THE ELLISON-ZOLLINGER SYNDROME AND HYPERPARATHYROIDISM IN RECURRENT PEPTIC ULCERATION

I. COLL, M.B., B.CH. (RAND), F.R.C.S. (ENG.), F.R.C.S. (EDIN.), *Registrar, Addington Hospital, Durban*

The occurrence of hyperparathyroidism does not often warrant its publication. However, the growing realization that recurrent peptic ulceration is not uncommonly associated with endocrine imbalance is the reason for this timely reminder. The unabated and relentless progress of ulceration in the upper gastro-intestinal tract has been, in recent years, tied up with non-insulin secretory tumours of the islet cells of the pancreas (α, γ, and Δ cells). The recent literature abounds with reports of the so-called Ellison-Zollinger syndrome;[1] they all stress the importance of multiple endocrine dysfunction. When we attempted to prove that our case was an example of this syndrome, this knowledge of endocrine interdependence was helpful and led to the diagnosis of a parathyroid adenoma.

CASE REPORT

Mrs. A. G., aged 37, first presented in November 1956 complaining of epigastric pain of 6 weeks' duration. The pain was related to meals and relieved by alkalis. She was often awakened by the pain at night, which was only partially relieved by the usual medication and diet. Vomiting occurred after meals and relieved the pain. Loss of weight had been quite marked. Examination revealed no obvious cause and a barium meal showed a duodenal ulcer. She was treated as an inpatient for 6 weeks without improvement. She continued on an ulcer régime and was first seen at this hospital in February 1957. Her symptoms and signs were of such severity that she was admitted with the diagnosis of pancreatitis.

A barium meal confirmed the presence of a duodenal ulcer, and she remained in hospital for 1 month on strict medical treatment. Her poor progress is shown by the fact that within 3 days of discharge she was re-admitted with the diagnosis of an acute flare-up of a peptic ulcer. A barium meal on this occasion (1 month after the previous X-ray) showed no change in the duodenal deformity. Gastric analysis showed a hydrochloric-acid level of 70 mEq. per litre (normal 20 - 50 mEq. per litre). The pH was not recorded. A decision was made to operate because of the lack of response to medical treatment. In April 1957 a laparotomy confirmed the presence of a penetrating duodenal ulcer and an ante-colic Polya gastrectomy was performed. Her convalescence was smooth and she was discharged from hospital fairly well 3 weeks after operation. The patient progressed favourably until November 1957, at which time she had vague abdominal pains after meals and occasionally at night, which were relieved by milk and alkalis. The pains continued irregularly until their intensity increased in December 1957 and she was re-admitted for emergency treatment. The severity of the pain and the physical features were such that a perforated anastomotic ulcer was diagnosed, and at laparotomy this was confirmed and sutured. She made a satisfactory recovery and before discharge a gastric analysis showed a hydrochloric-acid level of 40 mEq. per litre.

Soon after the operation she again experienced abdominal discomfort after meals, and excessive flatulence. She was re-admitted in February 1958 for re-assessment. A barium meal on this occasion showed no ulcer or hold-up or evidence of dumping. The blood-urea and urine examinations were normal. From this time until her next admission in December 1958 her story was one of persistent dyspepsia and epigastric discomfort, with considerable loss of weight. It is interesting to note the remark of the intern in his notes of 1958: '. . . she is a thin, wasted and unhappy patient. . . .'. A barium meal failed to reveal any abnormality. Gastric analysis was not significant; urine, blood count and blood urea were all within normal limits.

This patient certainly presented a vexing problem, and it was the general consensus of opinion that an attempt should be made to refashion her gastrectomy, or even to do a higher gastrectomy. At operation, on 4 December 1958, she had a large stomal ulcer penetrating the left lobe of the liver. The previous gastro-enterostomy was undone and a higher gastrectomy, with a new gastro-jejunal anastomosis, was performed. She remained well after this operation, and despite occasional attacks of what she called 'indigestion', she was able to take up her previous occupation as a shop assistant.

In January 1960 she presented with acute colicky pain, acute constipation and vomiting. The symptoms and signs were those of an obstruction. The next day laparotomy revealed adhesions binding the ileo-caecal junction. These were freed, and she made an uneventful recovery. However, from this date until her next admission in June 1960 her progress was one of continued episodes of epigastric pain, vomiting, weakness and gradual deterioration in health. She had lost 60 lb. in weight since 1957. She was finally re-admitted for reassessment on 12 June 1960. A barium meal showed stomal ulceration. Urine, blood, stool, and blood-urea examinations showed no significant change. After 2 weeks in hospital a surgical opinion was requested. The first impression was that, although recurrent ulceration can be most stubborn and resistant to treatment, it is not a common finding in females. It was felt that some other factor or factors could possibly be responsible for the continued ulceration of her upper gastro-intestinal tract. Bearing in mind the relentless nature of her peptic ulceration, we investigated the possibility that this was a case of ulcerogenic tumour of the pancreas. We failed, however, to find any marked gastric hypersecretion, or a very highly acid juice.

