THE EARLY RENAL SYMPTOMS OF PARATHYROID TUMOURS

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by

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THE PURPOSE OF this lecture is to emphasise the clinical course of patients with parathyroid tumours. In all our cases the first symptoms were renal ones—hence the title of this paper, which is based on the eleven cases diagnosed in the London Hospital between October, 1948 and May, 1952. October, 1948, was the month in which I returned to the London Hospital to take up my present post on the surgical unit, and May, 1952, was the application date for the Hunterian lectures.

According to the records department of the hospital there were just over 300,000 new patients between those two dates ; the diagnosis of a parathyroid tumour was correctly made eleven times. A twelfth patient was explored but no tumour could be found.

Obviously there is no way of estimating how often the diagnosis has been missed. A recent annotation in the *Lancet*[1] suggested that the symptoms were varied and diagnosis difficult. In our eleven cases the clinical course was monotonously similar and it was easy to suspect the diagnosis, provided that the possibility was kept in mind.

Six of the eleven cases were diagnosed in 1951. In that year Mr. A. J. Walton went through the genito-urinary follow-up and considered all patients with bilateral and recurrent renal stones. At the same time the pathologists were " stimulated " to look for parathyroid tumours whenever there was a remote possibility of one being present. In all the three cases where a tumour was found at necropsy, the diagnosis had already been made clinically. It was the pathologists who tended to be sceptical and who refused to commit themselves until they had examined microscopical sections. There was minimal bone disease, and as the tumours were unusual in appearance, they might easily have been missed, or passed over as lymph glands.

In diagnosis one finds what one seeks. Patients attending a teaching hospital are a highly selected sample. The Orthopaedic Department at the London Hospital is, however, just as large and as well-known as the Genito-urinary one. It seems to me unlikely that the patients with renal symptoms were sent to us, and that there is another group of patients with parathyroid tumours who have quite different symptoms, and who get sent to other hospitals, or who are missed at The London. In other words, I believe that the eleven cases are representative, and that the clinical picture which I am going to describe is the one which we have to look out for. Five of our eleven cases were referred from regional hospitals

because the diagnosis was difficult; six cases were referred directly by the general practitioner.

Renal disease often causes parathyroid hyperfunction; and parathyroid hyperfunction can cause renal disease. Table I shows that the distinction between these two possibilities is straightforward. This Table shows the size and weight of the pathological gland, the number of normal glands, the severity of the bone disease, and the response to removal of the pathological gland.

In this small series the correlation between the size of the tumour and the severity of the bone disease is unconvincing. Small tumours can produce severe bone changes, and large tumours can alter the level of the blood calcium without necessarily producing any diagnosable bone changes.

The Clinical Course

In many of our cases the symptoms persisted for a long time, and the patients took a lot of medical advice before the diagnosis was made. No criticism is implied. If the diagnosis had been suggested earlier, it might well have been harder, or even impossible, to verify it. Parathyroid tumours can obviously exist for a long time without causing bone disease or seriously interfering with health.

Table II shows the three main landmarks in the history—the date of the first symptom, the date when bone disease might first have been suspected, and the date when the diagnosis was made or verified.

Seven patients have had renal stones with their associated complications. Two had renal calcification. Diagram I shows the findings.

Whether or not a stone was present, polyuria probably always occurred. It is specifically mentioned in eight case histories. In Case 8 the 24-hourly and hourly urine volumes were large. In Case 3 there was frequency; and in the last case, Case 7, the patient was too ill to give a history. The concentration of the glomerular filtrate is presumably impaired by the damage to the tubules. This damage was demonstrated histologically in all the cases which came to necropsy. Possibly also there is an osmotic diuresis from the disturbance of mineral metabolism.

Gastro-intestinal symptoms, as in other series, were common. Many patients complained of anorexia, nausea, regurgitation, or indigestion. In Case 1 the loss of appetite and weight were so marked as to suggest the diagnosis of anorexia nervosa. In Case 5 a gastric ulcer was shown radiologically six weeks before death. Diagram 2 shows the effect of the disease on the patient's weight and the recovery after operation.

The familiar bone changes[2] were found in seven cases. In four cases there was no evidence of bone disease, but in two of these four, Cases 2 and 10, there was a form of rheumatoid arthritis. Possibly this was coincidental. Case 10 died after operation. Case 2 survived and there was very marked subjective improvement in the arthritis.

TABLE I

THE DIAGNOSIS

The Evidence for PRIMARY, as opposed to SECONDARY PARATHYROID disease

Patient	No. of normal glands seen	Size of pathological gland in cms.	Weight of pathological gland in g.	Mean weight of 4 normal glands from controls of same age and sex in g.	Bone Disease	Additional Evidence
Mrs. R. H. (6)	3 (at P.M.)	4·5 × 3·8 × 2·5	22·7	0·12	+	Post-mortem. Normal renal tract.
Mrs. A. T. (2)	2 (at op.)	—	10**	0·10	±	Post-mortem. Normal renal tract.
Mrs. D. M. (4)	0 (at op.)	3·0 × 2·5 × 2·0	6*	0·14	+++	Post-operative chemistry.
Mrs. F. B. (9)	1 (at op.)	2·5 × 2·5 × 2·0	5·5	0·12	+++	Post-operative course.
Mrs. M. D. (7)	2 (at P.M.)	2·5 × 2·0 × ?	—	0·14	0	Post-mortem. Normal renal tract.
Mrs. A. E. (11)	1 (at op.)	—	1·8	0·12	++	Post-operative chemistry.
Mrs. G. B. (1)	2 (1 at op.)	2·0 × 1·8 × 0·9	1·27	0·12	+++	Post-operative course.
Mr. J. G. (10)	3 (at op.)	1·8 × 0·9 × 0·8	0·95	0·12	±	Post-operative course.
Mr. E. W. (8)	1 (at op.)	2·2 × 1·3 × 0·9	0·85	0·11	0	Post-operative chemistry.
Mrs. J. F. (3)	Not known	—	—	—	++	Post-operative course.
Mrs. R. K. (5)	Not known	—	—	—	++++	Plasma in Phos. at early stage†

The patients have been put in order of the weight of their tumour.

Bone disease recorded as 0 = none
+ = mild
++ = moderate
+++ = marked
++++ = gross
± = rheumatoid arthritis

** = Weight of "thymus" = 10·3 g. Subsequent section showed this tissue to be a parathyroid adenoma with very little thymic tissue.

* = Weight estimated from size.

† = The plasma inorganic phosphorus was normal when first estimated.

TABLE II
THE CLINICAL COURSE

Patient	Age at onset	Interval from onset to first bone symptoms	Interval from first bone symptom to diagnosis	Total time from onset to diagnosis
Mrs. J. F. (3)	33	1 year	1 month	1 year. Operation.
Mrs. G. B. (1)	42	6 months	1 year	1½ years. Operation.
Mrs. A. E. (11)	47	2 years	1 year	3 years. Operation.
Mr. J. G. (10)	52	5 years	None	5 years. Operation.
Mrs. F. B. (9)	41	6 years	6 months	6½ years. Operation.
Mrs. A. T. (2)	25	10 years	None	10 years. Operation. Died.
Mrs. R. K. (5)	Before 44	Over 6 years	7 years	Over 13 years. Died.
Mrs. D. M. (4)	33	15 years	5 years	20 years. Operation. Died.
Mr. E. W. (8)	25	21 years	None	21 years. Operation.
Mrs. R. H. (6)	Before 46	"Years"	None	"Years." Died.
Mrs. M. D. (7)	Before 57	Unknown	None	Unknown. Died.

Table III sets out the cases in chronological order of operation or post mortem. It shows the sex and age, and the time of onset of the main symptoms.

Operation

At operation the colour, shape, site and size of the tumours has varied considerably from patient to patient. Recognition is less difficult if the field is bloodless, but confirmation by frozen section is essential. The resemblance to adjacent structures may be very close.

A thorough search should be made in each possible site before going on to the next; and, of course, great care must be taken to avoid removing normal parathyroid tissue.

Deaths and Post-Operative Course

Three patients died without surgical exploration. Case 6 died of an acute pancreatitis and Case 7 died of acute gastro-enteritis. Case 5 died of the progress of the disease with a gastric ulcer.

Two cases died following operation. Case 2 died of a pulmonary embolus; and Case 4 died of renal failure.

The cause of death in three patients was interesting; it was due to a severe electrolyte imbalance occurring in a patient with damaged kidneys. The electrolyte disturbance followed an acute pancreatitis, an acute gastro-enteritis and the removal of a functioning tumour.

