EFFECT OF PROLONGED TREATMENT WITH HYPOTENSIVE DRUGS ON RENAL FUNCTION IN HYPERTENSION

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Changes in the renal circulation in most subjects with essential hypertension long precede impairment of renal function (Goldring and Chasis, 1944). Early changes consist of a moderate reduction in effective renal blood-flow (E.R.B.F.) and of a smaller fall in glomerular filtration rate (G.F.R.). Later, E.R.B.F. and G.F.R. fall further, and it is recognized (Goldring and Chasis, 1944) that if the disease enters a malignant phase, although G.F.R. and E.R.B.F. may be only moderately reduced in the early stages, rapid reduction is the usual course, with extremely low values in the final stages. We have confirmed these observations, and our values in three normal

FIG. 1.—Comparison of glomerular filtration rate and effective renal blood-flow in three normal subjects and patients with benign and malignant hypertension.

1954). These changes are, however, short-lived, and a return to the original levels occurs despite continued reduction of blood-pressure (Grob *et al.*, 1953; Moyer and Mills, 1953; Mackinnon, 1954). In view of this acute effect of ganglion-blocking drugs it seemed possible that prolonged administration might affect renal function adversely, though it was hoped that continued reduction of blood-pressure might halt progressive vascular changes or even induce reversal of such changes, particularly in the malignant phase of hypertension.

We report here observations on renal function and the renal circulation in hypertensive subjects during prolonged treatment with hypotensive drugs.

Material and Methods

All the cases described were thought to have severe hypertensive disease requiring treatment. Indications for treatment were as follows: (1) malignant phase of hypertension with grade IV retinopathy (Wagener and Keith, 1939) (8 patients); (2) severe benign essential hypertension (7 patients, 4 with grade III retinopathy) (Wagener and Keith, 1939).

In all patients the diastolic blood-pressure after rest in hospital was 120 mm. Hg or more, and in most it was 130 mm. Hg or more. All patients had either electrocardiographic or radiological evidence of left ventricular enlargement, and most had both.

Patients were admitted to hospital for assessment, and renal clearances were carried out after a period of rest before hypotensive treatment was given. Treatment was started in all patients with a small subcutaneous dose of hexamethonium bromide (C6). This was given at eight-hourly intervals to patients without elevation of the blood urea but less often and in smaller doses if this was present. Frequent blood-pressure measurements were made, and the dose of C6 was increased as tolerance was acquired. The final dose of C6 varied from 105 to 570 mg. daily (average 218 mg.). While in hospital patients were taught to give their own injections, and continued to do so after discharge. Patients were also given hydralazine hydrochloride ("apresoline") 50–100 mg. by mouth two hours after each injection. Subsequently, when they became available, subcutaneous or oral pentolinium tartrate ("ansolysen") was substituted for C6 in three patients and mecamlamine ("inversine") in five, and the blood-pressure was restabilized. "Rauwiloid and veriloid" (4 tablets daily) was substituted for hydralazine in 11 patients and chlorothiazide ("saluric") 1 g. daily in one.

After stabilization on hypotensive drugs patients were discharged from hospital and seen regularly in the out-patient clinic for adjustment of the dose of drugs. They were readmitted for subsequent renal clearances during treatment. G.F.R. and E.R.B.F. were measured by the determination of inulin and *p*-aminohippurate (P.A.H.) clearances respectively, using the method of Smith *et al.* (1938). Inulin and P.A.H. were estimated by the technique of Dick and Davies (1949), and each clearance figure cited represents the mean of two consecutive clearance periods, each of 20 minutes' duration. Frequent estimations of the blood urea were performed during the early stages of treatment.

