We in Australia, after 15 years of running repairs and alterations, have a vehicle in need of a major overhaul. Like you in Britain, our difficulties are basically those of finance, how best to obtain and apply this to provide all members of the community with complete cover.

It has become apparent that our ideas on the basic philosophy of national health care are again approximating, and that our paths, at present as antipodean as our countries, are converging.

Both our countries can gain much from each other in their efforts to provide, on a national scale, readily available medical care of the highest standard. This we shall both achieve if all concerned approach the task with open minds, actuated by the highest motives, basing their decisions on facts and diligently pursuing one common purpose.

What would have been the reaction of those distinguished gentlemen who attended that 65th Annual Meeting if they could perchance be with us this week? Roddick would no

doubt have exhorted us to continue our efforts to achieve a national registration board. Lister would have experienced great satisfaction in the progress of surgery. Osler would doubtlessly have regarded our progress in the control of medical practice with "equanimity."

All three would assuredly survey the advances of science and technology with amazement, and we trust they would approve the progress made towards maturity, and promised in our "vigorous infancy," of "British Medicine in Australia."

When the time arrives for your return to your homes we hope that you will take with you many happy memories of your stay in this land of Australia, new friendships, and an enhanced knowledge and appreciation of our country, its people, and their way of life.

We, for our part, shall long cherish this occasion and treasure the wisdom you bring with you, as well as the great personal pleasure we have in this meeting with you.

Tertiary Hyperparathyroidism

D. R. DAVIES,* F.R.C.S.; C. E. DENT,* F.R.C.P.; LYAL WATSON,* F.R.A.C.P.

Brit. med. J., 1968, 3, 395-399

Summary: In our first 200 cases of primary hyperparathyroidism confirmed by operation 12 were also shown to have a long history either of a malabsorption syndrome or of chronic renal-glomerular failure. We consider that they first went through a phase of secondary hyperparathyroidism, during which one or more of the glands became autonomous adenomata. This then produced the biochemical changes of "primary" hyperparathyroidism, necessitating excision of the adenoma. This condition is best described as "tertiary" hyperparathyroidism. The transition from secondary to tertiary hyperparathyroidism occurred in four of the 12 patients while under our observation. We think the same process can be traced retrospectively in the other eight cases. The concept of tertiary hyperparathyroidism may help to explain the high incidence of other diseases in association with primary hyperparathyroidism.

The behaviour of the parathyroid glands provides a valuable model for the investigation of tumour formation in man. All states occurred in our patients with primary hyperparathyroidism, from normal through hyperplasia to adenoma formation and finally to parathyroid carcinoma.

Introduction

In 1956 Davies, Dent, and Willcox described the case of a patient with steatorrhoea and osteomalacia (their Case 2). She appeared to have suffered from lifelong coeliac disease, but her plasma calcium level was persistently raised even before treatment with vitamin D, and there was only a partial response of the osteomalacia when vitamin D treatment was given. After two parathyroid adenomata were later removed at operation the patient was cured of her hypercalcaemia and then responded normally to vitamin D. Davies *et al.* concluded: "In some cases of steatorrhoea a parathyroid hyperplasia occurs which is reversible with vitamin D treatment. In other cases, however, presumably of longer duration, one or more adenomata will develop."

* University College Hospital, London W.C.1.

Dent (1962) presented further evidence that autonomous hyperparathyroidism with adenoma formation may have developed from a background of secondary parathyroid hyperplasia both in malabsorption syndromes and in chronic renal-glomerular failure. Other reports followed. The Case Records of the Massachusetts General Hospital (1963) reported the case of a patient with a long history of progressive chronic pyelonephritis who gradually developed hypercalcaemia. At operation a parathyroid adenoma was removed and this patient was considered to be the first case of secondary hyperparathyroidism developing under biochemical observation into primary hyperparathyroidism in the way that Davies *et al.* (1956) had postulated retrospectively in their patient. During the discussion of the case Dr. Walter St. Goar suggested the use of the term "tertiary" hyperparathyroidism to describe such cases in which autonomous parathyroid adenomata causing hypercalcaemia apparently developed from a background of reactive (or secondary) parathyroid hyperplasia. Though the term is not ideal we think it is the best available.