Six patients had their parathyroid tumour removed and survived. In all six there was an initial rise in the blood urea followed, after a variable interval, by disappearance of the polyuria. In three patients, Cases 1, 9 and 11, renal function tests have been repeated after an interval of six months or more. The daily urine volume has decreased and the concentration of

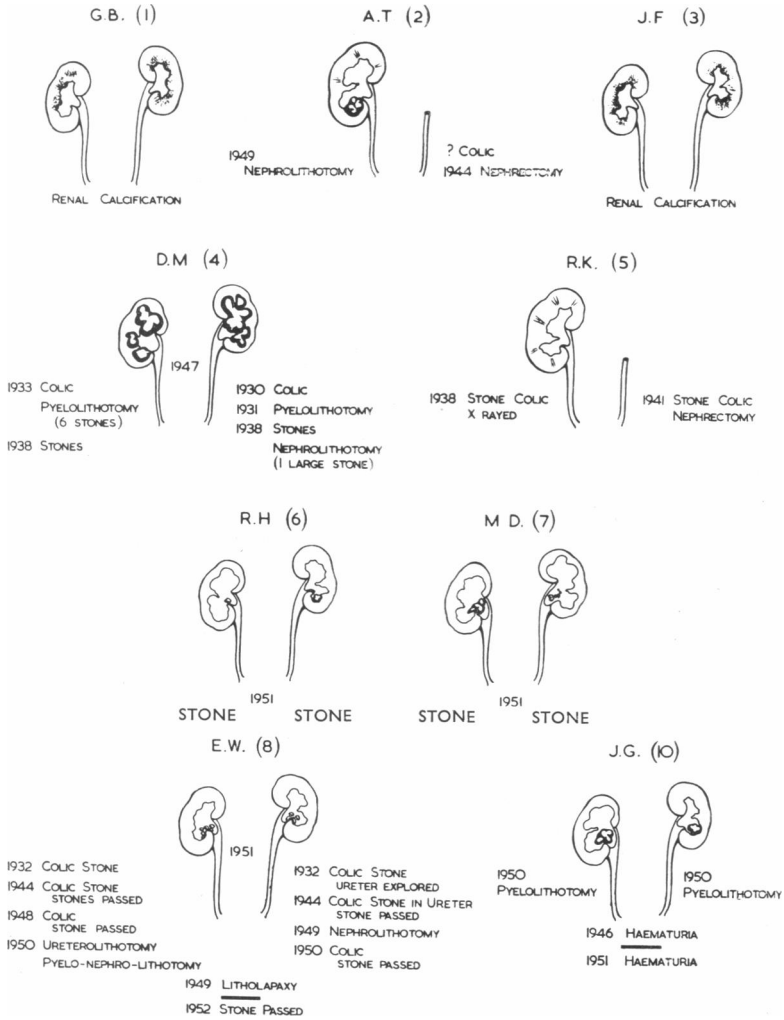

Diagram 1. Diagram to show renal lesions and operations. The lines in Cases 8 and 10 represent the time of removal of the parathyroid tumour.

urea has increased. In Case 1 the P.S.P. concentration has now been followed for three years, and the improvement, though slight, continues.

Diagram 3 summarises the changes in the serum calcium before and after removal of the parathyroid tumour.

Mistakes

Case 12 must be reported. In this patient no tumour was found. She later died and the lesions in the bones were found to be secondary carcinoma from a known primary in the breast. The renal changes were

similar to those in Cases 2 and 6. Probably a mistake was made ; but it is not convincing as only three parathyroids were found at necropsy and a small parathyroid tumour could have been missed.

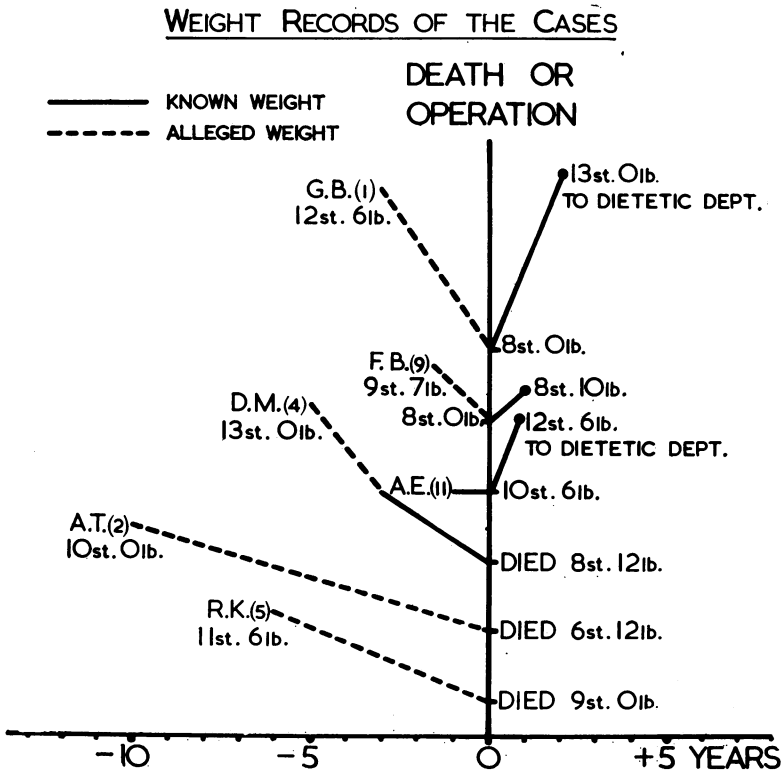

Diagram 2. Records of two other patients, Cases 3 and 4, simply state " lost weight." In Case 6 there was no record of weight alterations, and in Cases 8 and 10 there was no change in the weight.

Conclusions

A parathyroid tumour should be suspected or even diagnosed when a patient with renal calculi or renal calcification is found to have bone changes. The common mistake is to reject the diagnosis if the serum calcium proves to be normal. No fewer than four of these eleven cases had a normal serum calcium at one stage or another, and each time this led to delay in making the correct diagnosis.

Even if there are no bone changes, and the serum calcium is normal, the diagnosis may still be suspected if there is a good history of polyuria associated with renal stones.

The gastro-intestinal symptoms and loss of weight do not help in making a diagnosis.

TABLE III

THE LONDON HOSPITAL

Cases Parathyroid Tumour, October, 1948, to May, 1952

Case Name	Sex and year of birth	Year of Operation or Post-Mortem	First symptom	Other renal symptoms	Onset bone symptoms	Onset abdominal symptoms
1. G.B.	F. 1905	1948 Op.	1947 Polyuria	1948 Renal calcification	1947 Path. fracture	1948 Anorexia and vomiting
2. A.T.	F. 1914	1949 Op. & P.M.	1939 Polyuria	1944 Nephrectomy(?) 1948 Renal stones	1948 (Rheumatoid Arthritis)	
3. J.F.	F. 1915	1949 Op.	1948 Cystitis	1948 Renal calcification	1949 Path. fracture	1948 Anorexia and vomiting
4. D.M.	F. 1897	1950 Op. died	1930 Renal stones	1938 Polyuria	1945 Limb pains	
5. R.K.	F. 1894	1951 Died	1938 Renal stones	1941 Polyuria	1942 Limb pains 1944 Path. fracture	
6. R.H.	F. 1905	1951 P.M.	"Years" Polyuria	1951 Renal stones	P.M. Cyst humerus	1951 (Ac.Pancreatitis)
7. M.D.	F. 1895	1951 P.M.	1951 Renal stones	Nil	Nil	1951 (Ac.Gastro-enteritis)
8. E.W.	M. 1904	1951 Op.	1930 Renal stones	Nil	Nil	Nil
9. F.B.	F. 1904	1951 Op.	1945 Polyuria	1951 Impaired renal function	1951 Cyst of hand	1947 Anorexia malaise
10. J.G.	M. 1894	1951 Op.	1946 Haematuria	1949 Renal stones	1939 (Rheumatoid Arthritis)	Nil
11. A.E.	F. 1902	1952 Op.	1949 Polyuria	Nil	1951 Fibrositis	1945 Anorexia malaise

Case 2 ? = Condition of excised kidney not known.

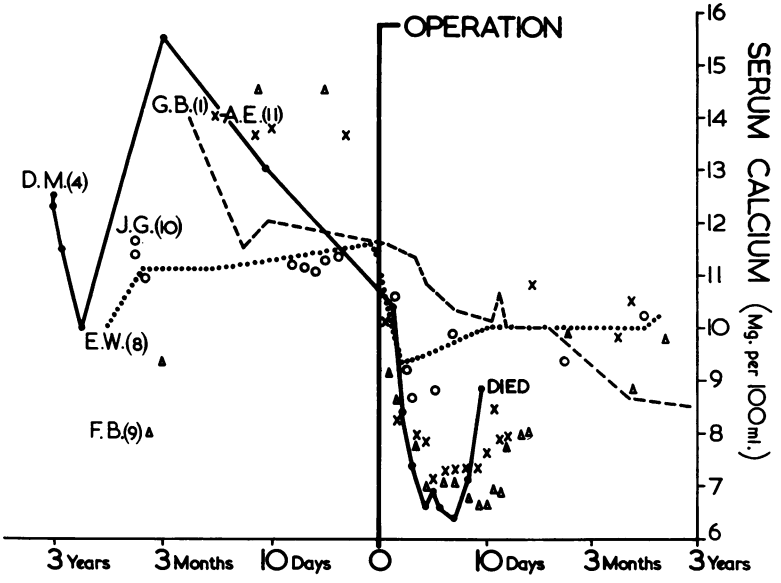

Diagram 3. Time has been computed on a logarithmic scale of 10, 100 and 1,000 days, the last two being taken as 3 months and 3 years.

