COMPLICATIONS AFTER PARATHYROIDECTOMY
Fractures from Low Calcium and Magnesium Convulsions

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In our experience signs and symptoms of hypocalcaemia almost invariably follow surgical removal of a parathyroid tumour or excision of hyperplastic parathyroid tissue for hyperparathyroidism. This happens because the parathyroid tumour is removed when we also routinely identify and biopsy the other normal parathyroid glands. In most patients symptoms are mild, the hypocalcaemia temporary, and treatment is not required. In a few, those with renal disease, bone disease or steatorrhoea, the hypocalcaemia is likely to be severe and need treatment. The routine management of this type of patient has been described by Dent (1962). We have recently studied two patients who had generalised convulsions after parathyroidectomy despite this routine treatment. The first patient, who had primary hyperparathyroidism with severe bone disease, developed hypomagnesaemia in addition to hypocalcaemia. The second patient underwent total parathyroidectomy for renal osteodystrophy secondary to polycystic disease of the kidneys, and developed severe hypocalcaemia which failed to respond until aluminium hydroxide was added to the routine therapy of calcium and vitamin D. In both patients severe tetany with convulsions caused multiple fractures. We wish to record these patients and make suggestions which should improve treatment after operation. The second patient is, to the best of our knowledge, the first recorded total parathyroidectomy for renal osteodystrophy.

CASE REPORTS

Case 1—A draughtsman of thirty-seven was seen at University College Hospital in 1962 with anorexia, nausea, vomiting, polydypsia and polyuria of eighteen months duration. There was no history of bone pain, fractures or renal colic. The blood pressure was 150/80 millimetres of mercury. There was no corneal calcification, and the only abnormality discovered was a small lump one centimetre across in the region of the left lobe of the thyroid gland. Investigations—The plasma calcium was 16-8 milligrams/100 millilitres; the ionised calcium was 10-8 milligrams/100 millilitres, and complexed calcium 0·1 milligram/100 millilitres. Protein-bound calcium was 5·9 milligrams/100 millilitres. Other findings were: plasma specific gravity 1·028—9; plasma phosphorus 2·4 milligrams/100 millilitres; alkaline phosphatase 42 King-Armstrong units; 24-hour urinary calcium 766 milligrams/24 hours; plasma sodium 137 milliequivalents/l; urea 28 milligrams/100 millilitres. The serum protein was 7·2 grammes/100 millilitres, with a normal electrophoretic strip. Amino-acid chromatogram revealed a moderate generalised aminoaciduria. Maximum urinary concentration was 1,006 and dilution 1,003. Radiography of the skeleton showed changes of osteitis fibrosa with typical subperiosteal erosions of the phalanges. Radiographs of the kidneys showed bilateral nephrocalcinosis. Operation—A large parathyroid adenoma weighing 12·9 grammes was removed from behind the lower pole of the left lobe of the thyroid gland. The right upper and lower parathyroid glands were biopsied and found to be histologically normal. Progress—By the third day after operation the plasma calcium had fallen to 9·1 milligrams/100 millilitres. By the seventh day the plasma calcium was 7 milligrams/100 millilitres, and he was complaining of tingling of his legs, hands and feet. There was a positive Trousseau and Chvostek's sign, and he had bouts of depression during which he wept for no reason at all.
He was treated with intermittent injections of 20 millilitres of 20 per cent calcium gluconate, with symptomatic relief. On the twelfth day after operation he had severe tetany which required large amounts of intravenous calcium gluconate. At this stage the plasma calcium was 6·2 milligrams/100 millilitres. The rest of the clinical picture was atypical. He developed a marked ataxic tremor of the upper limbs and the mental state changed from one of intermittent depression to one of excitable hyperactivity similar to that seen in patients with delirium tremens. He was started on dihydrotachysterol 8 milligrams a day reducing to 2 milligrams after five days.

In the early hours of the morning of the thirteenth day after operation the patient had a convulsion, lasting a few minutes, and was then completely irrational for some hours. He was found to have lateral rotation of both lower limbs with considerable pain at the hip joints on the slightest movement. Radiographs showed fractures of both femoral necks (Fig. 1).