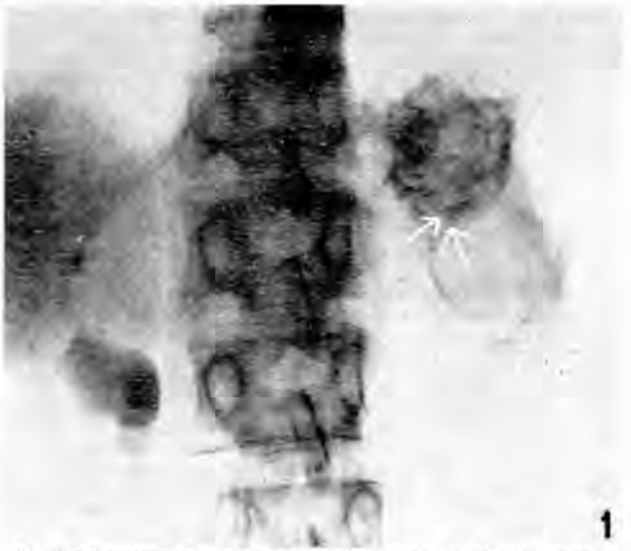

Fig. 1. Intravenous pyleogram film showing ectopic foci of calcification in the region of the left kidney.

At the same time we investigated the patient from the point of view of other endocrine imbalance. The glucose-tolerance curve was normal. The blood sugar was normal. The serum calcium was 15·2 mg. per 100 ml. A repeat examination of the serum calcium a few days later showed 14·6 mg. per 100 ml. and the serum phosphorus was 2 mg. per 100 ml. Alkaline phosphatase was 9 King-Armstrong units. A skeletal survey was normal, a carefully controlled urinary calcium-excretion test was within normal limits. An intravenous pyelogram showed normal excretion and no calculi were seen, but the control and intravenous pyelogram films showed ectopic foci of calcification in the region of the kidney on the left side. Screening and A-P views gave the impression that one of the foci was in the left lobe of the liver and the other in the left kidney. The nature of the calcification and the lesion in the kidney suggested a renal cyst with calcification (Fig. 1). The blood urea was normal.

Careful re-examination of the neck enabled us to feel a small swelling in the right thyroid lobe. An X-ray of the chest showed normal lungs and heart and no mediastinal masses. A repeat serum-calcium estimation was 14·4 mg. per 100 ml. and serum phosphorus was 2·6 mg. per 100 ml. The liver-function tests were normal. Serum proteins were 6·8 G. per 100 ml. and the serum albumin/globulin ratio was 1·3 : 1. Phenosulfophthalein and water-concentration tests showed reasonable renal function. It was not felt justifiable to do a 10-day cortisone test, since the diagnosis of primary hyperparathyroidism seemed almost certain. An electrocardiogram showed the typical picture of hypercalcaemia—an almost complete absence of the ST interval (Fig. 2). The diagnosis now seemed certain and was an added stimulus to finding the tumour.

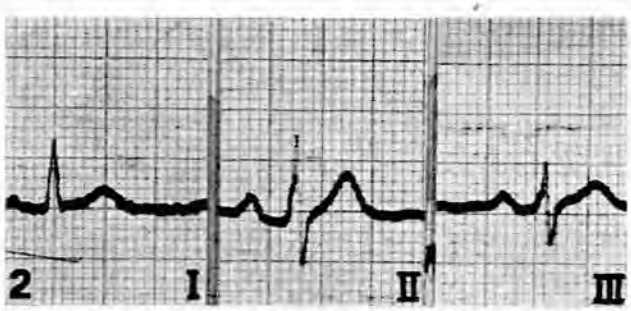

Fig. 2. ECG before operation. Lead II shows typical picture of hypercalcaemia with almost complete absence of the ST interval.