Serum calcium levels for E. W. shown by dotted lines shows a relatively flat curve. This patient did not have bone disease. J. G. shown by the circles was a similar case. D. M. with the continuous line shows a marked post-operative fall in the serum calcium level. A. E. and F. B. were very similar. G. B. with the dashed line had a much slower post-operative fall, an unusual type of curve.

At present it is difficult or impossible to estimate the frequency of parathyroid disease in patients with bilateral or recurrent renal calculi. We cannot throw the responsibility on the laboratory. The disease may well fluctuate so that the same patient gives a normal level one week, and an abnormal one a week later. The normal for different individuals differs. Laboratory errors occur ; and if we send many normal cases with normal calcium levels, the frequency of useful findings is reduced, and the technician may become bored and less accurate.

Surgical and even necropsy dissection is also unreliable. Parathyroid tumours may weigh less than a gram, and their site is variable. Failure to find a tumour, or even the demonstration of four normal parathyroids does not disprove the diagnosis.[3]

It would be interesting to follow up an unselected series of patients with severe renal calculi for a long period to see how many have parathyroid tumours. It seems as though at least 1 per cent. of them would prove to have this condition, and, though this is a small incidence, it is an important group to recognise.

CASE PROTOCOLS

Case 1.—Mrs. G. B. (L.H. record No. 652/48) was admitted to the London Hospital on July 29, 1948, under the care of Dr. Kenneth Perry with a provisional diagnosis of "anorexia nervosa." She had previously been in Wanstead Hospital.

Background.—She was born in 1905, and was married with one son, born 1932. Her husband, who was fit, was an insurance broker. She kept the house and was interested in dancing, gardening and sport. Previously she was a heavy smoker and occasionally had a drink. She said her weight had fallen from 12 stone in 1945 to 7½ stone at the time of admission. Before 1945 her periods had been irregular; since then they had been regular.

She said that for many years she had drunk much water and had to get up at night to pass it; by 1947 this was well established. Since about 1945 she had felt "out of sorts," began losing weight and complained of tiredness and fatigue. Her appetite became poor and she had occasional attacks of vomiting.

In 1947 while climbing the steps of a bus she was suddenly jerked on to her right arm and broke her clavicle. Later a lump appeared at the site of the fracture. About this time she developed pains in the left side of the chest and in the legs. The lump on the clavicle increased in size; in June, 1948, she was admitted to a local hospital for an operation on the "cyst." Apparently portions sent for microscopic examination showed only granulation tissue. Following operation she felt more cheerful but completely lost her appetite.

Examination on admission to the London Hospital showed a thin but healthy-looking woman, weight 7 st. 7 lb., height 5 ft. 4 in. There were no abnormal signs in the neck, chest or heart. (B.P. 130/80.) Her urine contained a haze of albumin, but no Bence Jones protein. The specific gravity was low. Her haemoglobin was 77 per cent., red blood cells 3,900,000, colour index ·98, leucocytes 12,000 with a normal differential count. The total plasma protein

TABLE IV

CASE 1

Date	Blood Urea mg. per 100 ml.	Serum Calcium mg. per 100 ml.	P. in Phos. mg. per 100 ml.	Alkali Phosphatase units
6. 8.48	45			
12. 8.48		14·0	4·3	24·0
17. 9.48		11·6	3·0	39·0
24. 9.48		12·0	3·8	28·5
8.10.48		Removal parathyroid adenoma		
9.10.48		11·6		49·5
11.10.48		11·4		40·5
12.10.48		10·8		43·5
15.10.48		10·4		37·0
20.10.48		10·2	3·3	33·0
21.10.48		10·6	3·3	
22.10.48		10·0		53·0
20.11.48		10·0	4·0	17·5
23. 2.49	54			
22. 9.49	39			
24. 3.50	42			
8. 1.51	38	8·6	4·6	3·0
10. 9.51		8·5	3·8	5·1

was 5·4 g. per 100 ml. An intravenous pyelogram on September 30 showed poor concentration of the dye. There was no evidence of enlargement of the ureters.

The renal function and biochemical tests are set out in Table IV.

She left hospital on August 13th, 1948, but was re-admitted on September 17th, 1948. On October 8th an adenoma of the parathyroid gland was removed by Mr. Charles Donald. Microscopical examination (S.D. 652/48) confirmed the diagnosis. Following operation she made a good recovery. Her appetite has improved; she has steadily put on weight; the fractured clavicle healed slowly; on March 27th, 1950, she weighed 13 stone, was referred to the diatetic department for a reducing diet. She was last seen October, 1952, when the urine was free of albumin with specific gravity 1006-1002. The nocturia had gradually subsided.

Renal Function Tests

		Volume of urine ml.	Urine urea mg. per 100 ml.	P.S.P. %
6.8.48:	Blood urea = 45 mg. per 100 ml.			
	1	200	840	13·2
	2	180	720	13·2
	3	110	900	
22.10.48:	Blood urea = 51 mg. per 100 ml.			
	1	194	960	16
	2	170	720	14·2
	3	110	780	
23.2.49:	Blood urea = 54 mg. per 100 ml.			
	1	220	780	21·7
	2	140	780	16·0
	3	122	900	
24.3.50:	Blood urea = 42 mg. per 100 ml.			
	1	225	660	not recorded
	2	150	850	
	3	110	900	
	Creatinine clearance = 63 ml. per minute.			
10.9.51:	Blood urea = 42 mg. per 100 ml.			
	1	115	960	not recorded
	2	125	1,020	
	3	110	1,080	
	Creatinine clearance = 70 ml. per minute.			
1.1.52:	Blood urea = 39 mg. per 100 ml.			
	1	120	1,140	25·2
	2	120	1,200	15·9
	3	80	1,200	

Case 2.—Mrs. A. T. (L.H. record No 10727/49) was admitted to the London Hospital on April 2nd, 1949, under the care of Dr Kenneth Perry from the Metropolitan Hospital, with a provisional diagnosis of " rheumatoid arthritis."

Background.—She was born in 1914, and was married with one adopted daughter, born 1946, and a son, born in 1947. Her husband, a joiner, was alive and well. She smoked about 30 cigarettes a day and had an occasional glass of beer. Her highest known weight was 10 st. in 1939; in 1949 at the London Hospital, she weighed 6 st. 5lb. She was 4 ft. 11 in. tall.

In 1939 she first developed polydypsia and polyuria. In 1944 she had a left nephrectomy when she was living in Ireland. The pathological condition of the kidney and ureter is not known. Before the operation she was having severe pain passing from the left loin to groin. In 1948 she developed pains in the fingers associated with swelling of the joints. In November, 1948, she developed pain in the arm; just prior to coming into hospital she developed pain in the left wrist.

When admitted she was found to be pale with spindle swelling of the joints of the hands. The heart and lungs were normal. (B.P. 125/85.) There was the scar of the previous operation. The urine contained a haze of albumin and pus. On March 4th, 1949, X-ray of the right kidney showed a large renal calculus. The haemoglobin was 78 per cent. and E.S.R. 28 mm. in 1 hour on May 7th. On April 8th her renal function tests were :—

Blood urea = 33 mg. per 100 ml.

Urea concentration and P.S.P. excretion test. 15 g. of urea given.

	Volume of urine ml.	Urine urea mg. per 100 ml.	P.S.P. %
1	375	300	33·2
2	140	780	14·3
3	110	750	

On April 22nd she excreted 370 mg. calcium in a 24-hourly specimen of urine while taking a normal diet. On April 2nd her blood urea was 39 mg. per 100 ml.; on April 6th the serum calcium was 13·6 mg. per 100 ml., phosphorus 2·1 mg. per 100 ml., and the alkali phosphatase 7·0 units. These investigations were repeated on April 12th when the serum calcium was 12·2 mg. per 100 ml., plasma inorganic phosphorus 2·3 mg. per 100 ml., and alkali phosphatase 4·6 units. On April 26th, an X-ray of the skull and pelvis showed no abnormality. There was no loss of density in the bones of the hand, the only abnormality being the deformity and small sub-articular erosions of the metacarpals.

On May 17th her neck was explored but no parathyroid tumour was found. On May 31st the stone in the right kidney was removed. She suddenly collapsed and died on June 3rd, 1949.

Necropsy (P.M. 195/49) showed death to be due to a pulmonary embolus. A parathyroid tumour was mistaken for the thymus; when routine sections of this gland were examined the error was corrected. The right ureter and the bladder were normal. Apart from the deformity of the hands there was no rarefaction fibrosis or cysts of the bones.

"The right kidney had undergone compensatory hypertrophy, weighing 10¼ oz., in response to previous surgical removal of the left. The cortex appeared oedematous, with distinct pattern on macroscopic examination. A few white streaks were observed, particularly in the medulla. The pelvis, from which a rubber drain extended to the surface of the body, was congested.