The failure of large doses of intravenous calcium to prevent the convulsion or control the ataxic movements of the limbs suggested the possibility of a state of magnesium deficiency in addition to calcium deficiency. This was confirmed by finding a plasma magnesium level of 0·8 milligram/100 millilitres (normal range 1·8–2·2 milligrams/100 millilitres). He was given intravenous magnesium sulphate and started on magnesium glycerophosphate 8 grammes a day by mouth. Over the next six days his symptoms improved considerably. The ataxia and coarse tremor disappeared, but the positive Trousseau and Chvostek’s signs remained. The plasma magnesium gradually rose to normal during the next ten days, but the plasma calcium took three weeks to return to normal (Fig. 2). He continued taking dihydrotachysterol 2 milligrams and magnesium glycerophosphate 8 grammes a day for eleven weeks, and when this was discontinued he did not develop signs of tetany again.

The fracture of the neck of the right femur was reduced and nailed, and healed without incident. The fracture of the left femur presented quite a different problem. Attempts at closed reduction failed, and at open operation comminution of the anterior surface of the neck made fixation by nailing impossible. Prolonged immobilisation ended in painful and restricted movement, so a year later subtrochanteric osteotomy was carried out.

FIG. 1
Case 1—Radiograph taken immediately after the generalised convulsion showing fracture of the femoral necks.
The patient now remains pain free. He walks without a stick but has a slight limp. Radiographs of the skeleton show complete healing of the changes of hyperparathyroidism. The plasma calcium and magnesium levels remain within normal limits.

**Case 2**—A woman of twenty-eight was seen at the Glasgow Royal Infirmary in 1957 when she was diagnosed as suffering from congenital polycystic disease of the kidneys. When first seen her plasma urea was 120 milligrams/100 millilitres. Thereafter there was a steady rise in the plasma urea, though throughout she remained normotensive. On account of drowsiness and nausea she was dialysed in April and December 1962. The first dialysis produced symptomatic improvement lasting two to three months. Early in 1962 she began to complain of pains in the knees, ankles and hips which interfered with walking and which tended to wake her at night. The pain increased so much that she became almost completely bedridden. In January 1963 she was referred to University College Hospital for investigation and treatment of renal osteodystrophy. There was marked pallor of the mucous membranes, the blood pressure was 120/80 millimetres of mercury, and the fundi were normal. Both kidneys were greatly enlarged and easily palpable. She could walk, but did so with a waddling gait and with pain. All sudden movement even when lying in bed caused pain. Bone tenderness was present especially over the femora and the tibiae. Pseudoclubbing of the fingers was present and as usual was more marked on the fingers she used most, in this case the index and middle fingers and the thumb.

**Investigations**—The plasma calcium was 8.2 milligrams/100 millilitres. The specific gravity of the plasma was 1.024-5; phosphorus was 6.2 milligrams/100 millilitres; plasma magnesium 1.6 milligrams/100 millilitres; alkaline phosphatase 42 King-Armstrong units; twenty-four hour urinary calcium 130 milligrams; twenty-four hour urinary phosphorus 180 milligrams. The plasma sodium was 139 milli-equivalents/litre; potassium was 5.8 milli-equivalents/litre; chloride 101 milli-equivalents/litre; bicarbonate 15 milli-equivalents/litre; urea 230 milligrams/
100 millilitres; the plasma proteins were 5·8 grammes/100 millilitres, with a normal electrophoretic strip. The haemoglobin was 6·2 grammes/100 millilitres; serum iron was 125 micrograms/100 millilitres; packed cell volume 19 per cent; mean corpuscular haemoglobin concentration 33 per cent. The urine contained no protein, nine to ten red blood cells, numerous pus cells, and was sterile on culture. Radiographs of the skeleton revealed advanced changes of hyperparathyroidism with resorption and collapse of the distal phalangeal tufts and marked subperiosteal erosions of the middle phalanges (Fig. 3). The skull was markedly affected. The lumbar spine showed a typical "rugger jersey" pattern. A triangular deformity of the pelvic brim was present suggestive of healed osteomalacia. We have reason to believe from other patients with chronic renal failure indicating that they may pass through a phase of severe osteomalacia early in the disease which may heal spontaneously. No Looser zones were seen. Extensive vascular calcification was seen both in the abdominal and the peripheral vessels.