On 2 August 1960 an exploration of the neck was undertaken. Both lobes of the thyroid were fully mobilized. In the left lobe of the thyroid a nodule was palpable in the inferior pole. This nodule was removed. The left superior parathyroid gland was identified and found to be normal, as was the lower parathyroid gland. On the right side at the upper pole postero-medially, attached to, but not completely embedded in, the thyroid was a solid tumour the size of an almond, brownish in colour with an admixture of yellow areas. A superior right parathyroid gland was not seen and the general impression was that this tumour was an adenoma of the right superior parathyroid gland. A right lower parathyroid gland was not identified. Inferiorly, in the suprasternal notch, tissue resembling adipose tissue was dissected and removed. This proved to be normal parathyroid and thymic glandular tissue. The tumour and the right lobe of the thyroid were removed as one block of tissue. Microscopy showed that the left-lobe nodule was a thyroid adenoma and the tumour in relation to the right upper lobe was a parathyroid adenoma (Fig. 3).

Three days after operation the serum calcium was 8·5 mg. per 100 ml., and serial calcium investigations have not shown a figure above 9 mg. per 100 ml. Urinary calcium was 16 mg. per 100 ml. (normal 50 - 300 mg. per 100 ml.). The latest serum-calcium estimation is 7 mg. per 100 ml. There is slight concern that the patient may be going into a state of hypoparathyroidism. At the moment there is no evidence to suggest incipient tetany. Her appetite has improved and she now partakes of a full diet without ill effect.

Recent barium-meal studies show there is no delay in passage of barium through the stoma. No gastric or jejunal ulceration is visible. The patient has put on 10 lb. in weight and is symptom-free.

A recent electrocardiogram has the typical prolonged ST segment of hypocalcaemia (Fig. 4).

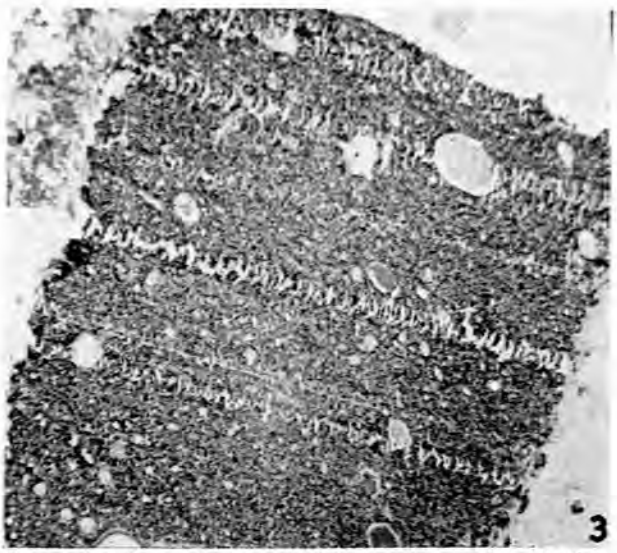

Fig. 3. Microphotograph of parathyroid adenoma removed at operation. It shows uniformity of cell pattern and absence of stomal and adipose tissue. The presence of colloid-like material, as seen in this section, occasionally makes differentiation from thyroid adenomata difficult.

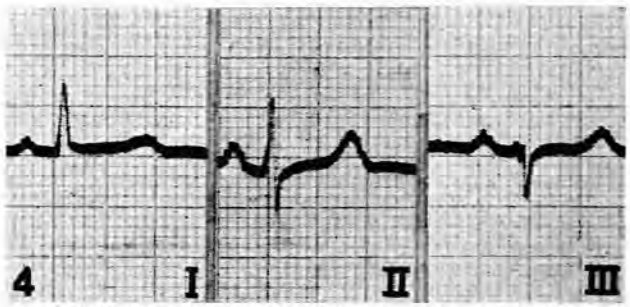

Fig. 4. ECG after operation, with typical prolonged ST segment of hypocalcaemia.

DISCUSSION

Ellison-Zollinger Syndrome

Ellison and Zollinger,[1] in 1955, first drew attention to the syndrome of: (1) A diathesis towards fulminating peptic ulcer, (2) gastric hypersecretion, and (3) an islet-cell tumour of the pancreas *not* composed of β cells.

More recently it has been established that this syndrome may incorporate other features, namely, diarrhoea, steatorrhoea and hypokalaemia. These may precede ulcer symptoms by months or years and may in themselves determine a fatal outcome.[2] In the past few years numerous cases have been described. The sexes are equally affected and the commonest age group is that between 30 and 50 years. The ulcers have several characteristic features: (1) They may be multiple; (2) they may be in unusual sites, such as the 3rd part of the duodenum or in the jejunum; and (3) the course of the ulcers is fulminant and characterized by serious complications, rapid recurrence after normal adequate surgical treatment, and considerable weight loss—many patients have had more than one operation, several have

had 5 or 6 and most have eventually died from complications of peptic ulcer or its treatment.