Other cases of supposed tertiary hyperparathyroidism have since been described by McPhaul *et al.* (1964), Golden *et al.* (1965), and Ludwig *et al.* (1967). In addition Glanville and Bloom (1965) described one of our patients with adult-presenting "vitamin D resistant" osteomalacia who developed hypercalcaemia under observation and from whom we then removed a parathyroid adenoma. Among our first 200 patients with hyperparathyroidism confirmed at operation there are 12 probable cases of tertiary hyperparathyroidism and two possible cases. Only three of these 14 cases arose on the basis of longstanding renal failure, a situation presenting particular difficulties in retrospective diagnosis, and in interpretation of plasma electrolyte levels.

Case Material

The 12 probable cases of tertiary hyperparathyroidism are listed in Table I. Five of these have been reported elsewhere (as shown in the Table), three as such and two others in papers dealing with other clinical aspects of hyperparathyroidism. Short case reports of the remaining seven are included in this

TABLE I.—Details of Patients with Tertiary Hyperparathyroidism

Case No.	Age and Sex	Year of Operation	Representative Preoperative Chemical Findings*			Evidence of Bone Disease		Operative Findings	Aetiological Factor	Previously Reported
			Ca (mg./100 ml.) S.G. in Parentheses	P (mg./100ml.)	P'ase (K.A. Units)	Osteomalacia	HPT†			
5	64 F	1951	14.5	2.5	63	None	X-ray	Adenoma 9.5 g.	Gluten-sensitive enteropathy	Dent and Garretts (1960)
11	41 F	1955	11.4	2.0	69	X-ray	X-ray	2 adenomata 150 mg. and 1 g.	Gluten-sensitive enteropathy	Davies <i>et al.</i> (1956)
57	60 F	1960	10.0 (1024)	3.9	9	None	X-ray	Adenoma 1.8 g.	Renal glomerular failure	Dent (1962)
59	48 M	1960	12.7	2.0	31	X-ray	X-ray	Adenoma 4.5 g.	Polycystic kidneys	
91	59 F	1963	10.9→12.6 (1028)	2.2	15	None	None	Adenoma 1.5 g.	Gluten-sensitive enteropathy	
107	46 M	1964	9.6→10.8 (1028)	1.8	28	X-ray	None	Adenoma 1.2 g.	Vitamin-D-resistant osteomalacia	Glanville and Bloom (1965)
138	67 F	1965	10.4 (1025-6)	2.8	17	X-ray	X-ray	Adenoma 800 mg.	Postgastrectomy	
144	46 F	1965	11.6 (1025-6)	1.9	13	Biopsy	X-ray	Adenoma 2.4 g.	Gluten-sensitive enteropathy	Smith and Stern (1967)
146	65 F	1965	9.3→10.7 (1021) (1024)	2.0	33	X-ray	None	Adenoma 500 mg.	Postgastrectomy	
147	47 F	1966	9.6→11.7 (1025-6) (1026-7)	1.4	37	X-ray, Biopsy	X-ray, Biopsy	Adenoma 3.1 g.	Gluten-sensitive enteropathy	
158	28 F	1966	9.7→10.3 (1024) (1024)	2.5	131	Biopsy	X-ray, Biopsy	Adenoma 2 g.	Gluten-sensitive enteropathy	
185	72 F	1967	11.3 (1024)	2.2	9	X-ray, Biopsy	None	Adenoma 1 g.	Postgastrectomy	

* Arrows indicate rises observed while under follow-up.
† Osteitis fibrosa generalisata.

paper. Data from three of these latter patients are plotted in Figs. 1-3. The chart of Case 107 has been redrawn from the original publication (Glanville and Bloom, 1965) and brought up to date as Fig. 4.

Total plasma calcium was determined on the Eppendorf flame photometer (normal range 9-10 mg./100 ml. after correction to a specific gravity of 1027 as described by Dent (1962)). Ionized calcium was determined by the method of Rose (1957), with minor modifications (normal range 5-5.8 mg./100 ml.).

FIG. 1.—Case 146. Plasma levels in married woman who developed tertiary hyperparathyroidism while under treatment for osteomalacia following long after a partial gastrectomy operation.