_Treatment and progress_—The clinical, biochemical and radiological findings confirmed the diagnosis of severe renal osteodystrophy. A calcium balance performed as described by Dent, Harper and Philpot (1961) showed the expected change found in chronic renal failure—negative calcium balance, with the faecal calcium greater than the intake (Fig. 4). Treatment presented a difficult problem. The high calcium phosphorus product in the plasma associated with gross arterial calcification contra-indicated treatment with vitamin D. It was thought that though vitamin D would heal the bones it would also increase arterial calcification.

**FIG. 3**

*Case 2—Index finger of left hand before operation, showing subperiosteal erosions of the phalanges with collapse of the shafts of the distal phalanx producing pseudoclubbing.*

It was decided to carry out total parathyroidectomy on the basis of the theoretical argument suggested from this department by Dent _et al._ (1961), and other reports of promising results following subtotal parathyroidectomy (Stanbury, Lumb and Nicholson 1960; Findley, Moore and Brackney 1961; Anderson, Mann, Kenyon, Farrell and Hills 1963). Two milligrams of dihydrotachysterol a day were given ten days before operation in anticipation of the development of severe tetany afterwards. Dialysis was performed using the method described by Shaldon, Chiandussi and Higgs (1961). In March 1963 a total parathyroidectomy was performed. The four glands weighed a total of 2·7 grammes and histological examination showed hyperplastic tissue consisting of predominantly clear chief cells. Immediately after operation dihydrotachysterol was increased by 5 milligrams, and 10 grammes of calcium lactate a day was added. In spite of this therapy and the preoperative loading with dihydrotachysterol, by the third day after operation the plasma calcium had fallen to 6·1 milligrams/100 millilitres (Fig. 5), and she developed the symptoms and signs of tetany. An intravenous infusion containing variable amounts of calcium gluconate was started, but even though at one stage she was having 100 millilitres of 20 per cent calcium gluconate per hour her tetany persisted, and she had a typical grand mal convolution during which she sustained multiple fractures involving both sides of the pelvis with the fracture line running through both acetabulae. At the time of the convolution the plasma calcium was 4·5 milligrams/100 millilitres, and her plasma magnesium was 1·2 milligrams/100 millilitres. She was given intravenous magnesium sulphate. The magnesium levels rose to the normal range over the next two days without further magnesium dosage. The dihydrotachysterol was increased to 10 milligrams a day, and at the same time she was given aluminium hydroxide Gel B.P. (which consists of 3·5 per cent weight in weight of Al₂O₃) 30 millilitres four times daily with meals in an effort to lower the plasma phosphorus. The reasoning behind the use of aluminium
Case 2—Metabolic balance studies. The balance data are plotted in the conventional fashion (Reifenstein, Albright and Wells 1945). The intake of calcium is measured downwards from the zero line. The output of faecal and urinary calcium is measured upwards. The clear space below the zero line represents the positive balance or retention of calcium, while the space above the line represents the negative balance. The pre-operative balance shows an average negative calcium balance of 180 milligrams a day with a faecal calcium greater than intake. In contrast the post-parathyroidectomy balance shows an average daily positive balance of 190 milligrams, with a faecal calcium less than 50 per cent of the intake. Ten days before beginning the post-operative balance the dihydrotachysterol was discontinued. It is of interest to note that throughout the balance period the plasma calcium tended to fall, probably due to working off of the previous dose of dihydrotachysterol. Soon after the end of the balance the dihydrotachysterol was restarted, and the plasma calcium quickly rose to normal levels.

