure reduction irrespective of the drug regimen in use. Failure of the patients to co-operate or abandonment of the regimen for other causes leads to a significant deterioration in survival prospects.

In patients afflicted with such a grave disorder as malignant hypertension, with underlying renal disease in about half the cases, a continuing mortality must be expected. Even if deaths from heart failure are reduced and progression of other complications such as retinitis reversed, the underlying nephritic or pylonephritic process usually continues its slow development over the

years. The necessary interruptions of dosage of ganglion-blocking agents during periods of ileus, etc., may permit cerebral haemorrhage to occur. The accompanying atherosclerosis in older patients creates a continuing liability to thrombosis. It is only fair, in considering the possibilities of treatment, to include those patients who come under observation only when the disease is already far advanced. Rapidly progressive renal vascular narrowing may often be irreversible. It is thus only in a highly selected group of non-uraemic hypertensives with papilloedema that a long-term good prognosis may be anticipated. It is possible that patients with malignant hypertension might be seen at an earlier stage before the renal vascular damage has become too advanced if more frequent fundus examinations were carried out in patients with very high blood pressures, particularly when headaches have suddenly made their appearance or become more severe in a patient previously uncomplaining in this respect (Kincaid-Smith, McMichael, and Murphy, 1958).

This reported experience gives a practical vindication of the value of blood-pressure reduction in severely hypertensive patients. Fears of accelerating the progress of uraemia are largely groundless so long as the pressure is not reduced too quickly or to extremely low levels. The patient who survived longest in the present series was a man with chronic renal hypertension whose blood urea was 70 mg. per 100 ml. when the diagnosis of malignant hypertension was made at the age of 38; he was still in full employment seven years later, although his blood urea had gradually risen to a level of 200 mg. per 100 ml. The benefits are most pronounced on retinitis and on heart failure. Improvement of effort tolerance does not always depend on reduction in heart size or electrocardiographic improvement.

The most convincing evidence of benefit is to be seen in the regression of pathological changes in the renal arteries and arterioles as described. It is interesting to note that similar retrogression of vascular changes has been recorded after hydrallazine treatment of rats with experimentally induced renal hypertension (Masson *et al.*, 1958). The more florid vascular lesions of the young patient with malignant hypertension regress to a state comparable to that seen in elderly subjects, whose liability to a "malignant" phase of hypertension seems to be much reduced (Kincaid-Smith, McMichael, and Murphy, 1958).

Beneficial results in the treatment of retinitis and heart failure may be expected when a similar regimen of treatment is applied in other severe forms of hypertensive disease. We have not yet encountered any evidence which would suggest that atherosclerosis is in any way ameliorated, or even prevented, by the use of hypotensive drugs. We have seen in a few instances the development of thrombotic complications in the coronary or cerebral territories during phases of severe hypotension. For this reason we are cautious about the use of hypotensive drugs in the presence of occlusive vascular disease, and particularly in the elderly. At the other extreme we do not yet recommend their use in younger symptomless hypertensives: only the development of ominous symptoms or signs can justify the use of a regimen difficult for the patient and exacting on the doctor.

SUMMARY

A series of 82 patients with malignant hypertension treated with ganglion-blocking drugs during the period

1951-8 is reported. The results observed in this group are compared with a control series previously reported from the same hospital.

The expectation of life of the treated patients was increased by a factor of six to eight times that expected from the control series. Prolonged survival was particularly seen in those patients whose renal function was normal or only slightly impaired at the start of treatment. Death was most frequently due to uraemia; heart failure as a cause of death was considerably diminished in the treated group.

The benefits of treatment were most pronounced on retinitis and in heart failure. Improvement in the electrocardiogram was seen in one-third of cases; reduction in cardiac size occurred somewhat less frequently.

Renal function tended to remain stationary or to improve slightly in patients with an initial blood urea level below 80 mg. per 100 ml.; where renal impairment was more severe than this progressive deterioration was the rule.

Patients with neurological complications did not derive much benefit from treatment. Accompanying atherosclerosis was a limiting factor in the success of treatment, particularly in older patients.

A survey of the histological lesions in the kidneys showed that after treatment with hypotensive drugs the main changes were a conversion of cellular intimal hyperplasia in the interlobular arteries to fibrous intimal thickening and a "healing" of fibrinoid degeneration to hyaline and fibrous tissue. Some correlation was likely between the degree of narrowing of the interlobular arteries at the start of treatment and prognosis.

The clinical observations have been documented through the years, especially by Drs. Brenda Morrison, Helen Mellanby, and Edmond Murphy. We are indebted to our clinical and pathologist colleagues who co-operated in the study. We are deeply grateful to Messrs. May and Baker Ltd., who contributed generously to the support of this research irrespective of the source of drugs under trial.

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CHRONIC Q FEVER

1. CLINICAL ASPECTS OF A PATIENT WITH ENDOCARDITIS

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The tendency of rickettsiae to persist in the tissues of human or animal hosts after an initial infection is well recognized. Perhaps the most striking example is that of Brill's disease, in which the rickettsia of epidemic typhus has been isolated during a recrudescence of illness occurring in persons first exposed to infection up to twenty or more years previously (Murray and Snyder, 1951). Other rickettsiae—namely, those of scrub typhus (Smadel *et al.*, 1952) and of Rocky Mountain spotted fever (Parker *et al.*, 1954)—have been recovered from lymphoid tissue taken from patients one to two years after the original illness.

Although the lengthy persistence of *Rickettsia burneti* (the causative organism of Q fever) in the tissues of experimentally infected animals has been demonstrated on a number of occasions, relatively little is known about its persistence—either as a latent infection or as the cause of a chronic illness—in human beings.

This paper describes the clinical aspects of a patient with chronic Q fever who had the symptoms and signs of endocarditis; it also briefly reviews the literature of the problem in general. A second paper by our colleagues, P. S. Andrews and B. P. Marmion (1959), gives details of the pathological and bacteriological observations which were made on the patient.

Case History

The Acute Illness

The patient, a geophysicist aged 47, first became ill in December, 1955, while his yacht was being refitted in Panama after damage at sea. The illness began suddenly with fever, rigors, severe headache, low back pain, and a dry cough. On examination in hospital he had a temperature of 102° F. (38.9° C.) and a scanty maculo-papular rash on the trunk. No other abnormal signs were described. A chest radiograph showed an area of consolidation in the right lower zone and a normal cardiac silhouette (cardio-thoracic ratio, 47%). The urine contained a few pus cells. All other investigations, including at least one blood culture and search for malarial parasites, were negative. He was given a course of sulphafurazole ("gantrisin"), and 12 days later (December 15) was afebrile and symptom-free. He returned to England, where in March, 1956, a chest radiograph showed nothing abnormal.

Retrospectively, the description of this illness is suggestive of Q fever, especially as Panama is a known endemic area and the patient had removed ticks from his dog and had also drunk raw milk. Unfortunately, however, no serological investigations for Q fever were undertaken at the time.