may physically obliterate the lumen (Meikle, 1955. Fig. 3). The cysts may induce a volvulus; the cysts may exert extrinsic pressure on other loops of bowel. They may give rise to inflammatory reactions and adhesions (Jones & Cole, 1967).

2. *Intussusception*. A submucosal cyst may act as the apex of an intussusceptum.

3. *Pneumoperitoneum*. In rare cases, tension pneumoperitoneum may occur.

4. *Interposition of the bowel between the liver and the diaphragm* (Case 4, Dhall *et al.*, 1968).

Discussion

PCI is a rare condition the diagnosis of which can usually be made with certainty if the possibility is considered. The disease may be discovered as an incidental finding on plain films of the chest and abdomen. The chest X-ray, which may show evidence of chronic respiratory disease can demonstrate interposition or a pneumoperitoneum with cysts and a 'foamy' appearance below the diaphragm. PCI should always be considered when a pneumoperitoneum occurs without other clinical evidence of perforation of a hollow viscus (Somerville, 1951). These appearances may also be found on the plain film of the abdomen and in addition cysts may be seen along the line of the bowel, particularly the colon. The plain film appearances are unmistakable once it is realized that the gas is not intraluminal.

A barium enema will confirm the findings in the large bowel. The differential diagnosis includes

faeces, polyposis, the pseudo-polypoidal form of ulcerative colitis, thumb-printing in mesenteric vascular disease and carcinoma but these conditions will not give rise to *translucent* filling defects.

The diagnosis is less easy if the disease is confined to the small bowel and will be best demonstrated in the follow-through examination. The preceding meal will also reveal any peptic ulceration or stenosis.

Once the diagnosis is made and alimentary tract malignancy has been excluded there is no specific treatment and spontaneous remission can be expected if complications do not supervene.

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Hypercalcaemia in thyrotoxicosis with and without hyperparathyroidism

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Summary

Two cases of thyrotoxicosis with hypercalcaemia are reported. The hypercalcaemia in one of the patients was a manifestation of hyperthyroidism and in the other was due to co-existent hyperparathyroidism.

The literature is reviewed and the effect of thyroid hormone on calcium metabolism is discussed. Routine plasma calcium estimations should be performed in all cases of thyrotoxicosis.

Introduction

Hypercalcaemia in thyroid disease occurs infrequently. Significant hypercalcaemia in thyrotoxicosis may occur with or without accompanying

hyperparathyroidism, and an example of each is reported.

Method

Plasma calcium was measured by the EDTA/calcon method (Bowden & Patston, 1963) and all values were corrected for total serum protein, as suggested by Dent (1962). The normal range of plasma calcium in this laboratory is 8.4–10.5 mg/100 ml.

Case 1: Thyrotoxic hypercalcaemia

A 25-year-old unmarried woman was admitted to Westminster Hospital in February 1969. She gave a

history of nausea and vomiting, weight loss and abdominal pain since November, 1968. Two months before admission, she developed amenorrhoea, but denied pregnancy. Her parents had noticed her eyes becoming prominent and the development of a goitre.

She was seen in the Out Patient Department of another hospital in January, 1969, where a barium meal was carried out, which was normal. No tests of thyroid function were performed, and she did not re-attend for follow-up.

There was no family or personal history of any serious past illnesses or thyroid disorder.

On examination she was thin, pale, with a stare, lid-lag and a fine tremor of the hands. She was not pyrexial, but had a sinus tachycardia of 128/min. The thyroid gland was diffusely enlarged, and there was a bruit over the more prominent right lateral lobe. There was no lymphadenopathy.

