Uraemia from Benign Hypertension

V. K. G. PILLAY, F. WANG, V. C. GANDHI, HWA JA LEE, G. DUNEA

SUMMARY

Criteria for the diagnosis of uraemia as a result of benign essential nephrosclerosis were established in a group of 12 patients, most of whom had a long history of inadequately treated hypertension, arteriosclerosis, cardiomegaly and mild proteinuria.

They are representative of a larger group of patients with long-standing hypertension and uraemia, in whom a presumptive diagnosis of essential benign nephrosclerosis was made on clinical grounds, but in whom histological confirmation was not possible. Thus, while we have firmly established the occurrence of uraemia from benign hypertension, the incidence of this condition remains to be determined.

S. Afr. Med. J., **48**, 953 (1974).

In 1914 Volhard and Fahr[1] first emphasised that hypertension could follow two courses: one benign, the other malignant. This concept soon gained widespread acceptance,[2] and the criteria for the recognition of malignant hypertension have become so well established that there is no dispute about the diagnosis when this condition ends in uraemia. By contrast, benign hypertension manifests itself mainly as cardiac or cerebrovascular disease,[3,4] and although the occurrence of renal damage is well documented, the criteria for the diagnosis of benign hypertension ending in uraemia are not as well defined. In fact, uraemia from benign hypertension is thought to be rare,[5-11] and at least one investigator categorically denies its existence.[3]

Can the renal damage from uncomplicated benign hypertension alone result in terminal renal failure, and if so, how often does this occur? In urban Black populations, where the incidence of hypertension is as high as 21,1%, these questions may be approached by observing the consequences of progressive hypertensive disease and the development of renal failure. The general clinical impression that benign nephrosclerosis not uncommonly causes irreversible renal failure can then be validated.

Department of Nephrology and Pathology, Cook County Hospital, and the Hektoen Institute for Medical Research; and the University of Health Sciences, Chicago Medical School, Chicago, Illinois, USA

V. K. G. PILLAY, M.R.C.P., F.C.P. (S.A.), F.A.C.P.
F. WANG, M.R.C.P.
V. C. GANDHI, M.B.B.S.
HWA JA LEE, M.D.
G. DUNEA, M.B., M.R.C.P.

Presented in part at the 5th International Congress of Nephrology, Mexico City, October 1972.
Reprint requests: Dr G. Dunea, Cook County Hospital, 1825 W. Harrison St, Chicago 60612.

PATIENTS AND METHODS

Out of a series of 150 patients with end-stage renal disease we have selected 12 who satisfied strict clinical and pathological criteria for the diagnosis of uraemia from benign hypertension. Most of the patients had been treated in the outpatient clinic over a period of several years and each was examined by 2 observers. The optic fundi were graded according to the classification of Keith and Wagener. Heart size was graded 1 + to 4 +, representing mild, moderate, considerable or severe enlargement. Electrocardiographic evidence of cardiac hypertrophy or strain was noted. A cardiothoracic ratio greater than 50% on X-ray examination confirmed cardiomegaly. Infusion urograms or retrograde pyelograms were done in all patients to rule out obstructive uropathy. Renal tissue was studied from specimens obtained at nephrectomy, at postmortem examination, and by percutaneous or open biopsy. None of the patients had malignant hypertension, diabetes, chronic glomerulonephritis, chronic pyelonephritis, or renal artery stenosis.

RESULTS

Clinical

All patients were Black, and their ages ranged from 35 to 71 years. The clinical data are summarised in Table I.

Most of the patients had a long history of irregular treatment or poorly controlled hypertension. The lowest diastolic pressure in untreated patients at rest was 110 mmHg, and the highest was 170 mmHg. Patients with the shortest duration of hypertension tended to have the highest pressures (cases 4, 6, 12), and a long history of hypertension was associated with lower readings and a better response to therapy (case 7). In some patients, however, hypertension persisted despite vigorous antihypertensive therapy, but many patients did not adhere to the regimen and at best received partial treatment.

Most patients had considerable cardiac enlargement and many had repeated episodes of left ventricular failure, which usually heralded the onset of uraemia by several months or years. In some instances there was only a brief history and a single episode of left ventricular failure (case 12). Although the symptoms of heart failure were readily controlled with diuretics and antihypertensive therapy, progression of renal failure was not arrested. However, continued treatment often resulted in a decrease in heart size and regression of electrocardiographic changes.