"*Microscopic.*—Irregular small areas of poorly defined fibrosis are scattered throughout the cortex, mostly in the outer third. In these the tubules are atrophied and patches of lymphocytic infiltration are frequent. The glomeruli are normal, except for a few that are in stages of ischaemic atrophy. The convoluted tubules and loops of Henle are often dilated; their epithelium is in stages of parenchymatous degeneration, but is nowhere fatty. The lumina

contain a few hyaline casts and occasional aggregates of spheroidal or irregularly-shaped deposits of calcium. The second convoluted tubules are the usual site involved. These deposits are more conspicuous, in number and size, in the tubules (presumably collecting) in the medulla. The epithelium here is often partly or wholly destroyed and sometimes there is an associated foreign-body giant-cell reaction about the deposits accompanied by fibroblastic proliferation and scanty lymphocytic infiltration.

" There is a diffuse zone of infiltration with plasma cells and lymphocytes beneath the pelvic epithelium, and here the adjacent tubules sometimes contain groups of fragmenting polymorphonuclear leucocytes."

Case 3.—Mrs. J. F. (L.H. record No. 24685/49) was sent to Switzerland following a diagnosis of renal tuberculosis. When there this diagnosis was disproved : a parathyroid adenoma was removed. She later attended the London Hospital for treatment of a pathological fracture.

Background.—She was born in 1914, married with one son, born 1940. In 1945 she had a still-birth after an 8 months' pregnancy, associated with an ante-partum haemorrhage. During the last part of the pregnancy the blood pressure readings were reported as " over 200 systolic."

Since that time she had never really felt well. About November, 1948, she developed anorexia, nausea and epigastric discomfort after meals. For about a week she vomited after each meal ; she lost weight.

In January, 1948, she had two attacks of cystitis with frequency and dysuria, but no haematuria. In April, 1948, the urine showed a little albumen, but neither pus nor tubercle bacilli were found. At this time X-rays showed calcification in the kidneys. She was recommended to go to Switzerland by two consultants as the X-rays were considered diagnostic of renal tuberculosis.

In October, 1948, in Lausanne, the diagnosis of tuberculosis was doubted. She was sent to Berne for further investigation and on the journey she knocked and broke her right forearm.

On November 11th, 1948, a parathyroid adenoma was removed. Following operation she made an uninterrupted recovery except for one attack of tetany.

Before operation the blood urea was reported as 100 mg. per 100 ml., the serum calcium 17·2 mg. per 100 ml., the phosphorus 4·1 mg. per 100 ml. and the alkali phosphatase 12·3 Bodansky units. The post-operative findings were reported as follows :—blood urea 31 mg. per 100 ml., serum calcium 8·2 mg. per 100 ml., phosphorus 2·8 mg. per 100 ml., potassium 20·6 mg. per 100 ml., and alkali phosphatase 7·2 Bodansky units.

On returning to England she was recommended to go to the London Hospital, where she was X-rayed on January 1st, 1949. There was little evidence of callus formation at the site of the fracture in her radius and ulna. On February 2nd her renal function tests were :—

Blood urea = 45 mg. per 100 ml.

Urea concentration and P.S.P. excretion.

	Volume of urine ml.	Urine urea mg. per 100 ml.	P.S.P. %
1	120	660	26·6
2	110	540	15·8
3	120	660	

On February 2nd X-rays again showed " thin bones " with a little callus. On February 21st the alkaline phosphatase was 41 units (King Armstrong), the serum calcium was 9 mg. per 100 ml., and the phosphorus 3·6 mg. per 100 ml.

When last seen, on March 22nd, 1949, the fracture of the radius and ulna were found to be united ; she was reported as being well and will not come up for any further investigation.

Case 4.—Mrs. D. M. (L.H. record No. 21072/50) was admitted to the London Hospital under the care of Dr. Donald Hunter on May 18th, 1950, with a diagnosis of hyperparathyroidism.

Background.—She was born in 1897 ; and spent the first seven years of her life in Russia. Her husband, who was a baker, was alive and well. She had five children, the youngest was born in 1930. In 1935 her periods ceased following a hysterectomy for fibroids. In April, 1931, during her second admission to the London Hospital, an appendicectomy was performed for acute appendicitis. She had always been constipated and took laxatives. In 1948 she was found to have sugar in the urine ; she was treated by dietetic means. Her weight has fallen from 13 st. in 1946 to 8 st. 11 lb. in 1950. She did not smoke or drink. She was helped in her home by her married daughter.

In 1930, when four months' pregnant, she first developed left renal colic. She was first admitted to this hospital on April 10th, 1931, when the diagnosis of left renal calculus was confirmed by X-rays. The stone was removed by pyelolithotomy, the right kidney and ureter at that time were reported as being normal. In February, 1933, she was admitted for a third time with right renal calculi. X-rays showed six stones. These were removed by right pyelo-nephrolithotomy. No calculi were seen in the region of the left kidney at this time.

In March, 1938, she was admitted for the fourth time with renal colic. X-rays showed bilateral renal calculi with mild hydronephrosis on the right side. At this time her blood urea was 40 mg. per 100 ml. The notes made at the time of this admission state that there was marked increase of frequency of micturition as she always drank a lot of water. A left nephrolithotomy was performed with removal of one large stone from the renal pelvis. Post-operative X-rays showed three smaller stones in the region of the kidney. Analysis of the stone showed that it consisted of calcium carbonate and phosphate.

In 1946 she first complained of heaviness of the legs. Her fifth admission to the London Hospital was from April 20th to May 23rd, 1947. Her weight at the time of this admission was 10 st. 5 lb. She was then found to have bowing of the tibiae. The B.P. was 180/115. X-rays showed stones in both kidneys and definite decalcification of skull, spine, legs and arms compared with controls. An intravenous pyelogram showed poor concentration of dye. There was gross impairment of the renal function tests. The urine contained albumin, a trace of sugar and had a low specific gravity. In view of the renal failure and doubt regarding the diagnosis, it was considered wiser not to explore the neck. The renal stones also were left for fear of damaging the little remaining renal tissue by operation.

Following discharge she attended Medical Out-Patients. On May 6th, 1950, her doctor, Dr. F. Bernstein, wrote requesting her re-admission with a view to surgery as she was having considerable pain in the legs and so was practically confined to bed.

She was admitted for the sixth time on May 18th, 1950 ; on examination the clinical findings were essentially the same as on her previous admission, except that her weight was now 8 st. 5 lb.

The biochemical findings are set out in Table V.

In view of her symptoms it was considered justifiable to remove the adenoma in spite of the impaired renal function. On June 7th, 1950, a parathyroid adenoma 2·5 × 2·0 cm. was removed from behind the right lobe of the thyroid. Microscopic examination (S.D. 2528/50) of the tumour confirmed the diagnosis. Following operation she was well for a week but then became drowsy and died on June 17th, 1950. Permission for post-mortem was refused.

TABLE V

CASE 4

BIOCHEMICAL DATA

Date	Blood Urea mg. per 100 ml.	Serum Calcium mg. per 100 ml.	P. in Phos. mg. per 100 ml.	Alkali Phosphatase units
23. 4.47	100	12·2	2·9	16·0
30. 4.47		12·4	3·0	
25. 5.47		11·6	4·0	33·1
15. 9.47	90			
18.11.47	45			
13. 5.48		10·0	4·5	
7.10.48	62			
13.10.49	171			
14. 2.50	150	16·0	6·8	44·0
19. 5.50	237			
22. 5.50	174			
26. 5.50		13·0	5·5	33·0
6. 6.50	210			
7. 6.50		Parathyroid tumour excised		
8. 6.50	225	10·4		
9. 6.50	198	8·4	5·0	19·5
10. 6.50	185	7·4		
11. 6.50		6·6		
12. 6.50	204	6·8	4·8	39·0
13. 6.50	225	6·6		
14. 6.50	255	6·4	6·4	46·0
15. 6.50		7·2		
16. 6.50	291	8·8		
17. 6.50		Died		

Case 5.—Mrs. R. K. (L.H. record No. 18047/51) was admitted to the London Hospital under the care of Dr.Donald Hunter on May 24th,1951, with a provisional diagnosis of " hyperparathyroidism." She died suddenly three days later.

Background.—She was born in 1894 of Russian descent. She was a widow with six children. The youngest child was born in 1923. She worked as a hairdresser in her own business until 1945. At one time she smoked 35 cigarettes a day. Her bowels were always constipated. Her periods ceased in the middle of 1945.

Owing to her condition the history was obtained from relatives. They were unable to give any clear or accurate account. Many of the previous notes have been lost. In 1938 she first had severe pain in the right loin; following an X-ray she was told that she had a stone in the right kidney. In 1941 she had a similar pain in the left loin. In 1941 a nephrectomy was performed for a lef renal calculus. Since this operation she had been a teetotaller but had drunk a lot of water. She had also passed a lot of water, up to 20 times by day and 7 at night. She had not felt well, and had had pains in the legs. In 1943 she was admitted to another hospital with weakness, malaise, anorexia and vomiting. She was treated by bed rest and medicine.

In 1944 she was pushed in the arm while walking in the street. An X-ray showed a fractured humerus. She was treated for this at Hackney Hospital. After four months the fracture had not healed, so she was referred to the Orthopaedic Department of the London Hospital, on September 26th, 1944. Investigations at this time showed the serum calcium to be 11·1 mg. per 100 ml.,

plasma inorganic phosphorus 2·6 mg. per 100 ml., and phosphatase 5 units. A drill biopsy on October 12th, 1944, was reported as " probably osteoclastoma, but with few giant cells—probably osteitis fibrosa." She was treated by deep X-rays. Her health improved and she was discharged from the ward five weeks later.