Investigations: Hb 82%; W.B.C. 5200 c/mm with a normal differential; ESR 22 mm/hr. (Wintrobe); urine specific gravity 1005. No proteinuria or glycosuria. Pregnancy test negative. Radio-active ^{131}I uptake 100%; plasma thyroxine (T_4) 27.4 $\mu\text{g}/100\text{ ml}$ (normal 4.0–11.0); thyroglobulin tanned cells test was positive, but the complement fixation test (CFT) was negative. Long acting thyroid stimulator (LATS) was not detected on assay. Plasma calcium was 12.7 mg/100 ml; plasma phosphate 2.7 mg/100 ml, and

the serum albumin 2.3 g/100 ml (normal 3.4–4.6). Further determinations confirmed the hypercalcaemia (Fig. 1). Urinary calcium was high, 426 mg/24 hr (normal up to 300 mg/24 hr). Plasma electrolytes were normal on admission with a slightly raised plasma urea of 48 mg/100 ml. The plasma potassium fell to 2.8 mEq/l, but this and the plasma urea became normal when normocalcaemia was established.

X-rays of chest, thoracic inlet, abdomen, skull and hands were normal. An ECG confirmed sinus tachycardia with QT interval at the lower limit of normal.

Oral hydrocortisone (40 mg 8-hourly) produced a fall in plasma calcium from 12.0 mg/100 ml to 9.7 mg/100 ml after 4 days. When hydrocortisone was stopped, the plasma calcium rose to its former high value and nausea and vomiting, which had ceased in the normocalcaemic phase, returned.

She was then started on propranolol 40 mg 6-hourly, and carbimazole 20 mg 8-hourly. The plasma calcium fell to normal after 2 weeks, and has remained so since discharge from hospital. She is now clinically euthyroid and symptom-free, taking carbimazole, 5 mg 8-hourly.

Alkaline phosphatase was slightly raised on admission to hospital (19 K.A. units/100 ml), but as an out-patient rose to 28 K.A. units/100 ml with a normal plasma calcium. It has subsequently fallen to normal, and she has not been given supplementary calcium or Vitamin D.

FIG. 1. Hypercalcaemia suppressed initially by hydrocortisone and later by treatment of thyrotoxicosis.

FIG. 2. No suppression of hypercalcaemia until after removal of a parathyroid adenoma.

Case 2: Thyrotoxicosis with hyperparathyroidism

A 63-year-old married woman first attended Westminster Hospital in May 1969, complaining of weakness, loss of appetite and weight loss for 1 year. She was also constipated, suffered intermittent abdominal pain, and had polyuria for 3 months.

The plasma calcium was found to be 13.3 mg/100 ml with a normal plasma phosphate and an alkaline phosphatase of 13 K.A. units/100 ml and she was admitted for further investigation in June 1969.

In the family history, two sisters had undergone partial thyroidectomy elsewhere for thyrotoxicosis, one in 1956, the other in 1968. Histology of both glands showed lymphadenoid infiltration.

On examination she was thin, anxious, with tremor of the hands and a slight degree of lid-lag. The thyroid gland was enlarged and nodular and the trachea was displaced to the right. The pulse was 110/min and the reflexes were brisk. She was apyrexial.

There was generalized abdominal tenderness, and one observer thought a mass to be palpable in the left upper quadrant. There was no lymphadenopathy.

Investigations: Hb 12.0 gm/100 ml; WBC 6300 c/mm; ESR 9 mm/hr. (Wintrobe). No albuminuria

or glycosuria. ^{131}I uptake 100%; plasma T_4 17 $\mu\text{g}/100$ ml; Thyroglobulin tanned cell and CFT negative. LATS assay not done. ^{131}I scan showed increased uptake over the left lobe of the thyroid. Repeat ^{131}I uptake, after triiodothyronine, 40 μg , 8-hourly for 6 days, was still 100%. Plasma calcium was raised (Fig. 2) and the serum albumin was 3.2 g/100 ml and the globulin 3.2 g/100 ml. Slit-lamp examination revealed calcification at the corneal limbi.

Plasma electrolytes and urea were normal on admission, but she developed moderate hypokalaemia, although the plasma potassium never fell below 3.0 mEq/l.

Chest X-ray confirmed tracheal deviation to the right and the heart was enlarged in its transverse diameter. Skull X-ray showed a decalcified sella, and X-ray of the hands showed osteoporosis. Barium meal and enema and pancreatic scan with ^{75}Se were normal. An ECG was normal.

