Progressive renal failure in surgically treated hyperparathyroidism

JANE DIXON,* JF SMITH

*From the *Department of Pathology, John Radcliffe Hospital, Headington, Oxford and the Department of Morbid Anatomy, School of Medicine, University College, London*

SUMMARY Of 570 patients operated on for hyperparathyroidism, 18 subsequently died (between one day and 12 yr after operation). Pathological findings at necropsy in these patients have been reviewed. Four necropsies on patients with untreated hyperparathyroidism have also been reviewed for comparison. Of these 22 cases, 14 had renal failure at the time of death. This was attributed to the following: nephrocalcinosis 6; chronic glomerulonephritis 4; analgesic nephropathy 1; cystinuria 1; sarcoidosis 1; and polycystic disease 1. Of those with renal failure due to nephrocalcinosis, three had persistent hypercalcaemia after operation; the other three survived only for a short time. There was no evidence of residual nephrocalcinosis producing progressive renal failure if the plasma calcium concentration was corrected. In those with chronic glomerulonephritis, cystinuria, and polycystic disease, the hyperparathyroidism was considered to be tertiary to the renal disease but renal failure was not always present at the time of diagnosis.

There is clinical evidence that successful surgical treatment for primary hyperparathyroidism may be followed by a deterioration of renal function and hypertension despite the restoration of plasma calcium concentrations to normal.^{1,2} The reasons for this are not clear. The roles of residual nephrocalcinosis, renal calculi, or possibly hypercalcaemic tubular damage unrelated to the deposition of calcium salts have not been fully elucidated. In some cases of hyperparathyroidism, renal disease is the cause rather than the result of parathormone hypersecretion. If this hypersecretion is appropriate in that it results from an attempt to compensate for hypocalcaemia by hyperplasia of the parathyroid glands, the condition is known as secondary hyperparathyroidism;³ if it subsequently becomes autonomous due to the development of an adenoma in one gland it is called tertiary hyperparathyroidism.^{4,5} Hence failure to prevent deterioration of renal function by parathyroid surgery may reflect tertiary rather than primary parathyroid disease.

To investigate the roles of nephrocalcinosis, renal calculi, hypercalcaemic tubular damage, and other renal pathology in the renal failure of treated hyperparathyroidism, a review was made of all patients who had undergone parathyroid surgery and later come to necropsy at University College

Hospital (UCH) between 1959 and 1978. Necropsies carried out in the same period on patients with hyperparathyroidism who had not had surgery, were also reviewed for comparison.

Material and methods

Between 1 January 1959 and 31 December 1978 necropsies were done on 22 cases of primary and tertiary hyperparathyroidism. Of these, 18 had been operated on at UCH at periods varying from one day to 12 years before death. Of the four not operated on, one had severe renal failure at the time of admission, one carcinomatosis, one motor neurone disease, and one long-standing cystinuria.

Post-mortem tissues were fixed in buffered formalin and paraffin sections examined with haematoxylin and eosin, EVG, periodic acid-Schiff and in certain cases von Kossa's and phosphotungstic acid-haematoxylin stains. Renal biopsies had not been performed in life on any of the cases.

Results

The major pathological findings in all cases are recorded in Table 1 together with the period of survival after parathyroid surgery (post-op survival). The case numbers in brackets are those in the UCH series of operated hyperparathyroid patients.

