SEVERE HYPERTENSION TREATED WITH GANGLION-BLOCKING DRUGS IN A GENERAL HOSPITAL

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Ganglion-blocking drugs have enabled physicians to lower the blood-pressure of patients with severe hypertension. Reports from specialized units have shown that the life expectancy of patients with malignant hypertension can be improved by this treatment (Smirk, 1954; Barnett, 1956; Dustan *et al.*, 1958; Perry and Schroeder, 1958; Harington *et al.*, 1959). The enthusiasm of physicians particularly interested in this problem has been thought by many to play an important part in the results achieved by these units, and it has been implied that treatment in general hospitals will be disappointing in comparison.

This paper reviews the results of treatment with ganglion-blocking drugs at a hypertension clinic in a general hospital. The recent introduction of bretylium tosylate and guanethidine, potent hypotensive agents with a different mode of action, makes the time opportune to survey the effectiveness of ganglion-blocking drugs.

Material

The series comprises 284 out of 836 patients referred to the hypertension clinic at Auckland Hospital over an eight-year period, who were regarded as having a blood-pressure high enough to justify treatment with ganglion-blocking drugs. The patients were classified according to the appearance of the fundi, using the grading of Keith *et al.* (1939): 35 patients had malignant hypertension with grade IV fundal changes (papilloedema, haemorrhages, and exudates); 71 patients were thought to have premalignant hypertension, their fundi showing haemorrhages and exudates but no papilloedema (grade III changes); and 171 patients had severe benign hypertension with lesser degrees of retinopathy. The criteria separating grade I and grade II fundi are difficult to use in practice, and these two grades are therefore merged in the present series. Initial fundal gradings were not available in seven patients.

It is not possible to define rigidly the conditions which warrant the use of ganglion-blocking drugs in the treatment of hypertension. With increasing experience fewer of the patients referred were placed on these drugs. They were given to all patients with premalignant or malignant hypertension. Patients with benign hypertension, according to fundal grading, were assessed individually and treated with ganglion-blocking drugs if they had developed a serious complication of high blood-pressure (particularly left ventricular failure), or if they had a sustained diastolic blood-pressure over 120 mm. Hg and evidence of left ventricular hypertrophy in the chest x-ray film or electrocardiogram. Only 36 of these patients had an average initial diastolic pressure below 120 mm. Hg. Younger patients were treated at a lower level of diastolic pressure than older patients.

The patients started treatment with ganglion-blocking drugs during the period 1951-8, and had been on treatment for at least 12 months when the results were reviewed at the end of 1959.

Patients who left the district were withdrawn from the survey at the time they ceased to attend the clinic

FIG. 1.—Age and sex distribution of 284 patients with severe benign or malignant hypertension.

(15 cases). Similarly, patients who stopped taking ganglion-blocking drugs because they were unable to tolerate them were withdrawn from the series at the time they stopped therapy (29 cases). Some patients stopped treatment owing to the development of a complication of hypertension which later proved fatal. These patients were included, and were regarded as having died while on treatment.

All surviving patients were personally assessed at the end of the period under review.

The age and sex distribution of the 284 patients (125 (44%) males, 159 (56%) females) is given in Fig. 1. Although there were more females than males in the whole series, as many males as females had premalignant hypertension, while in the group with malignant hypertension males outnumbered females by more than 2:1 (Fig. 2).

Aetiological Diagnosis.—In most cases the diagnosis was made on clinical grounds with the support of simple investigations of urine and blood. Intravenous pyelography and 24-hour urinary catechol amine estimations were performed in a proportion of the cases. On the available evidence 238 (83.7%) of the patients had

FIG. 2.—Fundal grading of 277 cases according to the criteria of Keith *et al.* (1939). The number of cases in each group is given above the columns.

"essential" hypertension, 24 (8.4%) had chronic pyelonephritis, 19 (6.7%) had chronic glomerulonephritis, and 3 (1.2%) had miscellaneous conditions (polycystic kidneys, Cushing's syndrome, and disseminated lupus erythematosus).

Complications Prior to Starting Treatment.—Most patients with premalignant or malignant hypertension, and over half the patients with benign hypertension, had had a complication of high blood-pressure before starting treatment with ganglion-blocking drugs. Complications included left ventricular failure in 78 cases (27%), congestive cardiac failure in 62 (22%), cerebrovascular accident in 71 (25%), and myocardial infarction in 26 (9%).