Oral hydrocortisone (40 mg 8-hourly) did not produce normocalcaemia after a 13-day course (Fig. 2). Treatment was then started with oral propranolol, carbimazole and potassium, and her appetite improved and she gained weight. Her pulse fell to 56/min. She was discharged in August 1969, taking carbimazole, 10 mg 6-hourly, and propranolol, 40 mg 12-hourly.

In view of the almost certain fact that she had co-existing hyperthyroidism and hyperparathyroidism, Lugol's iodine was given as an out-patient and she was re-admitted for exploratory surgery.

At operation on 10 September, a nodule, 2.5 cm in diameter, was found in the sternal notch. This proved on histology, to be a parathyroid adenoma. Other parathyroid tissue was searched for, but not found. The thyroid gland was enlarged and nodular and the left lobe was larger than the right. Sub-total thyroidectomy was performed and histology showed a small foetal adenoma with some hyperplasia.

The postoperative plasma calcium levels were normal. She was discharged feeling well and not on any medication. In October, it was noticed that her voice was hoarse, and she complained of 'pins and needles' in the fingers. A plasma calcium was 8.1 mg/100 ml, alkaline phosphatase 22 K.A. units/100 ml. She was started on oral Vitamin-D, 3000 units daily and is at present symptom-free.

Discussion

Thyrotoxic hypercalcaemia

This is becoming increasingly recognized, but up to 1963, only thirty-one definite cases had been documented, according to Torsti & Lamberg (1963). However, Baxter & Bondy (1966), on reviewing the records of 302 hyperthyroid patients, found nineteen to have hypercalcaemia, in only two of these due to associated hyperparathyroidism. Adams *et al.* (1967) have shown that the mean serum calcium of hyperthyroid patients tends to be higher than that of normal subjects, matched for sex and age; and the serum ionized calcium is also higher in hyperthyroid patients (Frizel, Malleson & Marks, 1967), possibly because of a tendency to hypoalbuminaemia (Man, Gildea & Peters, 1940).

The first authentic report of thyrotoxic hypercalcaemia was by Wijnblad (1937), and similar cases to to this present one have been reported (Stanley & Fazekas, 1949; Guyer, 1965; Harris-Jones, Nakadar & Wells, 1967). The height of plasma (or serum) calcium can be extremely variable, and bears no relation to the severity of the thyrotoxicosis (Bortz *et al.*, 1961; Baxter & Bondy, 1966). In the second case of Rose & Boles (1953), the serum calcium ranged from 11.2 to 19.9 mg/100 ml, and gradually fell following subtotal thyroidectomy. An interesting feature of that case is that recurrence of thyrotoxicosis did not then provoke a rise in the serum calcium.

In thyrotoxic hypercalcaemia, the symptoms of hypercalcaemia, namely nausea, vomiting, abdominal pain and constipation, are often predominant and may mask the accompanying thyrotoxicosis. Despite the hypercalcaemia and hypercalcuria, the

literature lacks reference to the occurrence of renal calculi in these patients, although nephrocalcinosis and renal tubular acidosis have been described (Epstein, Freedman & Levitin, 1958; Huth, Maycock and Kerr, 1959). The plasma urea is invariably raised due to dehydration, and with adequate hydration usually falls to normal, even though serum calcium remains elevated (Pribek & Meade, 1957). The low plasma potassium that is invariably found, as in case 1, is thought to be due to excessive renal loss of potassium, and this also occurs in hyperparathyroidism (Sanderson, 1967). A recent case report of thyrotoxic hypercalcaemia (Harper & Osborne Hughes, 1970) had a persistently raised serum alanine amino-transferase and gastro-intestinal bleeding; other liver function studies were normal. Liver function tests were not carried out on the present case.

To differentiate hypercalcaemia due to thyrotoxicosis from that due to hyperparathyroidism, the cortisone suppression test (Dent, 1956), now modified by the substitution of hydrocortisone (Dent & Watson, 1966), may help. Cases 1 and 2 demonstrate its usefulness. In case 1, normocalcaemia was attained 4 days after starting hydrocortisone, while in case 2, the plasma calcium was still above normal after 13 days. Prednisone has also been shown to cause a fall in serum calcium when this is due to thyrotoxicosis (Bortz *et al.*, 1961; Sataline, Powell & Hamwi, 1962; Harper & Osborne Hughes, 1970). Rarely, the raised serum calcium does not respond to steroids, and may only fall when the hyperthyroidism is controlled (David, Verner & Engel, 1962). Very occasionally, the hypercalcaemia of hyperparathyroidism may be suppressed by steroids (Gwinup & Sayle, 1961; Dent, 1962; Hodges & Waterhouse, 1967; Garcia & Yendt, 1968).