Table 1 Major pathological findings in all cases

Case no	Age	Sex	PT pathology at operation (weight in g)	Post-op survival	NC	Renal pathology, other	Cause of death
1 (11)	46	F	2A 1.0 + 0.15	5 years	+	—	Lymphoma (complicating gluten enteropathy)
2 (33)	60	F	A	12 years	++	Analgesic nephropathy	Chronic renal failure
3 (44)	70	F	A 4.1	5 years	+	End-stage kidneys GN I	Chronic renal failure
4 (57)	65	F	A 1.8	5 years	—	End-stage kidneys GN I	Chronic renal failure
5 (59)	55	M	A 4.5	7 years	++	Polycystic disease GN	Chronic renal failure
6 (65)	47	F	C	1½ years	+++	I	Metastatic calcification, recurrent PT carcinoma, renal failure
7 (71)	36	F	A 0.6	1 day	+	—	Cerebral embolism
8 (95)	62	F	A 11.0	19 days	+++	I	Cerebral infarction, fracture of femur, chronic renal failure
9 (129)	76	F	A 2.7	9 days	+	—	Pulmonary embolism, deep venous thrombosis
10 (176)	47	F	A 0.5	7 years	+++	I	Bronchopneumonia, recurrent PT carcinoma, chronic renal failure
11 (193)	22	F	C 8.0 A 0.2	8 months	+++	Stones in calyces, tubular degeneration and regeneration	Chronic renal failure, PT adenoma 3.2 g
12 (197)	30	F	C	6 years	+	—	Haemorrhage complicating Caesarian hysterectomy
13 (241)	62	F	A 3.0	14 days	+	—	<i>Klebsiella pneumoniae</i> , disseminated intravascular coagulation
14 (283)	68	F	A 27.0 A 0.3	1 month	+++	I	Gastrointestinal haemorrhage
15 (334)	63	M	H	14 days	+	Adenoma of cortex	Renal failure
16 (406)	60	F	H	9 months	+	End-stage kidneys GN I	Cardiac arrest during prostatectomy
17 (434)	61	M	H	2 years	+++	I	Chronic renal failure
18 (514)	65	F	A 9.6	3 months	+++	I	Bronchopneumonia, sarcoidosis, chronic renal failure
19	72	F	—	—	—	End-stage kidneys GN I	Myocardial infarction, chronic renal failure
20	55	F	—	—	+	Segmental dysplasia	Chronic renal failure, PT adenoma 4 g, hyperplasia of other parathyroids
21	69	F	—	—	—	Cystine stones	Chronic renal failure, cystinuria, PT adenoma 1.2 g, hyperplasia of other parathyroids
22	78	F	—	—	—	—	Carcinomatosis from argentaffinoma of ileum, PT adenoma
							Bronchitis, motor neurone disease, PT adenoma 1 g

A = Adenoma. C = Carcinoma. GN = Glomerulonephritis. I = Ischaemia. NC = Nephrocalcinosis. H = Hyperplasia. PT = Parathyroid.

Nephrocalcinosis was graded on a scale 0 to + + +. This table shows that 14 of the 22 cases had renal failure at the time of death. These could be subdivided into those in which nephrocalcinosis was thought to be the major cause of renal damage (summarised in Table 2) and those in which nephrocalcinosis was thought to play only a minor role (summarised in Table 3). Case 17 was excluded from further analysis as much of the renal damage was thought to be due to hypercalcaemia after long-standing sarcoidosis, together with ischaemic changes. It is possible that some was due to coexistent hyperparathyroidism, but it is impossible to unravel the various factors in this case.

Of the cases without renal failure two died without parathyroid surgery (21, 22) and three died shortly after operation (7, 9, 13). The remaining two (1, 12) survived five and six years respectively after parathyroid surgery and, while both showed evidence of mild residual nephrocalcinosis, neither had significant

impairment of renal function either preoperatively or terminally.

CASES WITH NEPHROCALCINOSIS CONTRIBUTING TO RENAL FAILURE (TABLE 2)

Of the six cases with renal failure related to nephrocalcinosis three had severe hypercalcaemia at the time of death. This was due to recurrent parathyroid carcinoma in two (6, 10) and to a residual adenoma in one (11). In the remaining three cases (8, 14, 18) hypercalcaemia was no longer present at death but the interval between operation and death was short—nineteen days, one month and three months respectively, and evidence of impaired renal function was present preoperatively. It is also worthy of note that the parathyroid adenomas of these three cases had the largest recorded weights of all those in the present study (11 g, 27 g, and 9.6 g respectively).

In all these cases the nephrocalcinosis was graded as + + +. At sites of deposition, which were mainly

Table 2 Cases with nephrocalcinosis contributing to renal failure

Case no	Post-op survival	PT pathology (weighting)	Blood pressure	Plasma Ca (mmol/l)		Plasma urea (mmol/l)		Cause of post-op hypercalcaemia if present
				Pre-op	Terminal	Pre-op	Terminal	
6	1½ years	C	$\frac{120}{80}$	5.0	4.1	18	8.3	Recurrent PT carcinoma
8	19 days	A 11.0	$\frac{110}{80}$	3.1	1.7	18	33	—
10	7 years	C 0.8 A 0.5	$\frac{140}{90} - \frac{160}{110}$	2.9	3.6	9.5	21.7	Recurrent PT carcinoma
11	8 months	A 0.2	$\frac{110}{70} - \frac{130}{90}$	3.7	3.9	5.7	55	Second PT adenoma 3.2 g
14	1 month	A 27.0 A 0.3	$\frac{140}{90}$	3.6	2.2	13.7	25	—
18	3 months	A 9.6	$\frac{190}{100}$	3.4	2.2	14.8	18.3	—

A = adenoma. C = carcinoma. PT = parathyroid.