Results

Control of Hypertension.—An attempt was made to reduce the standing diastolic blood-pressure to 100 mm. Hg or below in each case four hours after the last dose of the ganglion-blocking drug. This was achieved in most patients with careful adjustment of the dose as tolerance to the ganglion-blocking drug was acquired. In patients in whom the blood urea was initially elevated smaller doses of the drugs were used and we were satisfied with smaller reductions in blood-pressure. We felt that the best control possible with the drugs available at the time had been obtained short of producing severe side-effects. Papilloedema subsided in all patients with malignant hypertension who survived long enough (within two months), and retinal haemorrhages and exudates resolved when present. The electrocardiogram became normal or improved in most patients. Symptoms were usually strikingly improved, particularly headache and vision, which was often severely impaired before treatment in patients with malignant hypertension.

Renal Function: Malignant Hypertension (8 Patients)

Patients with Azotaemia.—There were four patients in whom the blood urea was elevated before treatment was given. The actual levels at this time were 109, 108, 105, and 88 mg./100 ml. G.F.R. (12 and 22 ml./min.) and E.R.B.F. (45 and 92 ml./min.) were extremely low

in the two patients in whom renal clearances were performed. Clearances were repeated in one of these (R. K.) after three months' treatment but showed no significant change. This patient died of uraemia after 10 months. Two patients survived for 10 months and during this time lost their severe symptoms. Vision improved remarkably in both. In each of them the elevated blood urea rose further during the first week of treatment but subsequently fell to the original level in one and slightly

FIG. 2.—Blood-urea levels in two patients with malignant hypertension during satisfactory blood-pressure reduction with hypotensive drugs.

below this in the other (Fig. 2). In spite of satisfactory control of the hypertension the blood urea did not rise again until shortly before death, when in both patients it rose abruptly. In one patient with chronic pyelonephritis and malignant hypertension the blood-pressure fell precipitously when very small doses of C6 were given. There was an associated increase in blood urea, which later fell as the blood-pressure rose after withdrawal of treatment (Fig. 3).

This patient was subsequently treated with hydralazine hydrochloride alone, but the hypertension was not adequately controlled, and she died of uraemia after three months. The fourth patient survived only one month after treatment was started, the blood urea rising steadily to 350 mg./100 ml. before death.

Patients Without Azotaemia.—There were four patients with malignant hypertension in whom the blood urea was normal before treatment. E.R.B.F. was severely impaired in three and moderately reduced in the fourth. G.F.R. was

severely reduced in one patient and moderately reduced in the remaining three. The changes in renal clearances occurring during treatment are shown in Table I. Two patients showed a moderate fall in both G.F.R. and E.R.B.F. after just over two years' and six years' treatment respectively. In two patients clearances were unchanged after treatment for one month (this patient died of uraemia after two and a half years' treatment, clearances not being repeated) and over six years respectively.

TABLE I.—Changes in G.F.R. and E.R.B.F. in Patients with Malignant Hypertension During Prolonged Treatment

Case	Sex	G.F.R. (ml./min.)	E.R.B.F. (ml./min.)	Duration of Treatment	Remarks
G.J.	F	68	589	Before treatment	Died cerebral haemorrhage
		87	593	8 months	
		64	489	18 "	
		55	447	26 "	
A.R.	M	69	563	Before treatment	" "
		73	590	14 months	
		43	318	6 years 2 months	
		47	344	Before treatment	
G.G.*	M	61	404	2 months	Alive and well
		70	493	5 "	
		46	374	5 years 1 month	
		71	705	Before treatment	
L.R.	M	74	600	1 month	Died uraemia after 31 months
R.K.	M	12	45	Before treatment	Died uraemia after 10 months
		7	53	3 months	

* This patient also had chronic glomerulonephritis.

In two patients a transient rise in blood urea to 60 mg./100 ml. occurred during the first week of treatment, the level subsequently falling to normal without interruption of treatment. Three of these patients have died at intervals of two years two months (cerebral haemorrhage), two years seven months (uraemia), and six years two months (cerebral haemorrhage) after starting treatment. The remaining patient is alive and well after over six years' treatment.