All patients had significant hypercalcaemia before diagnosis was finally established at operation. In four cases (Nos. 146, 147, 158, and 107) hypercalcaemia developed while the patients were under our observation, usually while treatment with vitamin D was being given for osteomalacia (see Figs. 1-4). In two of these (146 and 158) the important plasma ionized calcium fraction was shown to rise from normal to abnormal levels (normal range 5-5.8 mg./100 bl.). In a third (Case 107) the ionized calcium rose from 5.9 in 1957 (normal range then below 6.2 mg./100 ml.) to 6.4 in 1964 (normal range then below 5.8 mg./100 ml.); this was useful additional information in establishing the presence of significant hypercalcaemia in patients whose plasma total calcium levels were only marginally raised. It is likely that the biochemical changes observed in these four individuals show the course of development of all 12 cases.

FIG. 2.—Case 147. Plasma levels in married woman who developed tertiary hyperparathyroidism while under treatment for the osteodystrophy complicating gluten sensitive steatorrhoea. She has refused follow-up since 1966. DHT=Dihydroxycholesterol.

As in primary hyperparathyroidism women were much more commonly affected than men, 10 of the 12 patients being women. Their ages ranged from 28 to 72 years. It can be seen from the serial numbers that the apparent incidence of cases of tertiary hyperparathyroidism increased when its importance became clearer. Five different aetiological factors were concerned—gluten-sensitive enteropathy six times, postgastrectomy osteomalacia three times, adult presenting “vitamin-D-resistant” osteomalacia, polycystic kidneys, and prolonged renal-glomerular failure of unknown cause once each. In this series there were many more cases associated with malabsorption syndromes than with chronic renal failure.

It could be argued that the three patients who had undergone partial gastrectomy for peptic ulcer were suffering from primary hyperparathyroidism which was missed initially. It should be noted, however, that hypercalcaemia was seen to develop in one case (No. 146) and that in the other two cases gastrectomy was performed 16 years (Case 138) and 20 years (Case 185) before parathyroidectomy, with a clear-cut phase of osteomalacia intervening. It is more reasonable to suggest that all three were cases of tertiary hyperparathyroidism.

FIG. 3.—Case 158. Plasma levels in married woman who developed tertiary hyperparathyroidism while under treatment for the osteodystrophy complicating gluten-sensitive steatorrhoea.

Though osteomalacia was present in most cases, only eight patients had parathyroid bone disease (osteitis fibrosa generalisata) as determined by radiological and histological criteria. Thus it appears that tertiary hyperparathyroidism may occur with and without parathyroid bone disease, like primary hyperparathyroidism.

FIG. 4.—Case 107. Plasma levels in a man who developed tertiary hyperparathyroidism while under treatment for renal tubular (type 2) osteomalacia.

All patients were found to have at least one parathyroid adenoma at operation. In one (Case 11), the case reported by Davies *et al.* (1956), there were two adenomata. The histological features of these cases will be described independently by Professor J. Smith.

Case 59

This patient, a man born in 1912, became unwell at about the age of 40, when he complained of dyspepsia and upper abdominal pain. He became anaemic and had at least one episode of haematemesis and melaena. No peptic ulcer was demonstrated. He was treated symptomatically and was better until about the age of 46, when he began to suffer from bone pain and slowly to lose height. Two years later, when he developed muscular weakness and severe bone pain, he was fully investigated and found to have raised plasma calcium, lowered plasma phosphorus, and raised plasma alkaline phosphatase levels. Skeletal radiographs showed typical changes of both hyperparathyroidism and osteomalacia.

His neck was explored and a parathyroid adenoma weighing 4.5 g. was removed. He had a faecal fat excretion of 5.8 g./day and a slightly raised blood urea (45–48 mg./100 ml. before operation, rising to 99 mg./100 ml. a week after the stress of parathyroidectomy). Postoperatively his symptoms improved considerably but he continued to have high faecal fat excretions (up to 10 g. daily) and his blood urea slowly rose. About five years after parathyroidectomy he had become severely uraemic and he died of uraemia at the age of 55. At necropsy there was no abnormality in the gut, but both kidneys showed typical appearances of polycystic disease.