Table 3 Cases of renal failure not primarily due to nephrocalcinosis

Case no	Post-op survival	Blood pressure		Plasma Ca (mmol/l)		Plasma urea (mmol/l)		Cause of renal failure	Hyperparathyroidism
				Pre-op	Terminal	Pre-op	Terminal		
2	12 years	$\frac{150}{90} - \frac{210}{145}$	3.3	2.2	5	42		Analgesic nephropathy	Primary
3	5 years	$\frac{150}{80} - \frac{190}{130}$	2.9	1.9	7	64		Chronic glomerulonephritis	Tertiary
4	5 years	$\frac{160}{80} - \frac{200}{120}$	2.5	2.2	10	57		Chronic glomerulonephritis	Tertiary
5	7 years	$\frac{140}{90} - \frac{180}{110}$	3.2	1.4	7.5	50		Polycystic kidneys, glomerulonephritis	Tertiary
16	9 months	$\frac{160}{90} - \frac{190}{100}$	2.8	2.1	30.5	76.7		Chronic glomerulonephritis	Tertiary
19	—	$\frac{100}{65}$	2.3	—	59.7	—		Chronic glomerulonephritis	Secondary or Tertiary
20	—	$\frac{180}{100} - \frac{250}{150}$	3.0	—	66.6	—		Dysplasia of L kidney, cystinuria	Tertiary

intraluminal, there was damage to tubular epithelium. Apart from deposits there was some tubular atrophy and dilatation, possibly as a result of blockage of individual nephrons. There were also some areas showing ischaemic atrophy of glomeruli and tubules, maximal in subcapsular zones and associated with severe degenerative arterial disease. Glomerular lesions which could be attributed to a previous nephritis were not present in any of these cases.

Case 11 (193) is described in more detail. A 29-year-old negress was investigated because her newborn baby had temporary hyperparathyroidism. She had raised plasma calcium concentrations (3.7 mmol/l), osteitis fibrosa cystica and nephrocalcinosis radiologically. A 0.2 g adenoma was removed at operation but severe hypercalcaemia persisted. Attempts to lower it with oral phosphate were not successful and she died in renal failure eight months

after operation. At necropsy, a further large adenoma (3.2 g) was found situated much higher in the neck than usual. Other findings were osteitis fibrosa, a small renal calculus in the calyx of one kidney and extensive metastatic calcification (Fig. 1). The kidneys were enlarged (R 230 g, L 250 g) and showed extensive tubular degeneration and regeneration (Figs. 2 and 3). Neither of these features was present in the other patients in Table 2, four of whose kidneys were significantly reduced in size (less than 100 g each); in case 6 they were of normal size.

CASES OF RENAL FAILURE NOT PRIMARILY DUE TO NEPHROCALCINOSIS (TABLE 3)

The cases summarised in this table had more severe and prolonged uraemia than those in Table 2. In none of the operated cases was hypercalcaemia

Fig. 1 Case 11 (193) Extensive metastatic calcification, tubular degeneration and regeneration. Haematoxylin and eosin $\times 180$.

Fig. 2 Case 11 (193) Tubular degeneration and regeneration. Haematoxylin and eosin $\times 230$.

present at death. A minor degree of nephrocalcinosis was present in most, comparable with that found in the cases without renal failure. The only cases in this group in which calcification in the kidney was considerable were 2 and 5. In case 2 the major site of calcification was in necrotic medullary pyramids—a dystrophic calcification rather than a typical nephrocalcinosis, although some of the latter was also present. The cause of the necrosis of the medullary pyramids was excessive consumption of

analgesics over a long period and the renal failure occurred long after successful parathyroid surgery. In case 5 there was a moderate degree of nephrocalcinosis in addition to polycystic disease. This is the only case in which residual nephrocalcinosis (some years after successful parathyroid surgery) may have played a part in causing renal failure.

In all the remaining cases in Table 3 renal failure was attributable to lesions other than nephrocalcinosis and these, together with case 5, were all

Fig. 3 Case 11 (193) Tubular regeneration. Haematoxylin and eosin $\times 920$.

Fig. 4 Case 3 (44) End stage kidney showing hyalinisation of glomeruli from ischaemia and old nephritic lesions. Tubular atrophy and arteriosclerotic vessels also present. Haematoxylin and eosin $\times 180$.

thought to be examples of tertiary hyperparathyroidism (see Discussion).