Presence of Uraemia.—Other reports have shown that the degree of renal impairment affects the prognosis of malignant hypertension. In the present series 14 out of 35 patients with malignant hypertension had an elevated blood non-protein-nitrogen, but in only one case did this exceed 60 mg./100 ml.

Method of Treatment

The ganglion-blocking drug used as the major therapeutic agent changed as new compounds became available. Hexamethonium by injection or by mouth was used originally; from 1953, oral pentolinium was employed extensively. About one-half of the patients taking pentolinium were changed during 1957-9 to mecamlamine or pempidine because of inadequate blood-pressure control or side-effects. Rauwolfia alkaloids have been added to the regime of treatment in most cases since 1954. Chlorothiazide has also proved of value, reducing the effective dose of the ganglion-blocking drug.

The hypertension clinic at Auckland Hospital was established on principles recommended by Smirk (1953). All patients attended either for whole or half-day periods. Standing blood-pressure readings were taken every half-hour in order that the depth and length of blood-pressure troughs after one or two doses of the ganglion-blocking drug could be judged. Less than half of the patients were admitted to hospital for initial stabilization, the majority attending the clinic all day for three days each week until the optimal dose was found. The patients then attended for a whole day or half-day every six or eight weeks, or more frequently when the blood-pressure was unstable. Although the aim in treatment was to obtain a trough blood-pressure near normal levels, this was achieved in only a minority of patients.

The patients were advised to sleep with the head of the bed on blocks, but few did so, and most were given a larger evening dose of ganglion-blocking drug. Oral and written instructions were given to explain the principles of treatment and ways of reducing the parasympathetic side-effects of these drugs.

Results of Treatment

Length of Survival.—The length of survival after starting treatment is shown in Fig. 3. The survival curves were calculated by the method of life-tables (Hill, 1955), and include all patients treated with the exception of seven in whom initial fundal gradings were not available. The survival rates for one, three, and five years were 82%, 56%, and 44% for the malignant group, 84%, 67%, and 57% for the premalignant group, and 98%, 93%, and 81% for the group with benign hypertension. Survival curves constructed in

this way become less reliable as the number of patients at risk declines. In the present series the number of patients at risk at five years was only 65 compared with 277 who had started treatment.

FIG. 3.—Survival curves of 277 treated hypertensive patients divided according to the fundal grading.

Causes of Death.—Of 284 patients, 61 died during the period of study and the causes of death are given in Table I. Although death from uraemia was more

TABLE I.—Causes of Death in 61 Cases of Hypertension

Cause of Death	Males	Females	Total	
			No.	%
Renal failure	9	2	11	18
Congestive cardiac failure	7	3	10	16
Myocardial infarction	5	3	8	13
Cerebrovascular accident	13	11	24	40
Dissecting aneurysm	2	0	2	3
Embolism	1	2	3	5
Miscellaneous	2	1	3	5
	39	22	61	100

common in the males, this accounted for only 9 of the 39 male deaths, and did not alone explain the increased male death-rate.

Radiological Findings.—In most cases postero-anterior chest films only were available for assessment of heart size.

The cardiac silhouettes were divided into four arbitrary grades by one radiologist. Initially the heart was normal in size in 71 cases (25%), slightly enlarged in 128 (46%), moderately enlarged in 66 (23%), and markedly enlarged in 16 cases (6%).

Three patients did not have a chest x-ray examination before starting treatment. The changes in heart size in 224 patients as assessed radiologically during the course of treatment are given in Fig. 4. There was improvement in the heart size in 21% of cases, no change in 65%, and a deterioration in the

FIG. 4.—Effect of treatment on radiological assessment of heart size of 224 cases. The number of cases in each group is given above the column. Solid blocks under "marked" changes in heart size are cases in which left ventricular failure contributed to the change in heart size.

remaining 14%. One-third of the patients with a marked change in heart size had left ventricular failure; these cases are shown in Fig. 4 by solid black columns.

Effect of Treatment on the Electrocardiogram.—The electrocardiogram before treatment showed evidence of left ventricular hypertrophy in 87% of 271 cases. Electrocardiographic changes were regarded as slight in 31%, moderate in 35%, and marked in 21%; details (including the criteria used to assess hypertrophy) are given in Table II.