The role of thyroid hormone in calcium metabolism has prompted much discussion. Excretion of calcium in thyrotoxic subjects is high, due to a direct catabolic effect of thyroid hormone on bone (Aub *et al.*, 1929). Puppel *et al.* (1945) and Cook, Nassim & Collins (1959), found excessive loss of calcium via faecal and urinary routes, as compared with hyperparathyroidism, in which increased excretion of calcium occurs almost exclusively through the urine. Thyroid hormone has also been shown to have an elevating effect on serum calcium levels in the absence of the parathyroid glands (Aub *et al.*, 1932; Cope & Donaldson, 1937). The fact that the parathyroid glands are thought to play no part in thyrotoxic hypercalcaemia is supported by the tendency to hyperphosphataemia (Cook *et al.*, 1959) and the increased tubular re-absorption of phosphate (Adams *et al.*, 1967) which becomes normal when hyperthyroidism is treated (Parsons & Anderson, 1964). Harrison, Harden & Alexander (1964) demonstrated

that exogeneous parathyroid hormone produced a greater rise in serum calcium in hyperthyroid subjects than in normal controls. The interpretation is that endogenous parathyroid secretion is already suppressed by the increased calcium load imposed by the hyperthyroid state. The handling of an intravenous calcium load was studied in a hypercalcaemic, hyperthyroid patient and this led to a decrease of 79% in the excretion of phosphorus indicating that hyperparathyroidism was unlikely to be implicated (Koenig, Scholz & Salassa, 1957).

Bone lesions may occur in hyperthyroid subjects with or without hypercalcaemia. There is increased bone formation as well as increased bone destruction (Krane *et al.*, 1956) and these changes may occur in the absence of radiographic evidence of bone disease (Adams *et al.*, 1967). The bones involved are spine, ribs and pelvis, and less frequently skull, hands and long bones (Werner, 1962). The bone lesions have been reported as those of osteitis fibrosa cystica (Von Recklinghausen, 1891; Follis, 1953). Osteoporosis (Cook *et al.*, 1959), and osteomalacia have also been described (Follis, 1953), although the more recent studies of Adams *et al.* (1967) do not support the suggestion that osteomalacia is a feature of hyperthyroidism. Thyrotoxic bone disease is not seen more frequently because the underlying disorder in the majority of cases is corrected before the demineralization proceeds to a clinically demonstrable level (Kleeman, Tuttle & Bassett, 1958). Case 1 presumably had mild osteitis fibrosa as the phosphatase was raised before treatment and rose further after treatment, before eventually settling to normal, a phenomenon which has been noted previously by Dent & Harper (1958). Increased retention of an intravenous calcium load is seen in hyperthyroid subjects as compared with normal controls (Lim, Jacob & Khoo, 1969) and these authors postulate that this may be due to an increased calcitonin production. Other workers, from their studies on induced hypercalcaemia in hyperthyroid subjects, have debated a possible functional deficiency of calcitonin (Klotz *et al.*, 1968). Recently a case of thyrotoxic hypercalcaemia was treated with intravenous porcine calcitonin with a temporary fall in serum calcium (Buckle, Mason & Middleton, 1969).

It is likely that in thyrotoxic hypercalcaemia the level of calcitonin is raised—induced hypercalcaemia causes a rise in plasma calcitonin in normal subjects (Gudmundsson *et al.*, 1969), but the increase is still insufficient to counteract the catabolic effect of thyroxine on bone. Alternatively, thyroxine may increase peripheral utilization of calcitonin to the point of causing relative deficiency (*Lancet*, 1967). Assays of calcitonin in hyperthyroid subjects with and without hypercalcaemia obviously need to be carried out.