In four cases there was evidence of progressive glomerular disease. By the time of death all had end-stage kidneys with considerable glomerular loss (Fig. 4). The remaining glomeruli had a variety of lesions including segmental necrosis (Fig. 5), mesangial proliferation and capillary wall thickening (Fig. 6). Adhesions between tufts and capsules were occasionally present. Tubular atrophy and interstitial fibrosis were related to glomerular loss and in all there was severe degenerative disease of intrarenal

arteries, but no fibrinoid necrosis. As in many end-stage kidneys it was difficult to make a definite diagnosis of the initial process but in most the findings indicated a progressive focal and segmental glomerulonephritis. In case 5, glomerular lesions resembling those described above were present in polycystic kidneys. Two cases (4, 5) have previously been reported in a paper on tertiary hyperparathyroidism.⁶ Case 3 is now described to illustrate the problem in more detail.

Case 3 (44) This woman was first admitted to UCL

Fig. 5 Case 4 (57) Segmental necrosis in one glomerular tuft. Ischaemic atrophy of another. Periodic acid-Schiff $\times 180$.

Fig. 6 Case 4 (57) Mesangial proliferation in one glomerular tuft. Increased extracellular matrix in another. Periodic acid-Schiff $\times 180$.

in 1959 at the age of 65 with pain in the back, nausea, and vomiting. Radiological evidence showed osteitis fibrosa, hypercalcaemia, a blood urea concentration of 7 mmol/l and a trace of protein in the urine. She had mild acidosis, thought to be due to renal tubular dysfunction from hyperparathyroidism, but there was no radiological evidence of nephrocalcinosis. A 4.1 g adenoma was removed from the neck and three normal parathyroids were identified. After operation, her blood urea concentration rose to 23.7 mmol/l and was 13.7 mmol/l on discharge when her acidosis was still present. During the next four years she remained reasonably well but in 1963 she developed pain in the right loin. On examination her blood pressure was 190/130, blood urea concentration 21.0 mmol/l, and her urine contained albumin with only a few red cells, leucocytes, and casts. Symmetrical small kidneys were found on radiography. Her renal failure progressed and she died in 1964 with a blood urea concentration of 64 mmol/l

and plasma calcium concentration of 1.92 mmol/l. At necropsy two mildly hyperplastic parathyroids were identified. The heart was 540 g with left ventricular hypertrophy and the kidneys uniformly contracted (70 g each) with granular surfaces, narrowed cortices and normal pelvicalyceal systems. On microscopical examination there was loss of many glomeruli and severe arteriosclerosis. Some glomeruli showed focal, segmental, and other lesions as described above. The considerable tubular atrophy was commensurate with the glomerular disease and nephrocalcinosis was slight. In summary, these were end-stage kidneys in which the vascular element was predominant but with indications of a previous glomerulonephritis.

Discussion

The results of this survey indicate that an important cause of progressive renal failure after successful

parathyroid surgery is progressive glomerular and ischaemic disease not associated with stones or extensive nephrocalcinosis. There are three possible explanations for these findings.

The first is that hypercalcaemic damage occurring before surgery in some way initiates glomerular disease which continues even after correction of the plasma calcium concentration. It has been suggested that calcium phosphate deposition within tubules may lead to release of a tubular antigen. This may stimulate antibody formation and subsequently give rise to immune complex deposition within glomeruli.⁷ A second possibility is that glomerular damage is due to irreversible arterial disease initiated by hypercalcaemia. The third, and we believe the most likely explanation, is that hyperparathyroidism in the present cases was tertiary.

The survey indicates that nephrocalcinosis can persist for many years after parathyroid surgery without a significant effect on renal function, as indicated by cases 1 and 12. The degree of nephrocalcinosis in these kidneys did not differ significantly from that in all cases with chronic glomerular disease, except case 5. This was the only one in which long-standing residual nephrocalcinosis may have been a significant factor in causing renal failure, although two other major factors were also present. Thus the series provides little support for the view that nephrocalcinosis can progress in the absence of hypercalcaemia. There is no evidence that nephrocalcinosis is responsible for progressive glomerular damage. Calcification in glomerular tufts was found in only one case (8) and here it was insignificant.

The second possibility, that irreversible hypercalcaemic-induced arterial disease produces progressive glomerular loss postoperatively, is perhaps less easy to discount. However, some of the glomerular lesions were not typical of those produced by hypertension alone and none of the kidneys showed evidence of malignant hypertension.