In the untreated patient the volume and acidity of the gastric juice tends to be greater than that found with the usual duodenal ulcer. The resting juice often amounts to 2 - 3 litres in 12 hours, the pH is 1·4 and the mEq. per litre value is often above 100 (normal 20 mEq. per litre). The hypersecretion is not abolished by vagotomy, and in fact Zollinger and McPherson,[3] in 1958, advocated total gastrectomy.

More recently, however, less radical surgery seems to be indicated if the ulcerogenic tumour can be removed at the same time. Stammers[4] has shown that the removal of a non-beta-cell tumour of the pancreas in a patient presenting with diarrhoea, steatorrhoea and gastric hypersecretion had cured the patient. In two-thirds of the cases the tumour is in the body or tail of the pancreas. Often the tumour is so small that it is easily missed. On the other hand the tumours are often multiple and may even be in ectopic sites. It has been suggested that it may be wise to resect the distal two-thirds of the pancreas if a tumour is not found. If it is found in the head, enucleation may be possible. If not, pancreato-duodenectomy may be necessary.

The exact mechanism whereby ulceration in the upper gastro-intestinal tract is produced has not been definitely established, but facts gathered recently seem to point to a humoral agent of the nature of gastrin. Insulin can be ruled out because most patients with β-cell tumours do not have peptic ulceration, and hypoglycaemia is not found in the Ellison-Zollinger syndrome. Glucagon, the secretion of the γ-cells, is diabetogenic and it actually *inhibits* gastric secretion.[5]

Above all, in any patient presenting with the Ellison-Zollinger triad, a search should be made for *other* endocrine lesions. A glucose-tolerance curve should be obtained, an X-ray film of the pituitary fossa should be made, the serum-calcium and phosphate levels should be measured, the urinary tract should be X-rayed, and the adrenal-steroid excretion should be estimated. It has been shown that about 25% of cases of the Ellison-Zollinger syndrome have other endocrine adenomas. Ellison,[6] in a study of postmortem material, has shown an increased incidence of duodenal ulcer in diabetes mellitus, and a significant correlation between duodenal ulcer and the occurrence of adrenal cortical adenomas unaccompanied by any sign of hypercortism.[7]

Endocrine Aspect of Duodenal Ulceration

1. Gonads

The incidence of duodenal ulceration is much higher in men than in women, the ratio being 4 : 1. It has also been observed that ulceration symptoms frequently undergo marked changes during pregnancy and with the onset of the menopause.

2. Parathyroids

Approximately 25% of patients with hyperparathyroidism have peptic ulcers and a much greater percentage have gastro-intestinal symptoms. It is noted that, in hyperparathyroidism, there is (*a*) a much greater incidence of duodenal ulceration in women, (*b*) frequent absence of gastric hypersecretion, and (*c*) increased frequency of gastric ulcers in men.

3. Thyroid

Peptic ulceration is very uncommon in thyrotoxicosis. Hypochlorhydria or achlorhydria is often found in toxic goitre.

4. Pancreas

Whether diabetes predisposes to ulceration or not is controversial. Joslin's[8] experience is that ulceration is not commoner in diabetics, while Ellison, Abrams and Smith[6] are of the opinion that peptic ulceration is more frequent in diabetes.

5. Adrenals

In Addison's disease the gastric hydrochloric-acid level is low. Administration of ACTH and cortisone returns this level to normal. In cases of Curling's ulcer seen at autopsy there is invariably adrenal hypertrophy.[9] Ellison, in a survey of 812 gastro-intestinal ulcers in 20,000 consecutive autopsies, showed adrenal hyperplasia in 14%.

6. Multiple Endocrine Adenomata

Occasional cases have been described in the literature in which adenomata of various endocrine glands have been found simultaneously and have been associated with peptic ulceration.[10] The suggestion is that, owing to the failure of one of the target organ glands, the feed-back hyperplasia of the pituitary can produce hyperplasia of other end organs. The acid-peptic axis is stimulated directly through central activity and parietal-cell hyperplasia, or indirectly as a by-product of secretion of the adrenals, gonads or parathyroids. That the functional interdependence of the glands of the endocrine system may have an anatomical basis has been known as a postmortem-room curiosity for many years, but that this can be clinically significant is only now being recognized. It appears that some forms of peptic ulceration, and particularly the relentless fulminating types, are associated with a more complex pattern of pluri-glandular adenomatosis.[11]

The Parathyroids and Hyperparathyroidism

It is not intended to deal with the anatomy, embryology and surgery of the parathyroids, since this has been comprehensively dealt with in a fairly recent article in this *Journal*.[12] Certain facts pertaining to the physiology and pathology of the parathyroids will be dealt with, as well as the consideration of the diagnosis and differential diagnosis of hyperparathyroidism.