Case 91

A married woman, born in 1903, had a long history of steatorrhoea with pale bulky stools. She was investigated at University College Hospital in 1961, when she was found to have a daily fat excretion of 14.4 g., an atrophic jejunal mucosa, and a plasma calcium of 10.9 mg./100 ml. She was started on a gluten-free diet, and her plasma calcium slowly rose to 12.6 mg./100 ml. in June 1963. She was then readmitted for further investigation; this showed that the steatorrhoea was still present and that she also had three calculi in the right kidney. The chemical findings were typical of hyperparathyroidism and it was thought that she had tertiary hyperparathyroidism after a period of secondary hyperplasia resulting from gluten-sensitive enteropathy with malabsorption. A parathyroid adenoma was removed from her neck in July 1963.

Case 138

A married woman, born in 1898, had a partial gastrectomy performed at the age of 51 for pyloric stenosis complicating peptic ulceration. About 10 years later she began to experience difficulty in walking which became more severe and was later associated with bone pain and mental symptoms. A radiological diagnosis of osteomalacia was made and treatment with vitamin D was started. Her plasma calcium (initially 10.7 mg./100 ml., and interpreted as normal from that hospital laboratory) then rose rapidly to 13 mg./100 ml. and vitamin D was discontinued though her muscular weakness and mental symptoms had improved considerably during vitamin D treatment. She was first seen at University College Hospital in May 1965 at the age of 67, when her height was 156 cm. and weight 48.4 kg. She was found to have a slightly raised plasma calcium level with a high ionized calcium fraction (6.3 mg./100 ml.), neither of which fell during a standard hydrocortisone test (40 mg. eight-hourly for 10 days, tailing off over a few days after this, plasma taken for calcium determination at 0, 5, 8, and 10 days—for further discussion about our decision to change from cortisone to hydrocortisone, see Dent and Watson (1966)). The faecal fat excretion was 7.7 g./day.

She was thought to have tertiary hyperparathyroidism following a period of secondary hyperparathyroidism and osteomalacia resulting from partial gastrectomy. A parathyroid adenoma was removed at operation, after which she needed treatment with vitamin D for some months in order to prevent hypocalcaemia.

Case 146

A married woman, born in 1900, had a partial gastrectomy performed for peptic ulceration at the age of 45 following a 10-year history of repeated epigastric pain and frequent haematemesis. At about the age of 60 she began to suffer from muscular weakness and tender bones. She was first seen at University College Hospital in June 1961, when her height was 166 cm., weight 43 kg., and the clinical diagnosis of osteomalacia was confirmed by chemical and radiological findings. Plasma total and ionized calcium levels were normal (9.3 and 5.6 mg./100 ml. respectively). There was no evidence of steatorrhoea, and other negative findings included normal intestinal biopsy and normal urinary acidification following an acid load.

She was treated with vitamin D, which brought clinical improvement and radiological healing; her plasma alkaline phosphatase level, previously raised, also returned to normal. However, her plasma calcium level soon rose and remained above normal, with a high ionized calcium fraction (6.1 mg./100 ml.), even after vitamin D was stopped (see Fig. 1) and following a standard hydrocortisone test. A diagnosis of tertiary hyperparathyroidism was then made and a parathyroid adenoma was removed from her neck. There was no evidence of parathyroid bone disease, radiologically or on bone biopsy, at any time.

Case 147

A married woman, born in 1918, developed progressive bone pain followed by muscular weakness beginning in 1960 at about the age of 42. She was first seen at University College Hospital in January 1964, when her height was 153 cm. and weight 47.5 kg. She had bony tenderness and a waddling gait, and skeletal radiographs showed evidence of osteomalacia and hyperparathyroidism. She had steatorrhoea (27 g. fat daily) and subtotal villous atrophy consistent with a diagnosis of gluten-sensitive enteropathy complicated by osteomalacia and secondary hyperparathyroidism. The plasma calcium was 9.6 mg./100 ml. and the urinary calcium was 200 mg./day, and it was suspected at once that she might be developing tertiary hyperparathyroidism, as both values were higher than usual in uncomplicated steatorrhoea.

This suspicion was confirmed by the subsequent course (see Fig. 2). She responded well to gluten-free diet and vitamin-D administration, rapidly becoming pain-free and developing more muscular power. However, her plasma calcium level slowly rose to 11.2 mg./100 ml. and continued to rise even after vitamin-D was stopped. At the same time her plasma alkaline phosphatase fell to normal. A diagnosis of tertiary hyperparathyroidism was made, and a parathyroid adenoma weighing 3.1 g. was removed from the neck. Postoperatively she has remained well on a gluten-free diet as sole treatment.