She attended the Radiotherapy Outpatient Department. In 1945 she lost 2½ st. in weight and her appetite was very poor. Her second admission was from January 1st, 1946, to January 17th under the care of the Radiotherapy Department. Her weight was 9 st. 1 lb. on the day of admission. At this time an X-ray of the chest showed a calcified " cyst " of the right lung.

She was discharged from hospital and attended outpatients. In February, 1947, she again fell on the right arm, sustaining a fracture through the lower part of the diseased bone. This was treated by immobilisation. In February, 1949, she ceased to attend this hospital. In 1950 she apparently had a fracture of the right femur and in 1951 a fracture of part of the pelvis. From February, 1951, until the time of her last admission she had had epigastric pain, worse after food and causing regurgitation.

She was admitted, for the third time, to the London Hospital on May 24th, 1951, in a comatosed state. There is no record of her weight at this time. She died on May 27th.

Owing to her condition, examination was difficult. She was, however, a very pale, wasted Jewess, temperature 98·4, pulse 96, respiration 20, B.P. 90/70 ; there was the scar of the previous kidney operation. On May 25th the serum calcium was 13 mg. per 100 ml., the blood urea 60 mg. per 100 ml., and the alkaline phosphatase 23·0 units. The haemoglobin was 52 per cent.

After her death a letter was received from the Prince of Wales Hospital, where she had been earlier in the year, saying she had refused surgical treatment and giving the results of their investigations. On April 2nd the haemoglobin was 13·9 g., the blood urea 140 mg. per 100 ml., serum calcium 22 mg. per 100 ml., (this was repeated), a 24-hourly specimen of urine was reported as having 75 mg. calcium. X-rays showed general decalcification of the bones, a cyst in the right humerus and tibia, pathological fractures of the right humerus, femur, ischial and pubic bones. There was a cyst in the lung. A barium meal had shown a lesser curve gastric ulcer.

Comment.—Necropsy was refused, but in view of the clinical course, biochemical findings, and the examination of the bone removed in 1944, there can be no reasonable doubt about the diagnosis of a parathyroid adenoma.

This case has also been reported by Dr. A. Elkeles.[4] He considered that the swelling in the upper mediastinum was the parathyroid tumour. This was never confirmed by surgical or post-mortem examination He states that when he examined the patient radiologically he found she had a gastric and a duodenal ulcer. The X-rays are not reproduced in the article. The date of onset of renal symptoms is given as 1941 and of bone symptoms as 1949. The case protocol given here shows that the onset in each case was earlier and the duration of the disease longer than his report suggests.

When she was first in the hospital a letter was sent to Hackney Hospital asking to see their old notes, but these were not available as they had been destroyed during the war.

Case 6.—Mrs. R. H. (L.H. record No. 31443/51) was admitted to the London Hospital on August 7th, 1951, under the Surgical Unit as an emergency with a provisional diagnosis of " intestinal obstruction."

Background.—She was born in 1905 and had five sisters and one brother who had died of " pleurisy." She was married in 1934 and had one daughter, born in 1935. Her husband, a bus conductor, was alive and well but had not been on speaking terms with his wife for a month. She worked as a dressmaker, was a non-smoker and took occasional alcohol. She always had trouble with

her bowels for which she regularly took cascara. Previously her appetite and general health had been good, but she had given up fried food for the past year. In 1948 she had vaginal bleeding for which she was treated with radium.

The history was taken from the patient, a very sick woman, and the husband who, owing to the family quarrel, knew little about his wife. For many years she had drunk a lot of water ; for a long time she got up at night to pass water ; there had not, apparently, been undue frequency by day.

Her bowels were last open on August 1st, 1951 ; that night she took " black draught." On the afternoon of August 3rd she developed colicky abdominal pain, nausea and vomiting, since which time she had not eaten but had drunk fluids. The pain subsequently became easier but the vomiting persisted. Prior to admission she was given an enema by the district nurse without result.

About nine months previously (November, 1950) she had a similar but less severe attack ; this passed off after a few days. For some months she had been short of breath on exertion ; she had not noticed any swelling of the feet.

Examination on 7th August was difficult owing to the gross obesity ; her temperature was 98·6, pulse 102, respiration 32, B.P. 115/80. No definite abnormality was detected in the heart or lungs. In the upper abdomen there was a tender indefinite mass. The urine contained a 1/3 volume albumin, no sugar and a specific gravity of 1007. Straight X-ray of the abdomen showed fluid levels in the descending colon ; there were opacities in each renal pelvis. The architecture of the pelvis was said to suggest Paget's disease.

On August 7th the blood urea was 126 mg. per 100 ml., on August 8th the serum calcium was 11·8 mg. per 100 ml., the plasma inorganic phosphorus 8·3 mg. per 100 ml., and the serum amylase 160 units. The haemoglobin was 83 per cent. (12·3 g. per 100 ml.), leucocytes 23,000, blood urea 210 mg. per 100 ml., plasma chlorides 515 mg. per 100 ml., bicarbonates 54 Vols. of CO_2 per 100 ml., serum protein 7·1 g. per 100 ml., bilirubin 4·6 mg. per 100 ml., alkaline phosphatase 24·0 units. On August 10th the blood urea was 324 mg. per 100 ml., plasma chloride 465 mg. per 100 ml., and bicarbonate 48 Vols. of CO_2 per 100 ml. The urinary diastase was 4 units. The chest X-ray on August 10th showed pulmonary oedema with symmetrical bats-wing distribution.

She died at 5.15 p.m. on August 10th, 1951. Necropsy (P.M. 302/51) showed a cyst in the middle of the left humerus. The inner table of the skull was eroded. There was a parathyroid tumour 4·5 × 3·8 × 2·5 cm., weighing 22·7 g. situated to the left of the trachea in the thoracic inlet. The left upper and both right parathyroids were normal. The pancreas was destroyed by acute necrosis. No calculi were found in the duct. The ureters and bladder were normal. The patient's weight was 185 lb., height 5ft. 2in.

" The kidneys were enlarged, weighing 13½ oz. together. Their surfaces were granular and the cortical pattern much distorted. Chalky flecks were found in the medulla. The pelves were slightly dilated, each containing a small calculus (the larger measuring 1 × 0·2 cm.).

"*Microscopic.*—There is a rather diffuse, dense fibrosis in the cortex, especially about the glomeruli, but sparing a few groups of convoluted tubules. A considerable amount of doubly-refractive Sudanophil lipoid occupies both spindle-cells and small groups of foam-cells in the interstitial tissue. A good many glomeruli have undergone ischaemic atrophy ; others show stages of this process and the remaining are hypertrophied.

"There is considerable atrophy, occasionally with fatty degeneration, of tubules in the more densely fibrotic areas. Otherwise their appearances are similar to those in Case 2. In addition there is focal linear calcification of the basement-membranes in groups of convoluted tubules scattered throughout the cortex. In these the epithelium is often in stages of disintegration and necrosis, but

some groups can be identified as first convoluted. There are no deposits of calcium within the lumina in the cortex, but the medulla contains both small and massive (up to about 500μ) conglomerations of calcium. The larger have led to much distortion of the adjacent tissues but have excited no cellular reaction.

"There is medial and intimal hypertrophy of the arteries, with a good deal of intimal fibrosis without fatty degeneration. Plasma cells and fewer lymphocytes infiltrate the tissues beneath the pelvic epithelium."

Comment.—The acute pancreatitis may have lowered the serum calcium level in this patient.

Case 7.—Mrs. M. D. (L.H. record No. 31644/51) was admitted to the London Hospital on August 13th, 1951, under the care of Sir Alun Rowlands, as an emergency with a provisional diagnosis of " acute gastro-enteritis." She died three days after admission.

Background.—She was born in 1892. Her husband died in 1936 of " rheumatoid arthritis." Since that time she had brought up her six children, two of whom had died. One died as a baby and the other died while serving in the A.T.S. Her bowels were regular; there was no record of disturbance of micturition.

The history was given by the patient, who was at the time very ill. She had been in moderate health for a number of years and had apparently lost weight. Apart from this nothing is known until six days before admission when she suddenly developed vomiting; shortly after this diarrhoea started. The stools were very loose and green in colour. They were so frequent she could not count the number each day. This continued until she was admitted to hospital. During this time she did not eat and drank only a little fluid.

Examination after admission was difficult owing to her critical condition. She was a thin grey-haired lady with sunken eyes and cheeks. The skin was dry and inelastic. The nails were flat and brittle; there was no jaundice or oedema. Her temperature was 96·0, pulse 80, respiration 20, B.P. 120/50. No abnormality was found in the neck, heart or lungs. The urine contained 1/3 volume of albumin, there were pus cells, culture showed para-colon bacillus. The specific gravity is not known. There were 3 g. chlorides per litre in the urine. Straight X-ray of the abdomen showed bilateral renal stones. On August 15th, 1951, her blood urea was 210 mg. per 100 ml., plasma inorganic phosphorus 7·7 mg. per 100 ml., serum calcium 10·5 mg. per 100 ml., alkaline phosphatase 8 units and plasma bicarbonate 18 ml. CO_2 per 100 ml.