Renal Function: Severe Benign Essential Hypertension (7 Patients)

The blood urea was normal in all these patients, and remained so during treatment. E.R.B.F. was severely reduced in four and moderately reduced in three patients before treatment. G.F.R. was moderately reduced in three and more severely in four patients. The changes occurring during treatment are shown in Table II. One

TABLE II.—Changes in G.F.R. and E.R.B.F. in Patients with Benign Essential Hypertension During Prolonged Treatment

Case	Sex	G.F.R. (ml./min.)	E.R.B.F. (ml./min.)	Duration of Treatment
J.C.	M	87	956	Before treatment
		117	993	16 months
H.W.	M	96	650	Before treatment
		78	643	15 months
		77	374	6 years 6 months
G.J.	F	54	446	Before treatment
		30	242	5 years 7 months
J.S.	M	64	461	Before treatment
		59	494	10 months
M.W.	F	62	475	Before treatment
		70	446	5 years
W.J.	M	59	535	Before treatment
		67	476	5 years
D.B.	F	86	807	Before treatment
		92	568	5 years

patient treated for 10 months showed no change either in E.R.B.F. or G.F.R. One patient treated for 16 months showed an increase in G.F.R. to normal but no significant change in E.R.B.F. Of the remaining five patients who were treated for over five years, G.F.R. was unchanged in three but fell in two. E.R.B.F. was unchanged in one, but fell in four, though the change in one was slight. One patient died after a myocardial infarction after two years' treatment, five patients are alive and well after over five years' treatment, and in one treatment was withdrawn (at the patient's request) after 10 months.

Discussion

The four patients with malignant hypertension and azotaemia before treatment all died of renal failure within 10 months, nevertheless it was felt that life had

FIG. 3.—Increase in azotaemia due to excessive blood-pressure reduction in patient with malignant hypertension.

been prolonged and symptoms temporarily relieved in two of these. Two patients with malignant hypertension without azotaemia survived for over two years and two for over five years, but although only one of these died of renal failure, renal clearances fell in two of the others. Thus in patients with malignant hypertension further impairment of the renal circulation was prevented in only one patient—a man with chronic glomerulonephritis who was alive and well after treatment for more than five years. His renal clearances initially improved but subsequently returned to the original levels. This is interesting in view of the evidence of Harington *et al.* (1959) that the survival rate of treated patients with malignant renal hypertension is better than those with malignant essential hypertension.

Five patients with benign essential hypertension were treated for five years or longer. Renal clearances showed no significant changes in two and definite deterioration

in three. In two patients treated for shorter periods (10 months and 16 months) E.R.B.F. showed no significant change. G.F.R. rose to normal in one patient.

In the patients without azotaemia there is no indication that blood-pressure reduction for prolonged periods with ganglion-blocking drugs contributed to the reduced renal clearances. In fact, the clearances in all patients in whom they were repeated

FIG. 4.—Changes occurring in effective renal blood-flow during prolonged treatment with hypotensive drugs.

within 1 to 14 months after starting treatment showed no significant fall (Fig. 4), and it was only later that reduction occurred. This suggests that further impairment of the renal circulation occurred in the natural course of the disease rather than as a result of treatment. It is possible, however, for increasing azotaemia to result from blood-pressure reduction in patients in whom renal failure is already apparent (Fig. 3), and in one patient with malignant hypertension and azotaemia steadily increasing uraemia culminating in death within one month occurred in spite of satisfactory control of the hypertension. It seems possible that reduction of the blood-pressure in this patient contributed to the increasing uraemia. Transient increase in the blood urea during the first week of treatment occurred in two patients. A similar occurrence has been reported previously (Harington *et al.*, 1959) and was thought by these authors to be due to extrarenal factors. In spite of this, it is often possible in patients with azotaemia, by very careful blood-pressure reduction, to control symptoms for a time without resulting increase in blood urea (Fig. 2; Smirk and Alstad, 1951; Harington and Rosenheim, 1954; Abrahams and Wilson, 1957).