Case 158

A married woman, born in 1937, became unwell at the age of 24 during her first pregnancy. After delivery she had severe fatty diarrhoea and rapid weight loss (10 kg.). One year later progressive muscular weakness began, followed by bone pain and ankle-swelling. After extensive investigations at the National Hospital, Queen Square, which indicated that she was suffering from metabolic bone disease, she was referred to University College Hospital in June 1965 (height 164 cm., weight 45 kg.). She had marked proximal muscular weakness, and further investigation revealed steatorrhoea (faecal fat 23 g./day) and subtotal villous atrophy. Chemical and radiological findings were consistent with a diagnosis of secondary hyperparathyroidism (her plasma ionized calcium fraction was 5.6 mg./100 ml.) and osteomalacia complicating gluten-sensitive enteropathy. The diarrhoea and weakness responded well to gluten-free diet and vitamin D. She gained weight, but the bones remained tender.

The plasma calcium level rose to 10.5 mg./100 ml. and vitamin D was stopped (see Fig. 3). The level then fell somewhat, but it rose again without any further vitamin-D administration to 10.3 mg./100 ml. At this stage her plasma ionized calcium level was raised (6.4 mg./100 ml.) and radiological signs of parathyroid bone disease had increased. She had developed significant hypercalcaemia while under observation, and a diagnosis of tertiary hyperparathyroidism was made. A parathyroid adenoma weighing

2 g. was removed at operation. She needed vitamin D post-operatively, but has since remained well on a gluten-free diet as sole treatment.

Case 185

A married woman, born in 1894, had had recurrent epigastric pain for many years due to duodenal ulceration. Partial gastrectomy was performed at the age of 52; she was then reasonably well and had gained weight. About 15 years after operation abdominal pain recurred and she noticed a sense of "coldness" in the bones. She was shown to have steatorrhoea and iron-deficiency anaemia.

She was first seen at University College Hospital in April 1967, when she was found to have raised plasma calcium, lowered plasma phosphorus, and normal plasma alkaline phosphatase levels. Radiographs of the spine showed typical appearances of osteomalacia, and the bone biopsy showed excess osteoid tissue. There was no evidence of parathyroid bone disease. A diagnosis was made of tertiary hyperparathyroidism following postgastrectomy osteomalacia, and a parathyroid adenoma weighing 1 g. was removed at operation. Her postoperative recovery was uneventful and she has remained well without treatment.

Discussion

Primary hyperparathyroidism is not a rare disease, and in common with workers in other clinics we are meeting it with increasing frequency. At the time of writing we have diagnosed and treated over 200 patients with hyperparathyroidism, finding a single adenoma in most cases and much less commonly multiple adenomata, parathyroid carcinoma, or primary diffuse hyperplasia of all four parathyroid glands. Although there are reports of patients with primary hyperparathyroidism having normal plasma calcium levels, such cases have been uncommon in our experience even as a temporary phenomenon; all patients in our operative series have shown significant hypercalcaemia preoperatively, though the plasma calcium level was only marginally raised in many cases. They have usually presented with renal stones or osteitis fibrosa, though other modes of presentation, especially with mental and abdominal symptoms, are becoming increasingly common, and our list of accidental diagnoses (see Dent, 1962) increases steadily.

Secondary hyperparathyroidism is also a well-known disorder. It was defined by Albright and Reifenstein (1948) as "a condition where more parathyroid hormone is manufactured than is normal but where this hormone is needed for some compensatory purpose." Necropsy data indicate that hyperplastic enlargement of all four parathyroid glands may occur in chronic renal-glomerular failure and in association with rickets and osteomalacia of various causes. Such patients may also show the specific radiological signs of osteitis fibrosa as further evidence of excessive hormone production. They have low or normal plasma calcium levels, and the excessive parathyroid activity is presumed to be a purposeful reaction in an attempt to correct the hypocalcaemia which is the best, indeed the only definitely proved, stimulus to parathyroid hormone secretion. Our experience agrees with the views expressed by Albright *et al.* (1934), Howard (1961), David *et al.* (1962), and Golden *et al.* (1965) that true hypercalcaemia with a raised plasma ionized calcium level does not occur in uncomplicated secondary hyperparathyroidism, no matter how long the duration or how severe the degree of osteitis fibrosa.