Throughout the long clinical course none of the patients had papilloedema, but exudates and/or haemorrhages (grade III fundi) were observed in 4 patients. In some of these the clinical picture was indistinguishable from that of patients who were found to have malignant nephrosclerosis. There was no past history of renal disease or

TABLE I. CLINICAL DATA

Case No.	Age	Sex	Duration of hypertension (years)	Fundi (K - W)	Heart		Urinary protein (g/24 h)	Outcome
					Clinical	ECG		
1	47	F	10	II	3 +	HS	0,7	MD
2	55	F	11	III	3 +	HS	1,1	MD
3	51	M	12	III	4 +	HS	2 +	MD
4	41	M	3	III	2 +	H	2,1	MD
5	64	M	—	Corneal opacity	2 +	H	0,7	Died uraemia
6	71	M	3	II	2 +	H	2,2	Died uraemia
7	54	M	30	II	2 +	HS	0,4	Died uraemia
8	45	F	7	II	1 +	Normal	0,7	Died uraemia
9	37	F	13	II	3 +	—	0,5	Died uraemia
10	35	F	4	II	4 +	HS	2 +	MD
11	36	F	4	II	4 +	HS	—	MD
12	47	M	3	III	3 +	H	1,6	Transplant. Died

MD = Maintenance dialysis; H = Hypertrophy; S = strain.

urinary tract infection. Infusion urograms usually revealed symmetrically contracted kidneys. Radiological enlargement of the heart was demonstrated in 9 patients, and the electrocardiogram usually showed left ventricular hypertrophy and strain, or hypertrophy alone.

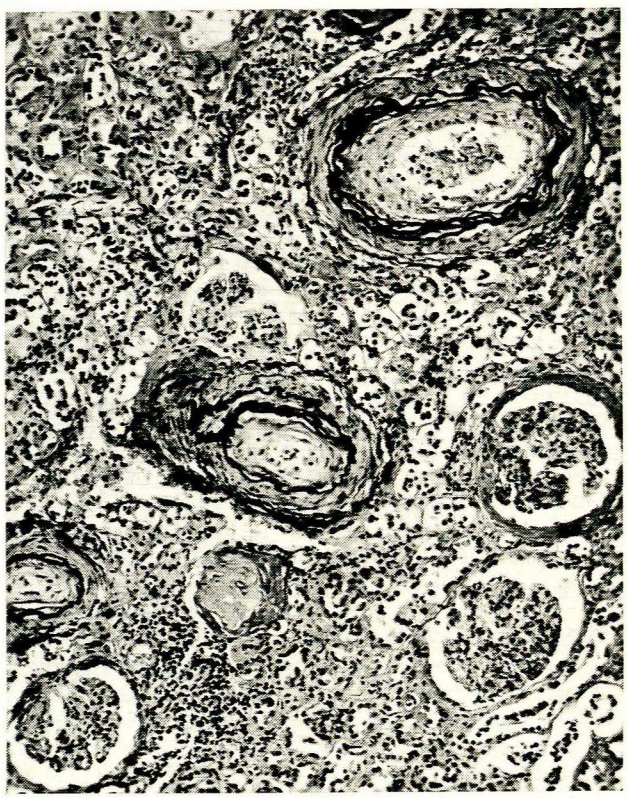

Fig. 1. Relatively well-preserved glomeruli. Occasional periglomerular fibrosis. Atrophy of tubules and lymphocytic infiltration of interstitial tissue. The interlobular arteries show thickening of the wall and reduplication of elastica (case 7).

Pathological

Kidneys were available from 4 necropsies, 3 bilateral nephrectomies and one unilateral nephrectomy. Renal biopsies were done in 7 patients.

The kidneys weighed between 40 - 150 g. The surfaces were finely granular, the capsules were non-adherent, and the pelves and calyces were normal. Sectioning showed the corticomedullary junctions to be well preserved.

On microscopy the glomeruli showed ischaemic changes; some glomeruli were virtually normal, while most showed varying degrees of hyalinisation (Fig. 1). Proliferative changes were absent. The lumina of interlobular arteries were narrowed as a result of reduplication of the internal elastic membrane and intimal thickening (Fig. 2). There was marked mural thickening of arterioles and 2 patients had hyaline changes in the arteriolar walls. There was scattered interstitial fibrosis with some chronic inflammatory cells and varying tubular atrophy and dilatation. The pelvic mucosa and submucous stroma were normal.

CASE REPORTS

Two patients, cases 1 and 3, are reported in detail to illustrate the characteristic clinical course of long-standing benign hypertension, heart failure and slowly progressive uraemia.