The argument against the third possibility, namely that these are cases of tertiary hyperparathyroidism, is that chronic renal failure was not always present at the time of diagnosis of parathyroid disease. This is illustrated by case 3. Here there was no anatomical evidence of a preceding secondary hyperplasia of parathyroid glands, one adenoma and three normal glands being identified at operation. Similar absence of diffuse parathyroid hyperplasia has been described in a previous paper in 12 cases of tertiary hyperparathyroidism in which parathyroid adenomas were associated with the malabsorption syndrome in 10 and renal disease in two.⁶ It was postulated that in such cases only some groups of sensitive cells within a parathyroid gland respond to a metabolic stimulus, possible hypo-

calcaemia, which may be transient or intermittent in character. Cellular division and hormone secretion may subsequently become autonomous. In the absence of either anatomical or biochemical evidence for a "secondary" phase, the distinction between "primary" and "tertiary" hyperparathyroidism may present considerable diagnostic difficulties. Where mild impairment of renal function is present in association with hyperparathyroidism, the clinical importance lies in recognising that renal disease may be the initial pathological process and that it is not only the prolonged hypocalcaemia of chronic renal failure that may provoke formation of a renal-related tertiary parathyroid adenoma.

Nephrocalcinosis was significant in this series in producing renal failure if the hypercalcaemia was not corrected by treatment (as in case 11) or if it recurred as in cases 6 and 10 where recurrent parathyroid carcinoma was the cause. It played a part in causing renal failure in three cases in which death occurred within a few months of parathyroid surgery, although in these, extrarenal factors were also important. These three cases had the largest parathyroid adenomas in this series and all had renal impairment before surgery. Previous studies have shown that in the absence of renal disease there is a correlation between the weight of a parathyroid adenoma and the degree of hypercalcaemia produced by it.^{8,9} A similar correlation is difficult to make in these cases because of the complicating factor of renal impairment, but the severity of nephrocalcinosis could be explained on this basis.

The only case in the present series in whom there was some evidence that sustained hypercalcaemia had caused extensive renal tubular damage was case 11. Severe tubular degeneration and regeneration were present in sites where deposition of calcium salts was not visible on light microscopy, although there was considerable nephrocalcinosis elsewhere in both kidneys. Whether or not this tubular damage was related to hypercalcaemia is not certain. It is possible that oral phosphate given in an attempt to lower the plasma calcium concentration after unsuccessful surgery may have played a role. Phosphate-induced tubular damage has been observed in experimental animals.¹⁰ Clinical impairment of renal function in man after oral phosphate treatment for hypercalcaemia has been observed and attributed to exacerbation of nephrocalcinosis.¹¹

Renal stones were not significant in the production of progressive renal failure, except in case 20 where they were of the cystine variety and not due to parathyroid disease. This is possibly a reflection of the more successful management in recent decades of

infection which complicates obstructive disease of the urinary tract.

References

- ¹ Britton DC, Thompson MH, Johnston IDA, Fleming LB. Renal function following parathyroid surgery in primary hyperparathyroidism. *Lancet* 1971;ii:74-5.
- ² Britton DC, Johnston DA, Thompson MH, Fleming LB. The outcome of treatment and changes in presentation of primary hyperparathyroidism. *Br J Surg* 1973;60:782-5.
- ³ Albright F, Reifenshtein EC. The parathyroid glands and metabolic bone disease. Baltimore: Williams and Wilkins, 1948.
- ⁴ St Goar WT. In: Case records of the Massachusetts General Hospital. Case 29. *N Engl J Med* 1963;268:943-53.
- ⁵ Davies DR, Dent CE, Watson L. Tertiary hyperparathyroidism. *Br Med J* 1968;iii:395-9.
- ⁶ Smith JF. Parathyroid adenomas associated with the malabsorption syndrome and chronic renal disease. *J Clin Pathol* 1970;23:362-9.
- ⁷ Thier SO. Renal insufficiency and hypercalcaemia. *Kidney Int* 1978;14:194-200.
- ⁸ Lloyd HM. Primary hyperparathyroidism. An analysis of the role of the parathyroid tumour. *Medicine (Baltimore)* 1968;47:53-71.
- ⁹ Hodgkinson A. Biochemical aspects of primary hyperparathyroidism: an analysis of 50 cases. *Clin Sci* 1963;25:231-42.
- ¹⁰ Craig JM. Observations on the kidney after phosphate loading in the rat. *Archives of Pathology* 1959;68:306-15.
- ¹¹ Dudley FJ, Blackburn CRB. Extraskelatal calcification complicating oral neutral-phosphate therapy. *Lancet* 1970;ii:628-30.

Requests for reprints to: Dr Jane Dixon, Department of Pathology, John Radcliffe Hospital, Headington, Oxford, England.