Four of the 12 patients with tertiary hyperparathyroidism reported here (Cases 146, 147, 158, and 107) were typical cases of secondary hyperparathyroidism when we first saw them (see Figs. 1-4) in that their plasma total calcium levels were normal (and in three cases the ionized also), they had x-ray or biopsy evidence of osteomalacia or osteitis fibrosa with raised plasma alkaline phosphatase levels, and, for what it is worth, high renal phosphate clearances. During treatment they slowly developed biochemical (and in some cases clinical) changes characteristic of primary hyperparathyroidism, and at operation they all had

parathyroid adenomata, removal of which quickly cured the hypercalcaemia. We consider that these four patients were suffering from tertiary hyperparathyroidism, and we think we can make the same diagnosis retrospectively in the other eight cases reported here.

These distinctions between primary, secondary, and tertiary hyperparathyroidism have practical importance. Secondary hyperparathyroidism is best treated medically, and adequate control both of blood levels and of bone changes can be achieved by using the correct dose of vitamin D. Primary and tertiary hyperparathyroidism need surgical removal of autonomous parathyroid tissue in order to control the hypercalcaemia. The clue that tertiary hyperparathyroidism was developing in some of these patients was the inability to control osteomalacia by vitamin D treatment without producing hypercalcaemia. Later hydrocortisone-resistant hypercalcaemia persisted after vitamin D was stopped. Some patients developed symptoms of hypercalcaemia, and in some cases the symptoms of parathyroid bone disease were added to those of inadequately treated osteomalacia. All these features (hypercalcaemia, osteomalacia, and osteitis fibrosa) could be cured only after removal of the parathyroid adenoma.

The concept of tertiary hyperparathyroidism is perhaps of even greater general importance than in any practical application. Our patients with primary hyperparathyroidism have shown all stages of parathyroid histology from normal through hyperplasia to adenoma formation and finally cancer. One recent patient with what we still have to call primary hyperparathyroidism had two normal glands, one adenoma, and one carcinoma of her parathyroids. Clearly it is easier to interpret this as an instance of tertiary hyperparathyroidism of cause unknown than to assume the remarkable association by chance of such pathological changes in two of the glands. We consider, therefore, that the parathyroid glands provide a remarkable, perhaps unique, tissue for the clinical investigation of factors involved in tumour formation. The search for such factors is not new. Albright and Reifenstein (1948) were impressed by the occurrence of two separate parathyroid adenomata in three of their first 50 patients with primary hyperparathyroidism, and they speculated that there may have been a predisposing factor to adenoma formation at some time affecting all parathyroid tissue. They considered the possible roles of pregnancy (noting that parathyroid adenomata are at least twice as common in women as in men), low calcium intake, rickets, and chronic renal failure. However, they concluded that they were "not aware of any clinical evidence which definitely links hyperparathyroidism with a pre-existing rickets." We consider that the cases reported here provide such evidence.

Apart from clear-cut predisposing conditions such as malabsorption syndromes and chronic renal-glomerular failure there are associations of primary hyperparathyroidism with other diseases which are less well understood. Our first table along these lines was published in 1962 and concerned the first 80 cases (Dent, 1962). This is brought up to date in our Table II, which lists the diseases found in our first 200 patients after omitting the 12 with tertiary hyperparathyroidism which form the main body of this paper, and also omitting four patients from three families with polyglandular syndrome and three patients from one family with simple hereditary parathyroid hyperplasia. Both these latter conditions carry the strong presumption of another form of "tertiary" hyperparathyroidism, the stimulus to the glands being due to an unknown but clearly hereditary factor. From Table II have also been omitted disease manifestations likely to be caused by, rather than possibly predisposing to, the parathyroid overaction, such as depressive psychosis, gastritis, peptic ulceration, chondrocalcinosis, and otherwise unexplained osteomalacia. We have also omitted two patients with Paget's disease, since this common disorder could well have occurred by chance.