She was treated with intravenous glucose and saline and phthalyl sulphathiazole. The diarrhoea continued and she died on August 16th, 1951.

Necropsy (P.M. 314/51) showed chronic miliary tuberculosis of the lungs and spleen. The ureters and bladder were normal. There was no rarefaction, fibrosis or cysts in the bones. There was an adenoma 2·5 × 2·0 cm. in the right upper parathyroid gland. The two glands on the left side of the neck were normal. The body weighed 88 lb. and was 5 ft. 0 in. tall.

" In both kidneys the pelves were distended by stag-horn phosphatic calculi; the mucosa was congested. As a result the kidney substance was deeply scarred and greatly reduced in thickness in many places, down to 0·5 cm. in the left and 0·1 cm. in the right kidney. The cortical pattern was blurred.

"*Microscopic.*—In the less contracted renal tissue (right kidney) there is diffuse fibrosis throughout the cortex, sparing a few small islands of convoluted tubules. The fibrosis is mainly slight, with delicate collagen fibres, but in the scarred areas it is dense and the included tubules are atrophied. A few groups of cells, as in Case 6, contain doubly-refractive sudanophil lipoid. The glomeruli are mostly normal, but some have undergone ischaemic atrophy and a few show a non-ischaemic form of degeneration in which the whole or part of the

tuft, usually near the hilum, has suffered loss of nuclei with obliteration of the normal structure.

"In general the tubules are greatly dilated ; a few contain hyaline or eosinophil granular casts. But no calcium deposits were observed either in the cortex or medulla.

"A greatly contracted strip of renal tissue from the left kidney shows the characteristic histological features of advanced hydronephrosis. There are no calcium deposits.

"*Comment.*—Metastic calcification of the kidneys is evident in Cases 2 and 6, but is absent in this case. In the latter there is a similar absence of deposits in the alveolar walls of the lung and in the mucosa of the stomach (body). If interstitial fibrosis is a criterion of the duration of the disease then Case 6 represents a later stage than Case 2.".

Case 8.—Mr. E. W. (L.H. record No. 6452/48) was admitted to the London Hospital under the care of the Surgical Unit on September 24th, 1951, with a diagnosis of hyperparathyroidism.

Background.—He was born in 1902. He served in the Army from 1919 to 1926 in India, Egypt and Turkey. He served again from 1941 to 1945 ; this time in the United Kingdom. From 1927 to 1937 he worked as a labourer for a scrap iron merchant ; from 1937 until he rejoined the Army he was in casual labour. After his discharge from the Army he was employed as a porter cleaner at a West End theatre. He was married in 1931 and has two children born 1932 and 1939. His wife and children are well. He smokes 20 cigarettes and has a pint of beer a day. When in the Army his beer consumption, at times, rose to 14 pints a day. His bowels are open regularly, his appetite is good ; there has been neither loss of weight, nor indigestion. He had attacks of malaria in 1921 and 1925 ; and an operation for right inguinal hernia in 1944.

In 1932 he was first admitted to the London Hospital with renal colic. X-rays showed stones in both kidneys. He was discharged and re-admitted the same year. The left ureter was explored but no stone was found.

He was well until 1944 when he again had pain of a colicky type radiating from the loins to the groins. X-rays showed several opacities in the left kidney, one in the right kidney and one in the line of the left ureter. He subsequently passed several stones in the urine. In 1945 he developed some increased frequency of micturition, up to twice at night.

His third admission to the London Hospital was from June 21st to July 5th, 1948, for repeated renal colic. The day after admission he passed two small calculi.

His fourth admission was from July 6th to July 23rd, 1949, for renal colic. A litholapaxy was performed removing a small stone from the bladder. Subsequently a left nephrolithotomy was performed removing four stones from the kidney.

He had further attacks of renal colic and was re-admitted for a fifth time from March 5th to April 26th, 1950. During this admission a right ureterolithotomy and a right pyelonephrolithotomy were performed. The ureters were normal. Analysis of the stones showed that they were composed of calcium carbonate and phosphate.

He subsequently had a further attack of left renal colic and passed a small calculus.

His sixth admission was from August 6th to September 6th, 1951, for study of his calcium metabolism. X-rays of the hands, dorsal spine and left humerus taken on August 25th did not show any abnormality. He left hospital as he was booked up for his summer holiday and was re-admitted for the seventh time on September 24th, 1951, for exploration of his neck.

Examination showed a well-built, healthy man with normal temperature, pulse and respiration. There was no abnormality in the heart, lungs or neck

apart from a B.P. of 200/120. The abdomen showed the scars of the previous operation.

On September 26th, 1951, the neck was explored; a parathyroid adenoma weighing 850 mg. and 2·2 × 1·3 × 0·9 cm. in size was removed. His post-operative course was uneventful. Microscopical examination (S.D. 4076/51) confirmed the nature of the tumour.

The biochemical findings are given in Table VI.

Since leaving hospital he has felt well. He passed a stone in April and a further stone in May, 1952. There was no pain or haematuria. In July the urine was sterile and an intravenous pyelogram showed small calculi remaining in each renal pelvis.

TABLE VI
E. W.
BIOCHEMICAL DATA

Date	Blood Urea mg. per 100 ml.	Serum Calcium mg. per 100 ml.	P. in Phos. mg. per 100 ml.	Alkali Phosphatase units
16. 6.48	30			
8. 7.49	33			5·1
7. 3.50	51	10·0	3·8	
9. 5.51		11·2		
17. 8.51	37	11·2	3·6	13·0
25. 9.51		11·6		
26. 9.51		11·4	Excision parathyroid tumour	
27. 9.51		10·2		
28. 9.51		9·3		
29. 9.51		9·3	4·0	
5.10.51		10·0		
2. 7.52		10·0	4·0	
23.12.52		10·2	3·3	

TABLE VII
E. W.
URINARY CALCIUM EXCRETIONS

Date	Diet	Volume Urine ml./24 hrs.	Total Urinary Calcium mg./24 hrs.	Calcium mg. per 100 ml.
18. 8.51	Normal Calcium	1,700	480	28·0
25. 8.51	Low Calcium	3,570	428	12·0
29. 8.51	,, ,,	3,135	526	16·8
1. 9.51	,, ,,	2,450	497	20·3
2. 9.51	,, ,,	2,300	529	23·0
3. 9.51	,, ,,	2,950	560	19·0
26. 9.51		Excision parathyroid tumour		
3.10.51	High Calcium	4,260	498	11·7
4.10.51	,, ,,	3,700	492	13·3

Case 9.—Mrs. F. B. (L.H. record No. 22147/51) was first referred by her own doctor to the London Hospital Surgical Out-Patients on June 6th, 1951, with a swelling of a metacarpal. This was first diagnosed as an enchondroma.

Further X-rays showed more extensive bone disease; she was therefore transferred to the Orthopaedic Department, and was admitted under the care of Mr. H. Osmond-Clarke on September 13th, 1951, with a provisional diagnosis of "multiple myelomatosis."

Background.—She was born in 1904 and was married in 1928. Her husband, a police officer, had recently had a partial gastrectomy for an ulcer. They have three children, born 1929, 1931 and 1939. The patient looks after the house and family. From 1944 to January, 1945, she was also doing war work, but gave this up as she found it was too much. Her bowels were constipated; she has taken aperients once or twice a week for many years. Her periods were regular until 1949 when they occurred about every fortnight. She smokes ten cigarettes a day.

She has always had a little frequency; since about 1945-46 this has been much worse, she has to get up every two hours at night and has to pass a lot of urine. About this time she says she became thirsty and drank a glass of water each time she got up in the night. She says she has lost 1½ st. during the last 18 months and over the same time has lost interest and has not had the energy to do her housework. She had attacks of giddiness. Early in 1950 she began having vague pains in the back and chest, and later in the legs. In October, 1950, she said her legs really became weak and she had difficulty in rising from a chair and walking. She was unable to do the shopping. In February, 1951, she noticed a swelling on the left hand, later it became painful and was useless.

Examination, after admission, showed an ill-looking woman. Her weight was 7st. 8lb. The upper part of the head seemed big, the hair was thin. The

TABLE VIII

F. B.

BIOCHEMICAL DATA

Date	Blood Urea mg. per 100 ml.	Serum Calcium mg. per 100 ml.	P. in Phos. mg. per 100 ml.	Alkali Phosphatase units
26. 6.51		8·0		20·0
3. 7.51		9·3		
19. 9.51		14·5	3·0	21·0
29. 9.51	60	14·5	4·0	
3.10.51		Parathyroid tumour excised		
4.10.51		9·2		
5.10.51		8·6		
6.10.51	96	7·8		
8.10.51	118	7·0	3·3	
9.10.51		7·0		
10.10.51	90	7·0		
11.10.51		6·7		
12.10.51	69	6·6		27·0
13.10.51		6·6		
15.10.51	66	6·9		29·5
16.10.51		6·8		
19.10.51		7·8	5·5	
22.10.51		7·9	5·7	
24.10.51	57	7·9		
26.10.51		8·0		
29.10.51		9·2		13·5
1.11.51		9·9		
15.11.51	57	10·0	5·4	12·0
2. 4.52	60	8·6	4·0	3·7
31.12.52	48	9·8	4·0	3·7

temperature, pulse and respiration were normal, B.P. 190/90. The head of the fourth left metacarpal had disappeared, there was swelling of the shaft of the bone. Apart from this there was no other clinical abnormality of the skeleton. The lungs and cardio-vascular systems were normal. The urine contained a faint haze of albumen, but no Bence-Jones protein. The W.R. was negative. The blood count showed Hb. 70 per cent., red cells 4,060,000, leucocytes 5,600, colour index 0·86. The red cells and platelets were normal. On August 29th the total plasma protein was 7·3 g. per 100 ml.