From our results there is no evidence that prolonged treatment was responsible for deterioration in renal function—a similar conclusion to that reached by

Abrahams and Wilson (1957) in patients with hypertension secondary to chronic renal disease. There is a suggestion that it may have slowed down the rate of deterioration, for in one patient with malignant hypertension and in four patients with benign hypertension, two of whom were treated for over five years, no deterioration occurred in clearance values whereas without treatment further deterioration might have been expected. It seems, however, that once changes have occurred in the renal circulation of hypertensive subjects they are not reversible by present methods of treatment, for renal clearances did not improve in any patient treated for a prolonged period. It may be possible in some patients to arrest the changes, but in most there is continued deterioration. This may be due to the inability to maintain the blood-pressure at normal levels throughout the 24 hours with the drugs available at the time this study was made, for there is no doubt that our patients remained hypertensive during a considerable proportion of the day and night. The more efficient and more easily controlled hypotensive drugs now available may be more effective in preventing continued renal vascular changes.

Harington *et al.* (1959) have clearly shown that treatment of malignant hypertension improves the expectation of life, but they have also stressed the prognostic significance of renal function before treatment. Prognosis remains extremely poor in these patients, and the aim must always be for earlier diagnosis and treatment before renal changes become severe; for hypotensive drugs are of little use in the later stages of renal failure.

Summary and Conclusions

Observations on renal function have been made in eight patients with malignant hypertension and seven patients with severe benign essential hypertension during prolonged treatment with hypotensive drugs.

Four patients with malignant hypertension and azotaemia died of renal failure within 10 months.

Two patients with malignant hypertension without azotaemia showed deterioration in renal clearances during treatment lasting two years and five years respectively, and one patient died of renal failure (renal clearances were not performed after one month's treatment). Renal clearances were unchanged in one patient with malignant hypertension and chronic glomerulonephritis after five years' treatment. Of the remaining five patients who were treated for over five years, G.F.R. rose slightly in three (the change is probably not significant) but fell in two.

Renal clearances did not improve in any patient treated for over five years, but G.F.R. returned to normal in one patient treated for 16 months. There was no evidence that prolonged treatment with hypotensive drugs affected renal function adversely, though the greatest care is necessary in avoiding excessive blood-pressure reduction in patients with severely impaired renal function. Prognosis in such patients is still extremely poor and the necessity for early diagnosis and treatment of malignant hypertension is stressed.

It was found that prolonged treatment with hypotensive drugs did not cause further impairment of the renal circulation in hypertensive subjects. Slow deterioration in renal clearances occurred in most patients during treatment, but this was thought to be the result of natural progression of the disease, possibly as a result of inability to maintain normal blood-pressure through the 24 hours

with present methods of treatment. In some patients renal-clearance values remained unchanged, and it was thought that further deterioration in these patients may have been prevented by hypotensive treatment.

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HYPERALDOSTERONISM

REPORT OF A CASE

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The syndrome of hyperaldosteronism is now being recognized with increasing frequency. The clinical picture is characterized by polyuria and polydipsia in addition to hypertension. The case reported here is of interest in that polyuria was absent and observations on the patient suggest a possible mechanism for the polyuria of this syndrome.

Case History

An assistant production manager aged 28 had previously enjoyed perfect health. When first seen in April, 1959, his sole complaint was some recent loss of visual acuity, noticed only while playing tennis. This led him to consult an optician, who referred him to hospital as a case of hypertensive retinopathy. On direct questioning he admitted to some recent tiredness but strenuously denied any polyuria, nocturia, or thirst. A routine medical examination in 1955 had shown a "high normal blood-pressure." There was no family history of hypertension.

On examination he appeared fit and active, with normal muscular power. His blood-pressure was 190/130. Both fundi showed haemorrhages, exudates, and arterial narrowing but no papilloedema.