Physiology

At the present time there are two known actions of the parathyroid hormone: (1) The mobilization of calcium from the skeleton, and (2) inhibition of re-absorption of filtered phosphate by the renal tubules.

These two mechanisms are independent of each other. There is no known tropic hormone from the pituitary which has any regulating mechanism on these glands. The regulating mechanism appears to be the level of calcium and phosphorus in the plasma. It seems to be independent of any nervous control. The plasma calcium and phosphorus bear a reciprocal relationship to each other under normal physiological conditions.

The plasma-calcium levels lie between 9 and 11 mg. per 100 ml. Only slight deviations from the normal range are tolerated and if they occur they may produce severe symptoms and disease. This accurate maintenance occurs in spite of a very rapid dynamic equilibrium between the relatively small amounts of calcium in the extracellular fluid and the very much larger quantities in the bones. An important basic fact is that any *acute* changes in plasma level must take place in the equilibrium between the plasma and bone.[14] On the other hand, more chronic changes of calcium level can be induced by an alteration in either calcium absorption or excretion or both.

Dent[14] has simplified matters by attempting to summarize calcium metabolism by a simple diagram (Fig. 5). The

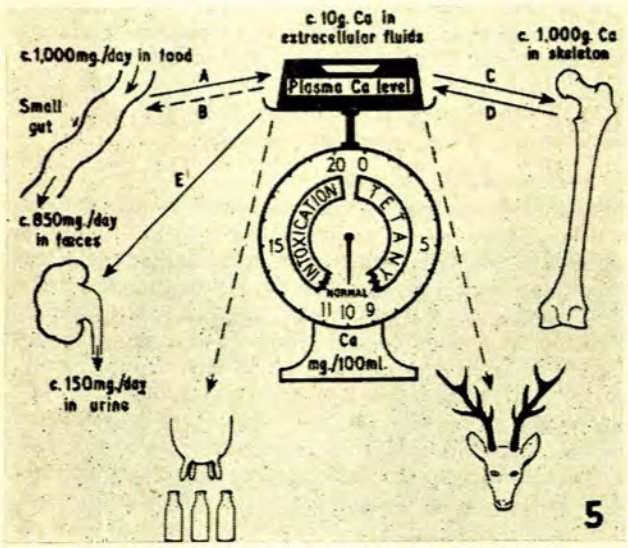

Fig. 5. A diagram illustrating calcium metabolism simply and concisely. [From: Dent, C. E. (1956): Proc. Roy. Soc. Med., **49**, 715.]

total serum-calcium concentration is dependent on the serum-protein concentration; for this reason the levels of both must be determined. The calcium bound to protein (5 mg. per 100 ml.) varies with the alterations in the serum-protein level and is not primarily affected by parathormone. In contrast, ionic calcium, 5 mg. per 100 ml., is specifically affected. Lowered serum proteins with normal serum calcium may indicate a raised ionic calcium from hyperparathyroidism. Although the ionic calcium and protein-bound calcium fractions cannot be determined individually, their relative concentrations can be determined. For example, the hypercalcaemia of multiple myeloma or sarcoidosis would be found to be associated with a rise in serum proteins.

Phosphorus metabolism is in some ways similar to calcium. They bear a reciprocal relationship to each other and they are both directly concerned with the formation of bone salts. They do, however, differ in that only half the total body store of phosphorus is in the skeleton, the rest being in the cells throughout the body. Also, acute changes in plasma phosphorus over a wide range do not appear to produce in themselves any symptoms or disease. The threat of poor absorption of phosphorus from the gut (as may happen with calcium) does not occur, since the supply and absorption is nearly always far in excess of body requirements. The normal kidney has a sharp threshold for phosphorus, and plasma levels do not alter with varying intake.