The X-rays on July 3rd showed a cyst in the fourth left metacarpal and a cyst in the spinous process of the fourth lumbar vertebra. The films of the long bones and radius suggested moderate osteoporosis with, in places, cyst formation.

TABLE IX
F. B.
URINARY CALCIUM EXCRETIONS

Date	Diet	Volume Urine ml./24 hrs.	Total Urinary Calcium mg./24 hrs.	Calcium mg. per 100 ml.
29. 9.51	Normal Calcium	2,380	316	13·3
30. 9.51	Low Calcium	1,500	181	12·1
1.10.51	,, ,,	1,980	247	12·5
3.10.51		Excision parathyroid tumour		
16.10.51	High Calcium	2,280	32	1·4
29.10.51	,, ,,	2,360	42	1·8
15. 4.52	Normal Calcium	1,100	25	2·3
16. 4.52	,, ,,	1,800	28	1·6
17. 4.52	,, ,,	1,800	28	1·6

TABLE X
F. B.
RENAL FUNCTION TESTS
15 gms. urea given for each test.

29.9.51 : Blood urea = 60 mg. per 100 ml.

	Volume of urine ml.	Urine urea mg. per 100 ml.
1	200	840
2	120	900
3	20	960

Creatinine clearance = 40 ml. per minute.

24.10.51 : Blood urea = 57 mg. per 100 ml.

	Volume of urine ml.	Urine urea mg. per 100 ml.
1	No specimen	
2	160	1,020
3	110	960

Creatinine clearance = 40 ml. per minute.

9.4.52 : Blood urea = 60 mg. per 100 ml.

	Volume of urine ml.	Urine urea mg. per 100 ml.
1	88	1,620
2	78	1,800
3	70	1,680

Creatinine clearance not recorded.

The skull showed diffuse miliary mottling. On September 19th, 1951, a sternal puncture showed active normoblastic marrow; there was no evidence of myelomatosis. On September 20th a part of the metacarpal was removed for biopsy. Microscopical examination (S.D. 3971/51) strongly suggested generalised osteitis fibrosa.

The biochemical and renal function tests are shown in Tables VIII, IX and X.

On October 3rd the neck was explored. A parathyroid tumour was removed; it weighed 5·5 g. and was 2·5 × 2·5 × 2·0 cm. in size. Microscopical examination (S.D. 4263/51) confirmed the nature of the tumour.

Following operation she was given large doses of calcium, calciferol and fluids. Her general condition gradually improved, her polyuria and polydypsia have slowly diminished. Serial post-operative X-rays showed that all the bones have recalcified and the texture of the skull has returned to normal. She was subsequently re-admitted for a gynaecological operation. When last seen in December, 1952, she was very well. Her weight was 8 st. 10 lb.

Case 10.—Mr. J. G. (L.H. record No. 15396/50) was first admitted to the London Hospital under the Surgical Unit from July 10th to September 15th, 1950, with bilateral renal stones. He was admitted for a second time on October 22nd, 1951, with a provisional diagnosis of hyperparathyroidism.

Background.—He was born in 1894, and is married with three children. His wife and children are all well. He served in the Royal Artillery from January, 1915 to 1918. After demobilisation he worked in a grocer's shop, subsequently working in a glass works, as a steeple-jack, and since 1921 as an electrical engineer. He smokes about ½ oz. tobacco a day and has an occasional glass of beer with friends. His bowels are regular without laxatives. In 1939 at the age of 45 he developed arthritis. This came on suddenly and has considerably incapacitated him. He had three courses of gold injections between 1939 and 1941. Since 1948 the deformity has not progressed, and he has been more free from pain than in the previous years.

TABLE XI

J. G.

BIOCHEMICAL DATA

Date	Blood Urea mg. per 100 ml.	Serum Calcium mg. per 100 ml.	P. in Phos. mg. per 100 ml.	Alkali Phosphatase units
12. 4.50	30			
5. 6.50	60	11·4	4·8	
8. 6.50		11·6		
1. 8.50	36			
16. 5.51		11·0		
23.10.51	42	11·2	3·0	10·5
24.10.51		11·2		
25.10.51		11·1		
26.10.51		11·3		
27.10.51		11·3		
31.10.51		Excision parathyroid tumour		
1.11.51		10·5		
2.11.51		9·4	4·8	7·0
3.11.51		8·6		
5.11.51		8·8		
7.11.51		9·8		
30. 1.52		9·3		
8. 7.52		10·4	4·4	5·5

TABLE XII

J. G.

URINARY CALCIUM EXCRETIONS

Date	Diet	Volume Urine ml./24 hrs.	Total Urinary Calcium mg./24 hrs.	Calcium mg. per 100 ml.
22.10.51	Normal Calcium	1,280	320	24·2
23.10.51	,, ,,	1,870	436	23·3
24.10.51	Low Calcium	2,030	294	14·5
25.10.51	,, ,,	1,970	306	15·5
26.10.51	,, ,,	2,170	293	13·5
31.10.51		Excision of parathyroid tumour		
6.11.51	High Calcium	2,180	113	5·2

He stated that he was always a great drinker of water and eater of bread. In 1946 he passed blood in his urine. In 1949 and 1950 he had attacks of left renal colic, and was referred to a local hospital in Kent where an X-ray showed bilateral renal stones. He was therefore referred to the London Hospital. X-rays of the skull, pelvis, radius and ulna taken on June 22nd, 1950, showed no abnormality. The total plasma protein estimated on June 5th was 8 g. per 100 ml. On June 9th and July 11th, 1950, right and left pyelolithotomies were performed. Analysis of the stones showed that they both consisted of calcium oxalate and phosphate. At the time of this admission his weight was 7 st. 13 lb. He was followed in Outpatients; an intravenous pyelogram on February 12th, 1951, showed good renal function and normal ureters. In view of the raised serum calcium he was again admitted to the London Hospital on October 22nd, 1951. Examination at this time showed a healthy-looking man with marked deformities of the hands. There were the scars of the previous operations. The B.P. was 140/80. His weight was 9st. 3lb. In view of the biochemical findings, which are set out in Table XI, his neck was explored on October 31st, 1951. Both upper and the right lower parathyroids were seen to be normal. In the position of the left lower there was a tumour weighing 950 mg.

Microscopical examination (S.D. 4572/51) confirmed the diagnosis of a parathyroid tumour. Following operation his progress was satisfactory except that he passed one small stone. When seen in November, 1952, he said that he had not felt so well for years, and could do more with his hand than at any time since the onset of his arthritis.

Case 11.—Mrs. A. E. (L.H. record No. 6571/51) was referred to the London Hospital on February 15th, 1951, with a letter from her private doctor. She was referred to the Department of Physical Medicine with a provisional diagnosis of " intercostal fibrositis." She was admitted from January 25th to March 14th, 1952, under the care of Dr. Donald Hunter.

Background.—She was born in 1902 and married in 1921. She has had ten pregnancies, the last being in 1946. One ended with a still birth at seven months; one child died at three weeks with gastro-enteritis; one child has paralysis following meningitis; the remaining seven are well. She takes senna regularly for her bowels. Her last menstrual period was in June, 1951. She does not smoke but has an occasional glass of beer. Her weight, 10 st. 6 lb., has remained constant during the year she has attended hospital.

Since her last pregnancy, in 1946, she has felt tired and found things too much for her. During 1948 she developed a craving for water and since then she has

taken a jug of water to bed ; she has passed a lot of urine. In 1950 she developed pain in the left loin but when this subsided in 1951 she developed pain under the right ribs. Following a normal cholecystogram she was given various placeboes. As these proved ineffective she was referred to the Department of Physical Medicine in July, 1951. Her symptoms improved until early 1952 when she developed a constant gnawing pain in the right groin and thigh. Following an X-ray of the pelvis and right femur which revealed cystic areas in both iliac bones, and the femur, and destruction of the superior ramus of the right pubic bone, she was referred back to Dr. Hunter's Outpatients.

Examination showed a pale, co-operative woman. No lump could be felt in the neck. The B.P. was 170/90. Apart from this there was no other abnormality. The specific gravity of the urine was 1011 ; it contained a trace of albumin. There was no Bence Jones protein. The haemoglobin was 75 per cent. Further X-rays of the skull, taken on January 7th, showed diffuse miliary mottling. There was a cystic area in the anterior part of the mandible.