Case 2—This shows the levels of calcium and phosphorus. The plasma calcium levels have been corrected for the specific gravity of the plasma specimen on which the calcium was measured as described by Dent (1962). Note the effectiveness of aluminium hydroxide in lowering the plasma phosphorus levels. The dihydrotachysterol at a dose of 2 milligrams a day was begun ten days before parathyroidectomy.
hydroxide was that we believe that after removal of all the parathyroid glands an extremely rapid suction of calcium into the bones developed, and that this resulted in the very severe hypocalcaemia which seemed to be resistant to the usual forms of therapy. We argued that by lowering plasma phosphorus we would be able to decrease the amount of phosphorus available for combination with calcium to form hydroxyapatite crystals and thereby impede the rate of new bone formation and slow down the removal of calcium from the plasma by its transfer into bone. That the bones were healing extremely rapidly was confirmed by a radiograph taken nineteen days after operation which showed a most remarkable degree of recalcification and healing of the phalanges (Fig. 6). With the introduction of the aluminium hydroxide and the increased dose of dihydrotachysterol there was a steady rise in the plasma calcium to normal levels associated with a fall in the phosphorus. Within three days she lost all signs and symptoms of tetany.

Apart from the problem related to the calcium metabolism the postoperative course was extremely stormy. Dialysis was carried out five times during the first ten days after operation. This was facilitated by indwelling percutaneous catheters. During one of the dialyses she developed a haemorrhage into the neck wound, due possibly to the anticoagulant used during the dialysis, and this caused temporary tracheal obstruction. She later developed staphylococcal pneumonia which required tracheostomy but this was controlled by cloxacillin. The fracture of the pelvis was treated conservatively, skin traction being applied to the left leg for three weeks.

**Fig. 6**

*Case 2—Index finger of left hand nineteen days after operation, showing remarkable recalcification of the phalanges.*

In spite of all these setbacks, six weeks after parathyroidectomy she was very well indeed. Bone pain had disappeared except for a slight pain in the left hip. She was allowed out of bed, and later allowed to walk with the aid of a stick. The plasma urea was 215 milligrams/100 millilitres and all the electrolyte levels were normal. We took the opportunity to do a further calcium balance and this showed a positive balance. In contrast to the balance before operation, on this occasion the faecal calcium was much less than the dietary intake of calcium. The dihydrotachysterol was discontinued ten days before the balance was performed and while on balance there was a steady fall in plasma calcium from 9·4 milligrams/100 millilitres to 7 milligrams/100 millilitres. This indicated that she certainly required the dihydrotachysterol and this was restarted after completion of the balance.

The reduction in the bone pain and the healing of the bones shown radiologically were extremely rapid for three weeks. After this the rate of healing decreased considerably, possibly due to the effect of the low plasma phosphorus. Radiographs of the pelvis six weeks after operation showed the development of Looser zones at the site of the fractures, and no evidence of healing (Fig. 7). At this time the patient was having 2 milligrams of dihydrotachysterol a day. Later the Looser zones healed well, while she was still receiving aluminium hydroxide, and the radiological signs of hyperparathyroidism had completely disappeared seven months after the parathyroidectomy (Figs. 8 and 9). After discharge from hospital she received a maintenance dose of 0·5 milligram of dihydrotachysterol a day and 30 millilitres of aluminium hydroxide four times a day. She remained completely pain free and had no further symptoms or signs of tetany. She was able to do light housework. We deliberately kept her plasma calcium and phosphorus levels low in order to facilitate possible dissolution of her arterial calcification which, however, was not observed during follow-up. During the next nine months she required intermittent peritoneal dialyses at four to six week intervals, after each of which she remained remarkably well for about four weeks. In February 1964 she became much more
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Case 2. Figure 7—Radiograph of the pelvis thirty-seven days after the convulsion, showing further collapse of the pelvis and fractures of both acetabulae where Looser zones have developed. Figure 8—Index finger of left hand seven months after operation. There is no longer any evidence of hyperparathyroidism. The distal phalanx remains deformed.

Case 2—Radiograph of the pelvis seven months after operation, showing healing of the pelvic fractures in spite of remaining on aluminium hydroxide since the time of fracture.
drowsy and peritoneal dialysis which, each time was becoming technically more difficult, was only partially effective.