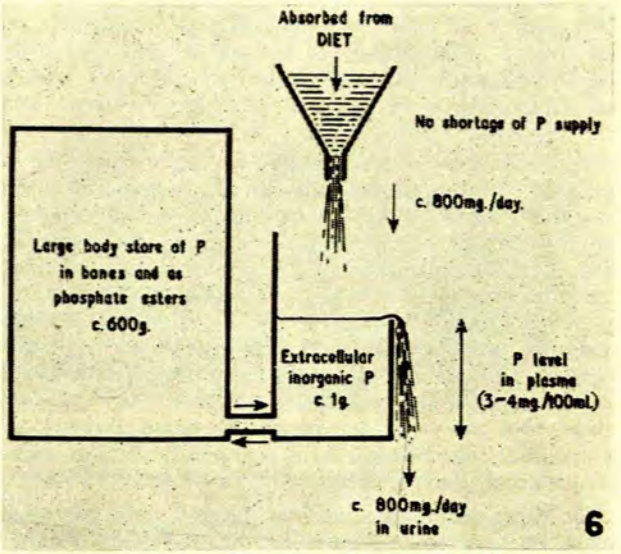

Fig. 6. A diagram illustrating phosphorus metabolism. [From: Dent, C. E. (1956): Proc. Roy. Soc. Med., **49**, 715.]

Chronic changes in plasma level, therefore, reflect changes in renal function rather than changes in supply. Dent[14] has again brilliantly illustrated phosphorus metabolism by a simple diagram (Fig. 6).

Pathology

Somewhat more than 80% of hyperparathyroidism results from a single adenoma; less than 10% from multiple adenomata, and about 10% from hyperplasia of all the parathyroids. Malignant tumours are fortunately rather rare, accounting for not more than 1 - 2% of cases. Adenomata vary in size from tumours as large as a normal parathyroid gland to tumours the size of the thyroid lobe. The average size is unfortunately not very large; this makes exposure and discovery difficult.

In over 80% of cases the tumour is in one or other of the upper pair of parathyroid glands. The adenoma may arise in an aberrant parathyroid in the mediastinum, not infrequently in the thyroid, and rarely behind the oesophagus. The adenoma is oval, soft, smooth, encapsulated, and reddish-brown in colour, especially on the cut surface. In primary hyperplasia all the glands are involved, but not always symmetrically, so that macroscopically one or even two glands may seem involved. They appear somewhat more chocolate-brown than the adenomata, and their size and form vary greatly. There is no connection between the intensity of the hyperparathyroid state and the mass of the hyperplastic tissue.

Microscopically, the most striking feature in adenomata is the virtual absence of stromal fat which makes up 40 - 60% of the bulk of normal parathyroid tissue. There is a mixture of chief cells, water-clear cells and oxyphil cells in varying proportions. Often one may predominate and the adenoma may consist mainly of chief cells or water-clear cells. Oxyphil-

cell adenomata do not appear to produce hyperparathyroidism. Acini containing colloid may be present, so that if the tumour is embedded in the thyroid gland it may be mistaken for a thyroid adenoma. In hyperplasia the cells are all of one type—usually water-clear cells ('wasserhelle'). These cells are often much larger than normal, sometimes being 40 microns in diameter. Carcinoma is one of the rarest of tumours. It grows rapidly, infiltrates the thyroid gland, muscle, and the trachea and metastasizes to the regional lymph nodes, the lungs and the bones. It may produce parathormone, but does not often cause hyperparathyroidism. Microscopically, the usual signs of malignancy are present, i.e. the variability in size of cells and nuclei, and mitoses.

Diagnosis

Hyperparathyroidism may be either primary or secondary. In primary hyperparathyroidism the diverse manifestations of the disease may be caused by more than one type of hormone. In one type, the symptoms are those of hypercalcaemia and hypercalciuria without bone involvement. In the other type the symptoms may be the same, but in addition the skeleton always shows some radiological change, either local or generalized. Primary hyperparathyroidism, resulting from adenoma of the parathyroid, is not uncommon, and is a potentially fatal disease which is curable in most cases if treatment is instituted before progressive renal disease develops. Diagnosis is rarely made before complications involving, in the majority of cases, the skeleton or urinary tracts, have developed.

In the skeleton, generalized or localized osteitis fibrosa cystica may occur, although this is unusual, whereas complications in the urinary tract are common. Probably 5% of all radiopaque renal stones and probably 15% of cases of recurrent lithiasis result from hyperparathyroidism. It is a widespread belief that a *sine qua non* for the diagnosis of hyperparathyroidism is some form of bone lesion, and this may be one of the reasons why an accurate diagnosis of hyperparathyroidism is not often made. In addition, it is well to remember that hypercalcaemia is not always constantly present in this condition. The symptom complex falls into three categories: (1) The result of high blood calcium, (2) excessive urinary calcium and phosphorus, and (3) secondary bone changes.

In the absence of any specific bone or renal lesion the diagnosis can only be made and confirmed by blood chemistry, since the symptoms simulate many functional disorders. They include: muscle weakness and abnormality of gait, vaguely localized pain, fatigue, anorexia, nausea, vomiting, loss of weight, constipation, lethargy, bradycardia and cardiac irregularities.