Case 1

A 47-year-old married woman was first told in 1961 that she had hypertension. At that time she was asymptomatic and received no treatment. In 1965 she developed headaches and dizziness, and treatment was begun with methyldopa, guanethidine and diuretics. Since 1968 she experienced progressive shortness of breath on exertion, paroxysmal nocturnal dyspnoea and swelling of the lower

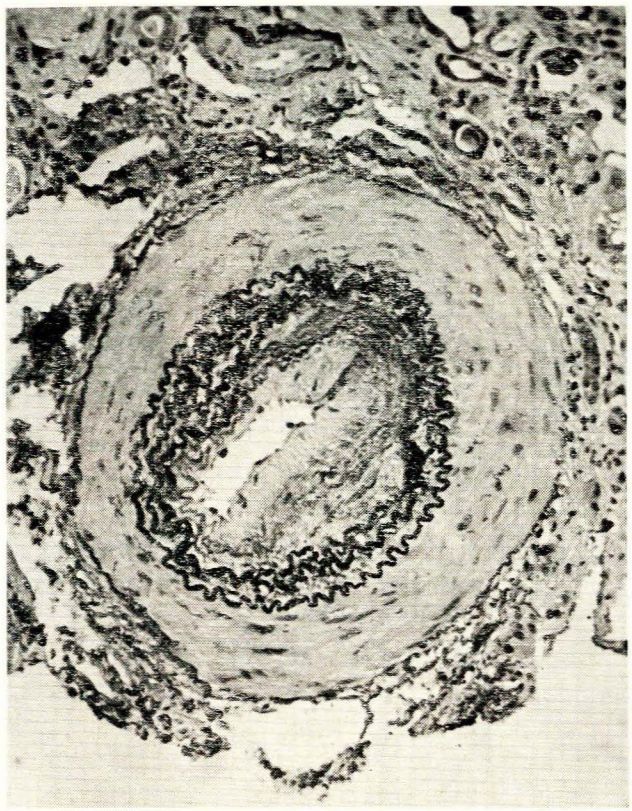

Fig. 2. Marked intimal thickening and narrowing of the lumen. Elastic reduplication and displacement of the lumen to the periphery (case 1).

extremities, requiring numerous admissions to hospital. By 1970 the blood-urea nitrogen (BUN) was 50 mg/100 ml and the serum creatinine was 4 mg/100 ml. In 1971 she was readmitted to the hospital because of anaemia and congestive heart failure. The blood pressure was 120/90 mmHg (on treatment), the optic fundi showed sclerosis but no exudates, and the heart was considerably enlarged. She was in congestive heart failure, and an apical pericardial friction rub and considerable peripheral oedema were found. BUN was 165 mg/100 ml. Renal biopsy showed marked arteriolar nephrosclerosis with preservation of glomeruli and severe sclerotic vascular changes. The patient has now been on maintenance haemodialysis for 30 months.

Case 3

A 51-year-old man had suffered from hypertension since 1959, and at first had received no treatment. Congestive heart failure developed in 1968, when his BUN was 50 mg/100 ml and serum creatinine 3,5 mg/100 ml. By 1970 BUN had risen to 100 mg/100 ml and the creatinine to 10 mg/100 ml, but he maintained a reasonable urine output and was managed conservatively for 18 months. In 1971 BUN had risen to 128 mg/100 ml and the serum creatinine to 18 mg/100 ml. The blood pressure was 160/110 mmHg. The fundi showed severe arteriosclerosis and hard exudates, but no haemorrhages. The heart was considerably enlarged and he had severe congestive failure. An open right renal biopsy revealed a very small kidney (about 7 cm long) and the histological diagnosis was benign nephrosclerosis. Since then the patient has been on maintenance dialysis.

DISCUSSION

In a report on the natural history of 212 patients with benign hypertension and 39 with malignant hypertension, death from uraemia occurred in 60% of the patients with malignant hypertension, but in none of the patients with benign hypertension.[12] In another study of 500 hypertensive patients, none with benign hypertension died in uraemia.[13] There is only one report where a significant number of patients had uraemia resulting from primary benign hypertension: in a retrospective analysis of 174 patients with hypertension, renal failure was the cause of death in 36 patients with benign hypertension, 7 of whom had a history of diabetes mellitus; in each of the remaining 29 microscopy revealed benign arteriolar nephrosclerosis.[14] The mean age of the patients was 45 years and the mean duration of hypertension 5 years. The mean heart weight was 607 g and the mean weight of the kidneys 112 g. In our series the mean age was also 45 years, but the mean duration of hypertension was 10 years.