It was finally decided not to carry out any further dialyses. She died in March 1964 almost a year after the parathyroidectomy. Necropsy confirmed advanced polycystic disease of the kidneys. Histological examination of the bones showed gross osteomalacia, but no evidence of hyperparathyroidism.

**DISCUSSION**

Generalised convulsions following parathyroidectomy may be a serious and disabling complication. When these occur in patients with severe bone disease pathological fractures may occur. If post-operative tetany proves resistant to the usual forms of therapy the possibility of hypomagnesaemia must always be considered in patients with severe bone disease.

There are a number of reports of magnesium metabolism in hyperparathyroidism in the literature. Bulger and Gausmann (1933) described a woman patient suffering from primary hyperparathyroidism with extensive bone disease who had a negative calcium and magnesium balance. After removal of a parathyroid adenoma she went into positive balance for both calcium and magnesium. Tibbetts and Aub (1937); Barnes, Krane and Cope (1957); Hanna, North, MacIntyre and Frazer (1961) confirmed these findings. There is little evidence yet to suggest a direct action of parathyroid hormone on magnesium metabolism. It appears that after the removal of excess parathyroid hormone, new bone formation increases while bone resorption decreases. As a result of this process there is a suction of both calcium and magnesium into the bone, giving rise to hypocalcaemia and hypomagnesaemia (Potts and Roberts 1958). In patients with severe bone disease the suction of calcium and magnesium is most marked, and hence in these cases the post-operative plasma levels are likely to be very low. It is likely that after parathyroidectomy both calcium and magnesium deficiency may occur together and confuse the clinical picture. MacIntyre (1963) claimed that tetany, in the sense of painful peripheral muscle cramps and paraesthesiae, does not occur in magnesium deficiency and considered the use of the word ‘tetany’ in relation to magnesium to be inaccurate. Mental changes are common in hypocalcaemia and usually take the form of tearfulness and marked depression, which respond remarkably well to intravenous calcium, the symptoms often completely clearing temporarily before the injection has been completed. Agitation, aggressiveness and irritability are uncommon with low calcium, but may occur with low magnesium. Tremor does not occur in low calcium states, though there may be some clumsiness in performing fine movements due to muscular spasm. Convulsions may occur both in association with low calcium and low magnesium states. The clinical picture may sometimes be of some assistance in helping to differentiate between hypocalcaemia and hypomagnesaemia, or what is more likely, to make one suspect that both conditions coexist.

In the first patient the clinical picture of hyperactivity and tremor fits in well with a magnesium deficient state. In addition the extremely low level of plasma magnesium (0.8 milligram/100 millilitres) makes it very likely that the magnesium deficiency played an important part in causing the convulsions, although at the time the plasma calcium was also low. The patient had severe bone disease and this is likely to be the major factor producing both low calcium and low magnesium states. In the second patient the plasma magnesium at the time of the convulsion was 1.2 milligrams/100 millilitres. The symptoms seemed to be those of calcium deficiency with marked paraesthesiae, positive Trouseau and Chvostek’s signs, and depression. We treated her with a single injection of magnesium and a calcium raising régime and it is therefore impossible to know what part the low magnesium level played in producing the convulsion but it seems unlikely to have been a prominent one, as the subsequent magnesium levels quickly returned to normal without any further replacement therapy.