Muscle weakness is often the precursor of the typical bone changes that occur in this condition. It varies from a general feeling of tiredness to a degree of extreme weakness in which the patient is bedridden and can only lie on his back and is unable to move his limbs. Once bone changes have occurred and bone pain is conspicuous, the muscular weakness is easily explained by the pain produced on movement. Associated with this weakness patients may have abnormal gaits. The only striking one is the waddling gait which may occur in many surgical diseases. Its commonest cause is probably coxa vara from softening of the femoral neck, but it may be seen before any bone changes take place and is possibly caused by weakness of the gluteal muscles. Vaguely localized pains, although common, with already existing bony changes, may precede them. In adults the commonest site is in the lower back, followed closely by pains in the hips and down the middle of the legs.

Osseous complications of hyperparathyroidism vary from minimal decalcification, which may be asymptomatic, to a full-blown osteitis fibrosa cystica. Localized cysts, giant-cell tumours, and fractures may be so prominent that sight is lost of the generalized lesion. The alkaline phosphatase is usually raised only when the bone lesions are radiologically visible. Pathognomonic features, radiologically, are subperiostial resorption of bone in the long bones (especially the metacarpals and phalanges) and the absence of the lamina dura of the teeth.

The kidney, as would be expected, is the main target for the abnormal calcium metabolism. The calcium freed into the blood is excreted by the kidneys in the urine. The excess calcium tends to be deposited in the urinary tract. The renal changes most easily recognized are calculus formation and nephrocalcinosis. Renal changes may occur with or without skeletal lesions. Commonly found with marked bony changes are soft, often bilateral, phosphatic calculi, at times so extensive as to show on X-ray as cysts of the renal pelvis. These are the stones that are likely to disappear after removal of the parathyroid adenoma. On the other hand, the widely diffused calcific deposits throughout the renal parenchyma—nephrocalcinosis—do not disappear after removal of the parathyroid adenoma. Following on these widespread changes, clinical hypertension may develop, and with it the train of events that follow on renal failure. The patient with a renal stone resulting from a parathyroid adenoma has less chance of normal health, and even of survival, than has the patient with idiopathic renal stone. It is therefore important that a possible diagnosis of hyperparathyroidism should be considered in every patient with a calcium-containing renal stone.

Primary disturbance of bone formation, although at one time thought to be the commonest manifestation of this

TABLE I. SERIES OF CASES OF PRIMARY HYPERPARATHYROIDISM PUBLISHED BETWEEN 1948 AND 1954[17]

Type	*Albright and Reifenstein (1948)*	*Burk (1948)*	*Lahey and Murphy (1953)*	*Richardson (1953)*	*Black (1953)*	*Hellstrom (1954)*	*Total*
Skeletal changes alone	11	3	16	—	16	13	59
Skeletal changes with nephrocalcinosis or renal calculi	24	7	9	7	16	10	66 (±7)
Nephrocalcinosis or renal calculi alone	28		4	4	73	27	136 (±7)
Neither skeletal changes nor calculi ..	1	—	—	—	7	—	8
Total	64	10	29	11	112	50	276

condition, has now taken second place to renal changes. In a summary of the world literature from 1947 to 1954, Pyrah's figures[17] show that there were 166 cases with primary renal changes compared with 66 cases with primary bone changes (Table I). The well-known bone changes of generalized osteitis fibrosa cystica (von Recklinghausen's disease) are the least common manner of presentation today. Single osteoclastomata or cysts, most commonly of the jaw, may be the only presenting sign. On the other hand, symptoms and signs may be most confusing and the distinction from other more purely orthopaedic conditions may be exceedingly difficult. Mention has already been made of vague localized pain in the back and legs, and the abnormality in gait. Pathological fractures bring a host of aetiological factors to mind; fortunately X-ray examination and biochemical analysis of the blood leave few undiagnosed. Kyphosis and scoliosis may produce reduction in the total stature of adults. Dent[14] suggests that any adult whose expected height is about 10 inches below normal should be considered as possibly having bone disease until proved otherwise. Whereas renal changes are not often reversible, most of the bone lesions are, once the parathyroid adenoma has been removed.

Among the less well-known modes of presentation are recurrent peptic ulceration and pancreatitis. The importance of recognizing the co-existence of peptic ulceration in cases of hyperparathyroidism is stressed by Alvarez *et al.*[18] They point out that treatment with antacids and milk leads to heightened calcium intake which might well push the patient into an acute stage of hyperparathyroidism, with possible fatal results. The problem is made more difficult by the fact that nausea, abdominal pain and vomiting are symptoms of primary hyperparathyroidism and may closely mimic the symptoms of peptic ulceration. More understandable is the occurrence of arterial thrombosis, where ectopic calcification in the arterial wall and increased coagulability of the blood both play their part.