TABLE II.—*Electrocardiogram of 271 Cases Prior to Starting Treatment*

Left Ventricular Hypertrophy	QRS Complex	T-Wave Change	Overall Assessment	
	No. of Cases	No. of Cases	No. of Cases	%
Nil	83	63	36	13
Slight	70	70	84	31
Moderate	58	101	95	35
Marked	60	37	56	21

QRS changes were assessed on the sum of SV_1 and RV_6 , or SV_2 and RV_6 : nil, <35 mm.; slight, 35–39 mm.; moderate, 40–49 mm.; marked, 50 mm. or greater.

T-wave changes were assessed as slight if the T waves in the left ventricular surface leads were flattened or isoelectric, moderate if shallowly inverted, and marked if steeply inverted.

It was easy to find individual examples of striking improvement in the electrocardiogram after treatment,

FIG. 5.—Effect of treatment on the electrocardiogram of 236 cases. The number of cases in each group is given above the appropriate column.

yet the overall results as shown in Fig. 5 were less impressive. Minor changes were ignored, so that a "slight" change indicates significant alteration in the QRS complex or T waves. The electrocardiogram was unchanged in 46%, significantly improved in 39%, and deteriorated in 15% of the cases. Marked improvement in the electrocardiogram occurred in only 23% of those with evidence on the initial electrocardiogram of moderate or marked left ventricular hypertrophy.

Functional Capacity.—Although nearly all patients experienced some side-effects from ganglion-blocking drugs, 78% of surviving patients were able to live a normal life—that is, continue in their employment or manage the house and family responsibilities. Side-effects of the drugs imposed minor limitations on the activities of a further 10% and severely limited 2%. Complications of hypertension such as cerebrovascular accident or congestive cardiac failure were responsible for limitation of activity in the remaining 10% of patients.

Discussion

Malignant hypertension with papilloedema is a well-defined condition, and survival rates of these patients can, with some reservations, be compared in different series (Table III). The results of treatment in our patients parallel those of Björk *et al.* (1960) from five

Swedish hospitals. It appears that a general hospital with adequate facilities can attain a reduction in the mortality of patients with malignant hypertension similar to that achieved by specialized units (Dustan *et al.*, 1958; Perry and Schroeder, 1958; Hodge *et al.*, 1961).

TABLE III.—*Results of Treatment of Malignant Hypertension*

Author	No. of Cases	Survival Rate (%)			
		1 Year	3 Years	4 Years	5 Years
Present series	35	82	56	45	44
Hodge <i>et al.</i> (1961)	57	74	57	46	36
Björk <i>et al.</i> (1960)	93	76	54*	52*	50
Dustan <i>et al.</i> (1958)	84	70	50	48*	33
Harington <i>et al.</i> (1959)	82	50	30*	25	22*
Perry and Schroeder (1958)	—	—	—	50	—

* Estimated from figures.

Harington *et al.* (1959) had a higher mortality in 82 cases of malignant hypertension, with one-, three-, and five-year survival rates of 50%, 30%, and 22%. However, in their series the number of patients with a raised blood urea was higher than that observed in this centre or reported by Björk *et al.* (1960). Perry and Schroeder (1958) found the proportion of their patients with azotaemia was similar to that reported by Harington *et al.*, but their criterion of azotaemia was less rigid: a blood non-protein-nitrogen of over 25 mg./100 ml. compared with the criterion of Harington *et al.* of a blood urea over 60 mg./100 ml.

Most series of cases are to some extent selected. They may include severe cases referred from other hospitals, or a hospital may select only a proportion of the acute admissions offered to it. Selection in this sense may contribute to the higher mortality observed by Harington *et al.* The present series is reported from the only hypertension clinic in its area, and the clinic accepts all cases referred to it. Case selection, probably common to all series, has occurred because some cases of malignant hypertension were admitted to hospital wards and died before they were referred to the clinic. Dustan *et al.* (1958) included only cases in which the patient survived for a minimum of three months after diagnosis, and their results are therefore not strictly comparable with other series.

The importance of vigorous treatment for patients with premalignant hypertension (fundal haemorrhages and exudates but no papilloedema) has been stressed previously by Smirk (1957); this is supported by our results. The mortality of these patients was only slightly lower than that of patients with malignant hypertension, and their treatment therefore needs careful supervision.

In benign hypertension results of treatment are very similar to those of Smirk (Hodge *et al.*, 1961). Case selection invalidates the comparison of survival rates of our patients with large series of untreated cases (Frant and Groen, 1950; Palmer and Muench, 1953). Previous attempts (Palmer *et al.*, 1948; Keith *et al.*, 1949; Dustan *et al.*, 1958) to improve the comparison of groups of cases of benign hypertension by giving points for abnormal findings have not found general acceptance. The fact that each author has introduced a new system emphasizes the difficulties involved.