TABLE II.—Other Diseases Present in 51 of 181 Patients with Primary Hyperparathyroidism

Relapsing pancreatitis ..	7	Cancer of cervix ..	1
Pulmonary tuberculosis ..	5	Cancer of breast ..	1
Thyrotoxicosis ..	5	Ulcerative colitis ..	1
Rheumatoid arthritis ..	5	Sarcoidosis ..	1
Gallstones ..	4	Horseshoe kidney ..	1
Gout ..	4	Pituitary tumour ..	1
Parkinsonism ..	3	Ankylosing spondylitis ..	1
Cushing's syndrome ..	2	Rheumatic fever ..	1
Diabetes mellitus ..	2	Nephrogenic diabetes insipidus ..	1
Epilepsy ..	2	Fluorosis of teeth ..	1
Pernicious anaemia ..	2	Nodular goitre ..	1
Gammopathy ..	2	Idiopathic osteoporosis ..	1
Cancer of thyroid ..	1	Alzheimer's disease ..	1
Cancer of ovary ..	1	Raynaud's phenomenon ..	1

28 diseases in 51 patients, occurring 59 times altogether.

Even with these omissions 181 patients are left, of whom 51 have 28 diseases between them, many repeatedly occurring and all being of chronic duration. We think the list is much larger than would be expected from 181 members of a comparable group taken at random from the community. We suspect that in time some of these diseases may be shown to produce secondary hyperparathyroidism commonly enough for a proportion of them to progress to the condition of tertiary hyperparathyroidism. We commented on this question before when discussing the cases in which hyperparathyroidism was associated with carcinoma of the cervix uteri (Dent and Watson, 1964) and with sarcoidosis (Dent and Watson, 1966). Since our knowledge of sarcoidosis and of cervical cancer is itself so inadequate it was difficult to guess intelligently at the nature of the association; but we suggest that it is feasible to check the theory by systematically searching for secondary hyperparathyroidism in any patient with one of the diseases shown in Table II. This would require measurement of plasma calcium, phosphorus, and alkaline phosphatase levels in life, and also bone x-ray and biopsy examination if possible. If the patient dies, post-mortem studies of the parathyroid glands would be most important, since this was how most of our knowledge of secondary hyperparathyroidism was first obtained. If thus proved, still more cases of primary hyperparathyroidism will need to be reclassified as tertiary.

We wish to thank all the doctors, nurses, biochemists, and dietitians who helped us with the care of these patients. We are grateful to Mr. V. K. Asta for the diagram. One of us (L.W.) is in receipt of a generous grant from the British Empire Cancer Campaign.

REFERENCES

- Albright, F., Baird, P. C., Cope, O., and Bloomberg, E. (1934). *Amer. J. med. Sci.*, **187**, 49.
- Albright, F., and Reifenstein, E. C. (1948). *The Parathyroid Glands and Metabolic Bone Disease*. London.
- Case Records of Massachusetts General Hospital (1963). *New Engl. J. Med.*, **268**, 943.
- David, N. J., Verner, J. V., and Engel, F. L. (1962). *Amer. J. Med.*, **33**, 88.
- Davies, D. R., Dent, C. E., and Willcox, A. (1956). *Brit. med. J.*, **2**, 1133.
- Dent, C. E. (1962). *Brit. med. J.*, **2**, 1419, 1495.
- Dent, C. E., and Garretts, M. (1960). *Lancet*, **1**, 142.
- Dent, C. E., and Watson, L. (1964). *Brit. med. J.*, **2**, 218.
- Dent, C. E., and Watson, L. (1966). *Brit. med. J.*, **1**, 646.
- Glanville, H. J., and Bloom, R. (1965). *Brit. med. J.*, **2**, 26.
- Golden, A., Canary, J. J., and Kerwin, D. M. (1965). *Amer. J. Med.*, **38**, 562.
- Howard, J. E. (1961). *The Parathyroids*, edited by R. O. Greep and R. V. Talmage, p. 460. Springfield, Illinois.
- Ludwig, G. D., Kyle, G. C., and de Blanco, M. (1967). *Amer. J. Med.*, **43**, 136.
- McPhaul, J. J., jun., McIntosh, D. A., Hammond, W. S., and Park, O. K. (1964). *New Engl. J. Med.*, **271**, 1342.
- Rose, G. A. (1957). *Clin. chim. Acta*, **2**, 227.
- Smith, R., and Stern, G. (1967). *Brain*, **90**, 593.