We used careful clinical and pathological criteria to exclude conditions such as healed malignant hypertension, chronic pyelonephritis, chronic glomerulonephritis, diabetes mellitus, renal artery stenosis and arteriosclerosis. It is important to note that benign nephrosclerosis was the sole cause of renal failure and that, in the absence of dialysis, the patient would die in uraemia. With such stringent criteria, 12 patients fulfilled all the requirements for uncomplicated primary benign hypertension ending in uraemia. When heart failure and other conditions known to impair renal function were present, they were treated in the conventional manner, but only patients with irreversible uraemia were included in this report.

Undoubtedly the high frequency of hypertension, its long duration, often extending over decades, and the intermittency of therapy are important factors. Indeed, the hypertension was often not severe and usually responded quite well to therapy, but the poor economic status, the paucity of symptoms and the side-effects of treatment discouraged regular taking of drugs and led to only episodic control.

The ease with which episodes of heart failure may be controlled makes for a long survival and allows the vascular damage to progress over many years. If the patients escape cerebrovascular accidents, progressive vascular damage to the kidneys may result in deterioration of renal function and development of uraemia without supervention of malignant nephrosclerosis. The vascular damage, however, is widespread; most of our patients had heart failure and two had had strokes.

The diagnosis of benign nephrosclerosis may be suspected clinically when a patient has long-standing hypertension

with grade II fundi, a considerably enlarged heart, mild proteinuria, impaired renal function and some reduction in kidney size. Progression to uraemia is usually slow,[8] but occasionally the clinical course is acute and suggests malignant hypertension or primary renal disease (case 12). It should also be noted that 4 of our patients had grade III fundi and, in our experience, it may be difficult to predict whether a patient with soft exudates and haemorrhages will have benign or malignant nephrosclerosis.

A definitive diagnosis of primary benign nephrosclerosis cannot be made clinically, and one often has to be satisfied with a presumptive diagnosis because a renal biopsy may not be justified.[8] Definitive diagnosis requires at least a thorough histological examination of a biopsy specimen by serial sections, to exclude active or healed malignant nephrosclerosis, and ideally the kidneys and renal arteries should be examined grossly. Moreover, precise pathological diagnosis in end-stage renal disease is not easy, and the distinction between chronic glomerulonephritis, interstitial nephritis and hypertensive vascular disease may be difficult.[9] Problems may arise when chronic glomerulonephritis is complicated by long-standing hypertension, or when hypertension is complicated by asymptomatic bacteriuria and recurrent urinary infection.

No clinical or pathological evidence of glomerulonephritis, pyelonephritis or malignant hypertension was found in our series. None of the patients had asymptomatic bacteriuria or urinary tract infection. Interstitial fibrosis, tubular atrophy and mild cellular infiltration in the interstitium were observed, but these changes could be the result of ischaemia. Thus the findings in this series, both clinical and histological, point to benign nephrosclerosis as the cause of terminal renal failure.

REFERENCES

1. Volhard, F. and Fahr, K. T. (1914): *Die Bright'sche Nierenkrankheit*. Berlin: Springer.
2. MacMahon, H. E. (1968): In *Pathology Annual*, vol. 3. New York: Appleton-Century-Crofts.
3. Pickering, G. W. (1965): Brit. Med. J., **2**, 1021.
4. *Idem* (1968): *High Blood Pressure*, 2nd ed. New York: Grune & Stratton.
5. Bechgaard, P. (1946): Acta med. scand. suppl., **172**, 1.
6. Fishberg, A. M. (1954): *Hypertension and Nephritis*, 5th ed. New York: Lea & Febiger.
7. Goldring, W. and Chassis, H. (1944): *Hypertension and Hypertensive Disease*. New York: The Commonwealth Fund.
8. Hamburger, J. (1968): *Nephrology*. Philadelphia: W. B. Saunders.
9. Heptinstall, R. H. (1968): Amer. J. Med., **44**, 656.
10. *Idem* (1966): *Pathology of the Kidney*. Boston: Little, Brown.
11. Papper, S. and Vaamonde, C. A. *in* Strauss, M. B. and Welt, L. G., eds. (1971): In *Diseases of the Kidney*, 2nd ed., vol. 2. Boston: Little, Brown.
12. Hagans, J. A. and Bount, A. A. (1960): Amer. J. Med., **28**, 905.
13. Perera, G. A. (1955): J. Chron. Dis., **1**, 33.
14. Goss, L. Z., Rosa, R. M. F., O'Brien, W. M., Ayers, C. R. and Wood, J. E. (1969): Arch. Intern. Med., **124**, 160.