Investigations.—A chest x-ray film showed slight cardiac enlargement and an E.C.G. showed left ventricular prepon-

derance. The blood urea varied from 24 to 39 mg./100 ml. and the creatinine clearance was 90 ml./min. After 5 units of "pitressin" the urinary specific gravity rose to 1018. Urinary catechol amines were 90 µg./24 hours. The plasma electrolytes showed a consistently abnormal pattern of hypokalaemia and alkalosis. There were seven pre-operative measurements of potassium, with a mean of 3.1 mEq/l. (range 2.8 to 3.4 mEq/l.), and six measurements of bicarbonate, with a mean of 35.6 mEq/l. (range 33 to 38 mEq/l.). This suggested the possibility of an aldosterone-secreting tumour of the adrenal cortex, and a search was made to demonstrate a tumour but with negative results. Intravenous pyelogram, aortogram, and presacral insufflation of oxygen failed to show any abnormality.

Aldosterone and Electrolyte Excretion.—The sodium intake was varied to assess changes in aldosterone excretion and the patient's ability to get into sodium balance. The Chart shows the results of these investigations. When the sodium intake was 110 mEq/day the aldosterone excretion varied between 24 and 76 µg./day (normal values 4 to 15 µg./day on free sodium intake); the 24-hour-urine volume was then between 1.9 and 2.3 l. Reduction in sodium intake to approximately 10 mEq/day was followed by a sharp fall in sodium excretion, so that the new balance was established in three days. This was achieved without a change in aldosterone excretion but was associated with a marked reduction in urine volume (and water consumption). There was some decrease in potassium excretion during this time. When the sodium intake was raised to 210 mEq/day a new balance was again established in three days, and this time there was a rise in the urine volume (and water intake) but no depression of aldosterone excretion. During this period the potassium excretion rose considerably. After the operation, when all replacement therapy had been withdrawn and the patient was on a normal sodium intake the aldosterone excretion was extremely low (1.4 µg./day). Four months later, under the same conditions, the aldosterone excretion was 1.3 and 1.2 µg./day.

Operation.—On June 8 a laparotomy was performed. A small tumour was palpated in the left adrenal and the whole gland was removed. During this procedure cardiac arrest occurred, requiring massage for three minutes, after which ventricular fibrillation began. After one shock with the defibrillator normal rhythm was restored.

Histology.—The tumour was a spherical cortical adenoma 10 mm. in diameter. The histology showed cells with an eosinophilic cytoplasm like those of the zona reticularis, but a few were filled with lipid. In places the cells showed a tubular formation with a clearly defined fibrous stroma.

Post-operative Course.—During the first two days the patient was mentally confused, but after this his mental and intellectual functions appeared to be completely normal. The blood-pressure remained at pre-operative levels for three days and then gradually fell, and by the fourteenth day was down to 140/90. A week after operation the plasma potassium had risen to 4.6 mEq/l. and the bicarbonate was then 35 mEq/l. Three days later the potassium was 5.0 mEq/l. and the bicarbonate 31 mEq/l.

Subsequent Course.—The blood-pressure has remained at normal levels since operation, the average pressure four months after being 140/90. However, although the blood-pressure and plasma electrolytes remained normal, the blood urea rose to 50 mg./100 ml. a month after the operation, confirmed on two occasions. This was interpreted as indicating renal damage, and he was readmitted in September for reassessment. This time the creatinine clearance was 130 ml./min., and after pitressin the urinary specific gravity rose to 1022. The blood urea during this stay in hospital varied between 26 and 43 mg./100 ml. A renal biopsy was attempted but no tissue was obtained. However, the white-cell excretion in the urine after an artificially induced fever did not rise outside normal limits and all urinary cultures were sterile, so there appeared to be no evidence of chronic pyelonephritis. Ten months after operation the blood-