Up to now only primary hyperparathyroidism has been considered, but hyperparathyroidism (secondary) may occur as a compensatory mechanism under certain circumstances and, if the march of events is not halted, may become indistinguishable from primary hyperparathyroidism. Hyperplasia, which may go on to adenoma formation, occurs secondarily to a fall in serum calcium or a rise in serum phosphorus, and may be classified thus:

1. When the serum-calcium level falls, caused by—
(*a*) deficient intake, or
(*b*) deficient absorption, resulting from (*i*) deficiency of Vitamin D (rickets, osteomalacia); (*ii*) resistant rickets; (*iii*) steatorrhoea; (*iv*) gastrectomy; (*v*) small-bowel resection; (*vi*) biliary obstruction; (*vii*) excessive phytic acid in diet; (*viii*) pancreatic insufficiency; or (*ix*) old age.
2. When the serum-phosphorus level rises, caused by—
(*a*) chronic glomerular nephritis, or
(*b*) Fanconi's syndrome.

It may be pointed out that in chronic renal failure patients occasionally present with symptoms of bone disease, while primary hyperparathyroidism is often associated with chronic renal failure. The distinction is not always easy although very important, since the treatment in one case is medical, and in the other, surgical. An interesting table, drawn up by Dent,[14] indicates the biochemical changes that can occur in various conditions which may be confused with primary hyperparathyroidism (Table II).

It is well documented that surgery for primary hyperparathyroidism is usually successful and that recurrence is rare; so much so that persistence or reappearance of symptoms and high serum-calcium levels has come to be regarded as evidence of inadequate surgical therapy. There is no doubt that the greater awareness of the early symptoms and signs of hyperparathyroidism on the part of the medical profession is helping an earlier diagnosis of these patients before the relentless progress of renal failure has taken place.

The present case helps to re-emphasize the truism that these rather uncommon conditions will rarely be diagnosed unless they are *borne in mind* when dealing with signs and symptoms that defy the usual routine medical care. Here, more than ever, the cooperation and integration between clinician, radiologist and biochemist will be of maximum benefit.

CONCLUSION AND SUMMARY

The relentless progress of gastroduodenal ulceration which did not respond to routine surgical treatment led to the wrong conclusion that an ulcerogenic tumour of the pancreas was present. Ellison and Zollinger first discovered this syndrome in 1955. It consists of: (1) A fulminating ulcer diasthesis, (2) marked gastric hypersecretion, and (3) a non-β-cell tumour of the pancreas.

In the case reported there was no gastric hypersecretion. With the knowledge that these cases may have some other endocrine basis, further tests were done and the serum calcium was found to be markedly raised. This led to the

TABLE II. BIOCHEMICAL CHANGES IN METABOLIC BONE DISEASES[14]

Disease	*Plasma calcium (mg./100 ml.)*	*Plasma phosphorus (mg./100 ml.)*	*Plasma bicarbonate (mEq./l.)*	*Blood urea (mg./100 ml.)*	*Alkaline phosphatase (K-A units)*	*Urine calcium (mg./24 hrs.)*
Normal (adult)	9 - 11	3 - 4	24 - 28	20 - 35	5 - 12	120 - 220
Idiopathic osteoporosis	normal	normal	normal	normal	normal	(high if in an active phase)
Primary hyperparathyroidism	11 - 16	1 - 3	normal	normal	15 - 100	300 - 800
Chronic renal failure Renal-glomerular osteodystrophy Secondary hyperparathyroidism	6 - 11	4 - 12	10 - 22	50 - 400	15 - 100	50 - 200
Rickets or osteomalacia, any origin, non-acidotic	8 - 10	1 - 3	20 - 28	normal	5 - 50	10 - 100
Rickets or osteomalacia, acidotic	7 - 11	1 - 4	10 - 22	30 - 80	15 - 50	150 - 350
Hypophosphatasia	9 - 15	4 - 8	20 - 28	20 - 100	1 - 2 (adult) 3 - 8 (infant)	Insufficient data, probably high normal or high

biochemical confirmation that the aetiological factor was a parathyroid lesion. This was proved by operation and microscopy.

The physiology and pathology of hyperparathyroidism are dealt with, and the diagnosis and differential diagnosis are discussed. Finally, the point is stressed that these conditions will only be diagnosed if kept in mind in dealing with patients with chronic ill health who do not respond to routine medical care.

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