She was admitted on January 25th, 1952. The serial biochemical data and renal function tests are set out in Table XIII. The total plasma protein on January 10th, 1952, was 7·2 g. per 100 ml.

On February 15th, 1952, a parathyroid adenoma 2·4 × 1·0 × 0·8 cm. in size weighing 1·8 g. was removed from behind the right lobe of the thyroid. Microscopical examination (S.D. 715/52) confirmed the nature of the tumour.

The pains in her limbs and the craving for water ceased immediately after operation.

Her weight went up to 12 st. 6 lb. in July, 1952, when she was referred to the Dietetic department. It has since remained about 12 st. She feels very well. The cysts in the femur and pelvis have recalcified ; the skull has regained its normal pattern.

TABLE XIII

MRS. A. E.

BIOCHEMICAL DATA

Date	Blood Urea mg. per 100 ml.	Serum Calcium mg. per 100 ml.	P. in Phos. mg. per 100 ml.	Alkali Phosphatase units
10. 1.52		14·0	3·0	21·0
26. 1.52		13·6	3·0	33·0
30. 1.52	45			
5. 2.52		13·7	2·6	37·0
11. 2.52		13·6	2·8	30·0
15. 2.52		Parathyroid tumour excised		
16. 2.52	65	10·2		
17. 2.52		8·4		
18. 2.52	120	7·8		
19. 2.52	138	7·7	3·0	41·5
20. 2.52	96	7·0		
21. 2.52	75	7·2		
22. 2.52	66	7·2	3·3	28·5
23. 2.52	60	7·2		
24. 2.52		7·2		
25. 2.52	45	7·6		
26. 2.52	45	8·4		
27. 2.52		7·8		
28. 2.52	38	7·8		
14. 3.52		10·8	3·0	19·5
6. 8.52	36	9·8	4·4	11·0
17.12.52	51	10·5	3·8	3·2

TABLE XIV

MRS. A. E.

URINARY CALCIUM EXCRETIONS

Date	Diet	Volume Urine ml./24 hrs.	Total Urinary Calcium mg./24 hrs.	Calcium mg. per 100 ml.
30. 1.52	Normal Calcium	1,960	400	20·3
31. 1.52	,, ,,	680	104	15·3
1. 2.52	,, ,,	2,955	563	19·0
2. 2.52	Low Calcium	1,620	380	23·5
3. 2.52	,, ,,	1,920	389	20·3
4. 2.52	,, ,,	2,105	190	9·0
5. 2.52	,, ,,	1,930	371	19·3
15. 2.52		Excision parathyroid tumour		
25. 2.52	High Calcium	960	21	2·2
28. 2.52	,, ,,	2,700	32	1·2
29. 2.52	,, ,,	1,490	44	3·0

Case 12.—Mrs. M. S. (L.H. record No. 41373/51) was first admitted to the London Hospital under the care of Dr. John Ellis from October 27th, 1951, to December 16th, 1951. Her second admission was from May 26th, 1952, to August 1st, 1952. She died September 16th, 1952.

Background.—She was born in 1907 and was married but had no children. Her husband, a bank official, was well. In 1944 she was found to have pulmonary tuberculosis. Her periods ceased in February, 1950.

In 1948 her right breast was removed for a carcinoma at Whipps Cross Hospital. In September, 1950, she developed attacks of polyuria and polydypsia. During these attacks she had anorexia and vomiting. The length and frequency of the attacks increased. She said that she had lost two stone in weight in the few months prior to her first admission. Examination on October 27th, 1951, showed a thin woman who weighed 6 st. 7 lb. There was the scar of the previous operation. The B.P. was 125/80. No abnormality was detected in the lungs, heart, or nervous system.

The serum calcium was 11·8 mg. per 100 ml. on November 13th, and 12·0 mg. per 100 ml. on November 24th. The plasma inorganic phosphorus was 3·8 mg. per 100 ml. On November 14th the total plasma proteins were 6·5 g. per 100 ml. with 4·0 g. albumin and 2·5 g. globulin. The alkaline phosphatase was 21 units. A blood count on October 29th, 1951, showed 86 per cent. haemoglobin, 9,900 leucocytes with a differential count of 81 per cent. polymorphs, 12 per cent. large lymphocytes 6 per cent. monocytes, and 1 per cent. neutrophil-myelocytes. The red cells and platelets were normal. On November 15th sternal puncture showed a normal bone marrow. A chest X-ray on October 29th showed the fibrosis of pulmonary tuberculosis. There was a cyst in the sixth right rib. No abnormality was found in the right humerus, radius, ulna or hand. The skull showed fine mottling. The renal function tests on November 1st, 1951, were as follows :—

Blood urea = 54 mg. per 100 ml. 15 g. of urea given.

	Volume of urine ml.	Urine urea mg. per 100 ml.
1	140	1,140
2	110	1,260
3	110	1,320

Creatinine clearance = 30 ml. per minute.

These tests were repeated on November 23rd, 1951 :—

Blood urea = 48 mg. per 100 ml. 15 g. of urea given.

	Volume of urine ml.	Urine urea mg. per 100 ml.
1	150	1,200
2	70	1,260
3	90	1,380

Creatinine clearance = 44 ml. per minute.

The results of measurements of urinary calcium excretions are shown in Table XV. The urine contained albumin but no Bence-Jones protein. The specific gravity was also low, about 1007.

At the time of the second admission, on May 26th, 1952, she weighed 7st. 3lb., the serum calcium was found to be 16·5 mg. per 100 ml. (this was checked) and the alkaline phosphatase 7·7 units. On June 6th the serum calcium was 17.0 mg. per 100 ml. and the alkaline phosphatase 9·0 units. The plasma inorganic phosphorus was 3·0 mg. per 100 ml. on June 11th. On May 25th the blood count was essentially unchanged and the renal function tests on June 3rd were :

Blood urea = 66 mg. per 100 ml.

	Volume of urine ml.	Urine urea mg. per 100 ml.
1	80	660
2	240	840
3	120	1,020

Creatinine clearance = 58 ml. per minute.

On May 27th, 1952, all X-rays of the chest, skull, and right femur were reviewed by Dr. Jupe who said there was, after seven months, very little change and he did not think the appearances were like those of secondary bone deposits. The patient died on September 16th, 1952, and at necropsy (326/52) there was diffuse secondary carcinoma in the mediastinal gland and in the affected bones. There was evidence of the previous pulmonary tuberculosis. Three normal parathyroid glands were found.

" The kidneys were slightly unequal in size (weighing 16oz. together); their surfaces were smooth and the cortical pattern unaltered. Fine chalky flecks were occasionally identified in the cortex, and were more abundant in the medulla.

"*Microscopic.*—There is extensive fibrosis, of uneven density, throughout the cortex but occasional small islands of tubules are spared. Atrophy of the tubules and a few ischaemic glomeruli are found in the denser areas of fibrosis. The glomeruli are otherwise normal.

" The tubules show advanced post-mortem degeneration. Fairly abundant conglomerations of calcified material occupy the lumina of second convoluted tubules and are impacted, as larger masses, in the collecting tubules. The basement-membranes of occasional groups of first convoluted tubules are thickened by similar material. The larger collections in the medulla are sometimes associated with foreign-body giant-cells and proliferating fibroblasts. In the medulla and lower cortex of the left kidney the calcified masses sometimes occupy cyst-like spaces.

"*Comment.*—The kidney in Case 12 closely resembles those of Cases 2 and 6, and particularly Case 6. That metastatic calcification was a pronounced feature in this case is also demonstrated by calcified deposits in the mucosa of the stomach, the alveolar walls in the lungs and in the endocardium of the left auricle. The metastatic calcification was attributable to osteoclastic carcinomatous deposits in the bones secondary to a primary carcinoma of the breast."

TABLE XV

MRS. M. S.

URINARY CALCIUM EXCRETIONS

Date	Diet	Volume Urine ml./24 hrs.	Total Urinary Calcium mg./24 hrs.	Calcium mg. per 100 ml.
23.11.51	Normal Calcium	3,040	14·5	435
24.11.51	,, ,,	3,350	15·0	472
25.11.51	,, ,,	3,320	13·2	438
26.11.51	Low Calcium	2,870	13·0	373
27.11.51	,, ,,	2,460	15·8	388
28.11.51	,, ,,	1,960	18·0	353

NOTES

The alkali phosphatase, except where stated, has been recorded in King-Armstrong units, the normal range being 3-13. The content of calcium in the normal diets is about ·900 g., a low calcium diet contains ·200 g. and a high calcium diet at least 10 g. A full bibliography and a discussion on the physiological disorder is given in *The Lancet* annotation. The control weights for normal parathyroids are taken from J. R. Gilmore's paper.[5]

I wish to thank the physicians and surgeons of the hospital who allowed me to use their cases, Professor V. W. Dix and Mr. G. C. Tresidder for giving me access to all their cases of renal stones, Mr. A. J. Walton who screened these cases, and Dr. Denys Jennings for his help in preparing this paper. The pathological reports on the kidneys are by Professor Dorothy Russell to whom I am most grateful.

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