Centres have differed widely in the regime of drugs used to lower the blood-pressure. In the present series, and in those reported by Harington *et al.* (1959) and by Hodge *et al.* (1961) hydralazine was not employed, although it was used extensively by Perry and Schroeder (1958) and by Björk *et al.* (1960). In the early days of treatment with ganglion-blocking drugs Harington

et al. relied on parenteral therapy more than the other physicians.

The assessment of degrees of change in heart size from serial chest x-ray films is inexact. In our cases the size of the heart was judged to have decreased significantly in 21% and increased in 14% of 224 cases. Smirk (1954) reported in 76 patients a decrease in heart size of more than 0.5 cm. in 36% and an increase in 16%.

The initial optimism of Doyle (1953) on the value of ganglion-blocking drugs in reducing left ventricular hypertrophy, as measured by electrocardiographic changes, has not been sustained. In a series of 75 cases he reported improvement in the QRS voltage in 76% and improvement in the S-T segment and T waves in 85%. Hay (1957), from the same unit, found that improvement occurred in the electrocardiogram in 47% of 143 hypertensive patients treated from two to six years on ganglion-blocking drugs and deterioration in 18%. In the present survey, with the use of similar criteria, electrocardiographic changes were less impressive, 39% of the patients showing improvement and 15% deterioration.

Summary

Results of treatment with ganglion-blocking drugs are reviewed in 284 patients with severe hypertension. In 35 cases with malignant hypertension one-, three-, and five-year survival rates were 82%, 56%, and 44% respectively. In 71 cases with premalignant hypertension (fundal haemorrhages or exudates but no papilloedema) comparable survival rates were 84%, 67%, and 57%. The remaining 171 cases with lesser degrees of retinopathy had benign hypertension. They had significant cardiac enlargement or had developed a complication from high blood-pressure. The prognosis on treatment for this group was 98%, 93%, and 81% survival at one, three, and five years. These results from a general hospital are similar to those in series reported from special units; our facilities could be provided in any general hospital.

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INCIDENCE OF HAEMAGGLUTINATING AND COMPLEMENT-FIXING ANTIBODIES

BY

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I. ULCERATIVE COLITIS

Broberger and Perlmann (1959) observed a haemagglutinating antibody in the serum of certain patients with ulcerative colitis. This antibody agglutinated red cells coated with antigen prepared by the hot phenol-water extraction of fresh human colon and liver, and occurred in the serum of 28 out of 30 children with ulcerative colitis and in a few patients with rheumatoid arthritis, acute nephritis, and the nephrotic syndrome.

Gajdusek (1958), Mackay and Gajdusek (1958), Asherson (1959), and Deicher, Holman, and Kunkel (1960) described complement-fixing antibodies against human and animal tissue components in the serum of certain patients with systemic lupus erythematosus, parenchymal liver disease, and occasional patients with rheumatoid arthritis.

Both these antibodies have been regarded as auto-antibodies, and their occurrence in a disease allows the possibility of tissue damage being due to immune mechanisms. This communication describes the incidence of haemagglutinating and complement-fixing antibodies in the serum of 14 children and 36 adults with ulcerative colitis.

Methods

Haemagglutination was undertaken as described by Broberger and Perlmann (1959) using sheep red cells coated with colon or liver antigen prepared by hot phenol-water extraction of fresh human tissue obtained from children who died during their first day of life. The sera were titrated in M.R.C. pattern "perspex" trays, using a final volume of 0.2 ml. The test was read after shaking. We read the trays independently. On the few occasions when we differed a joint decision was reached.

In certain cases after haemagglutination reaction had been completed complement (guinea-pig serum) was added. The degree of haemolysis was noted visually after incubation at 37° C. for one hour with occasional shaking.

The complement-fixation technique of Donnelley (1951) as modified by Gajdusek (1958) was employed. Calcium magnesium veronal buffered saline (Mayer, Croft, and Gray, 1948) was used as a diluent. Because of the necessity of using fresh tissue advantage was taken of Gajdusek's (1958) observation that sera reacting with human tissue also reacted with animal tissue. Rat liver and kidney antigens were prepared by homogenization in 0.25 M sucrose followed by centrifugation to remove the nuclei. A titre of 1/16 was regarded as positive provided the 1/8 serum control was negative.

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