At present the treatment of choice for most patients with renal osteodystrophy is vitamin D. This was first suggested by Liu and Chu (1943) and shown to be effective by Dent, Harper and Philpot (1961) and Stanbury and Lumb (1962). In the appropriate doses, which may sometimes
be very large indeed, vitamin D brings about healing of the bone lesions and loss of disabling bone pain. At the same time there is a change in the calcium balance picture which before treatment shows a high faecal calcium, often greater than intake, and a low urine calcium, producing a negative balance. After treatment there is an increased absorption of calcium from the gut and a positive balance is restored. Circumstantial evidence seems to point to a circulating anti-vitamin D substance which is either produced or alternatively not destroyed by the diseased kidney. The parathyroid glands are stimulated by the low level of ionised calcium or possibly by the circulating anti-vitamin D substance. The former explanation is unsatisfactory as it does not explain the cases of renal osteodystrophy occurring when the plasma calcium is normal throughout the disease. The action of vitamin D seems to depress the activity of the parathyroid glands and produce healing of the bone lesions. One of the dangers and drawbacks in the use of vitamin D is that it is often necessary to raise the level of the plasma calcium in order to produce healing of the bone disease. This would tend to raise the calcium phosphorus product which carries a grave risk of increased metastatic calcification, a complication which is common in renal osteodystrophy (Herbert, Miller and Richardson 1941) even when untreated.

An alternative approach to treatment in the case difficult to control with vitamin D, or with extensive metastatic calcification, is removal of the parathyroid glands. This would remove excess parathyroid hormone, and the remaining bone disease could be healed with vitamin D in smaller doses than that required to suppress parathyroid hormone secretion. A number of case reports, where subtotal parathyroidectomy has been carried out, have been published (Stanbury, Lumb and Nicholson 1960; Findley, Moore and Brackney 1961; Anderson, Mann, Kenyon, Farrell and Hills 1963). It seemed to us that the more logical operation to perform would be total parathyroidectomy; this would prevent the recurrence of further hyperplasia of the remaining parathyroid tissue, similar to that occurring in subtotal adenectomy for adrenal hyperplasia.

The second patient had extensive vascular calcification, and treatment with large doses of vitamin D for any length of time would have been dangerous. We therefore thought that she would be a suitable case for total parathyroidectomy. In common with the observation of many other workers we found that all the parathyroid glands were enlarged and showed chief cell hyperplasia histologically. A post-operative fall in her plasma calcium was anticipated because of the severity of her bone disease and for this reason 2 milligrams a day of dihydrotachysterol was started ten days before the operation and increased to 5 milligrams a day immediately after the operation. A combination of dihydrotachysterol, oral and intravenous calcium was ineffective and failed to prevent a generalised convulsion and fracture of her weak pelvic bones. It was only with the introduction of aluminium hydroxide to the therapeutic régime that we were able to produce a rise in her plasma calcium levels. Aluminium hydroxide acts by combining with the dietary phosphate in the gut (and therefore must be given with the main meals) to increase faecal phosphorus and thereby decreases the plasma phosphorus.

Albright and Reifenstein (1948) originally suggested the use of a low phosphorus intake to control post-operative tetany. They considered that this would keep the calcium from going into the bones, as calcium leaves the blood as calcium phosphate to be precipitated in bone. They suggested that the patient should be maintained on a high calcium, low phosphorus régime. They stated that in their experience the only successful way of dealing with post-operative tetany was to put the patient on a continuous intravenous infusion containing calcium lactate or calcium gluconate. We feel that the use of aluminium hydroxide to lower the plasma phosphorus has an important place in the control of severe post-operative hypocalcaemia. It is of great interest to note that while the second patient was on aluminium hydroxide there was a delay in callus formation at the site of the pelvic fractures. The radiological appearance was that of a Looser zone. This occurred in spite of the administration of dihydrotachysterol, and at necropsy marked osteomalacia was seen in all the bones examined.
SUMMARY

1. Convulsions causing fractures complicated the post-operative course of two patients after parathyroidectomy.

2. One patient with primary hyperparathyroidism and osteitis fibrosa developed tetany which was controlled with difficulty with the usual measures to correct hypocalcaemia. The convulsion occurred during hypomagnesaemia. This seemed the main immediate cause of symptoms and was easily corrected when recognised.

3. The second patient had been subjected to total parathyroidectomy for treatment of renal glomerular osteodystrophy. The complications were entirely due to hypocalcaemia and the usual treatment was inadequate until oral aluminium hydroxide was given.

4. Further experience shows that aluminium hydroxide can be a valuable addition to other measures for dealing with hypocalcaemia due to the "hungry bones" phenomena.

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