Thyrotoxicosis with hyperparathyroidism

This is a rare association. Since the first clearly documented case by Noble & Borg (1936), only thirty other cases, including the present one, are known to my knowledge to have been described or referred to (Table 1), and this includes eight cases,

TABLE 1. Thyrotoxicosis with hyperparathyroidism

No.	Author	Sex	Age
1.	Noble & Borg (1936)	F	33
2.	Miller & Evans (1942)	F	51
3.	Koenig, Scholz & Salassa (1957)	F	60
4.	Hubble (1958)	F	56
5.	Randall & Keating (1958)	F	70
6.	Frame & Durham (1959)	M	63
7.	Gassmann & Haas (1960)	F	50
8.	Bortz <i>et al.</i> (1961)	F	68
9.		M	65
10.	Gadeholt (1961)	F	37
11.	Jackson <i>et al.</i> (1961)	F	37
12.	Ellenberg <i>et al.</i> (1962)	—	—
13.	Gordan <i>et al.</i> (1962)	—	—
14.		—	—
15.	Hellstrom & Ivermark (1962)	F	55
16.		F	32
17.		M	59
18.	Torsti & Lamberg (1963)	—	—
19.		M	56
20.	Bryant, Wulsin & Altemeier (1964)	F	61
21.		F	44
22.	Fields & Burkett (1964)	M	48
23.	Austoni (1965)	M	22
24.	Breuer & McPherson (1966)	M	42
25.	Ahuja & Chopra (1968)	F	38
26.	Davies, Dent & Watson (1968)	—	—
27.		—	—
28.		—	—
29.		—	—
30.		—	—
31.	Present case	F	63

full details of which are not known. (Gordan *et al.*, 1962; Ellenberg *et al.*, 1962; Davies, Dent & Watson, 1968). Earlier case reports have been lacking in either definite histological evidence of hyperparathyroidism or clinical evidence of thyrotoxicosis and are not included in this list (Wendel, 1930; Ball, 1930; Meyer-Borstel, 1930; Cooley, 1931; Ballin & Morse, 1931; Bergstrand, 1931; Hellstrom, 1932, 1954).

It is difficult to see any causal relationship between hyperthyroidism and hyperparathyroidism. There appears to be a preponderance of females in cases where the sex is known, and the thyroid is usually nodular. Many diseases are now known to be associated with primary hyperparathyroidism (Davies *et al.*, 1968) and it is probably fortuitous that thyrotoxicosis happens to be one of them.

In some of the cases, thyrotoxicosis was detected first, in others hyperparathyroidism, while in a few hyperparathyroidism was discovered incidentally at operation (Randall & Keating, 1958), or a para-

thyroid adenoma was found embedded in the goitre (Frame & Durham, 1959). In the present case, hyperparathyroidism was thought likely in view of the presenting symptoms and was confirmed by the finding of corneal calcification, and the failure to respond to a hydrocortisone suppression test. Hand tremor, brisk reflexes, and a nodular goitre, as well as a family history of thyroid trouble suggested co-existing thyrotoxicosis, and this was confirmed by radio-active iodine uptake. Hypophosphataemia (below 2.3 mg/100 ml) in the present case was another pointer towards hyperparathyroidism, but a normal plasma phosphate should not deter one from making this diagnosis as normophosphataemia was recorded in 41% of cases of hyperparathyroidism by Keating (1961). Renal tubular reabsorption of phosphate is usually low in hyperparathyroidism and this was shown in the two patients of Bortz *et al.* (1961), although this is not always the case and may be normal (Ahuja & Chopra, 1968).

Whenever a raised plasma calcium is found in a case of thyrotoxicosis, hyperparathyroidism must be the first diagnosis to consider and exclude, rather than attributing the raised calcium level solely to the thyrotoxicosis. Surgical exploration is obligatory if the plasma calcium remains high after treating the thyrotoxicosis. By adopting this approach, serious renal and bone disease may be avoided.

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Addendum

Since the submission of this paper, the following has been published:

PARFITT, A.M. & DENT, C.E. (1970) Hyperparathyroidism and hypercalcaemia. *Quarterly Journal of Medicine*, **39**, 171.