HYPO-HYPERPARATHYROIDISM

BY

J. M. COSTELLO and C. E. DENT

From the Paediatric Department and Medical Unit, University College Hospital, London

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Many interesting problems still require explanation concerning the role played by the parathyroid gland. The recent isolation (Rasmussen and Craig, 1961) of a seemingly pure hormone from the gland, which has both plasma calcium raising and plasma phosphorus lowering activity settles one point, namely that these two activities can be shown by the one substance. We still do not know, however, if the pure hormone can also produce osteitis fibrosa. Indeed there is some clinical evidence based on the study of primary hyperparathyroidism, which suggests that the osteitis fibrosa when present is not produced by the same factor that causes the plasma Ca and P changes (Dent, 1962). Even more difficult to consider is the problem of secondary hyperparathyroidism since its presence as a complication, say, in a patient with steatorrhoea or renal failure, can only be surmised from the indirect evidence provided by a study of calcium and phosphorus metabolism or of the bone radiographs or biopsy, or by a study (usually *post mortem*) of the parathyroid glands. We will not solve many of these problems till we can assay directly in plasma for the one or more parathyroid hormones which may be produced. Till such time we will remain largely dependent on clinical studies of patients selected because of some particularly significant feature.

In this paper we describe a child with what we believe to be a new syndrome in which apparently contradictory findings with respect to parathyroid function are simultaneously present, namely, biochemical hypoparathyroidism as shown by plasma calcium and phosphorus levels, and radiological and biochemical hyperparathyroidism as shown by the pathognomonic x-ray changes in the bones with a raised plasma alkaline phosphatase level. Both states have, as expected, reverted to normal with a suitable large oral dose of vitamin D. The patient shows no other physical or metabolic

abnormalities, indeed she has enjoyed quite normal health while under treatment over the past six years. She is becoming a champion netball player in her locality, and is of above average intelligence.

Metabolic Studies

Biochemical determinations and metabolic balances were done as described previously (Dent, Harper and Philpot, 1961).

Case History

Before Admission to University College Hospital. The patient (Gail P.) was born on April 16, 1948, following a normal delivery. Her birth weight was 8½ lb. (3.48 kg.). She was breast fed. She received cod liver oil and orange juice supplements until the age of 2 years. She walked at 11 months. She was well until March 1955 when (at the age of 6 years 11 months) she began to walk with waddling gait and soon afterwards complained of fatigue. On examination at that time she had almost complete limitation of abduction of both hip joints and tenderness over the left hip. She was admitted to the Mount Gold Hospital in Plymouth under the care of Mr. F. T. Wheeldon from May 31, 1955 to August 13, 1955.

Investigations at this time included radiographs, which were considered to show the changes of renal rickets (Fig. 1a and b). Serum calcium estimation 8.4 mg./100 ml.; serum alkaline phosphatase 19.2 King-Armstrong units; blood urea 26 mg./100 ml.

Treatment consisted of administration of 7,800 units of vitamin D (in the form of cod liver oil) daily throughout her stay in hospital and for one month following this. Orthopaedic traction of both legs was carried out and at the time of discharge from hospital she was able to walk with the aid of crutches.

She was admitted to hospital a second time under the care of Dr. Hugh Jolly at the South Devon and East Cornwall Hospital, Plymouth, from October 21, 1955 to December 14, 1955. At this time she was free of pain but only able to get about with crutches. Repeated further investigations at this time confirmed her low serum calcium values (8.4-8.7 mg./100 ml.) and raised serum phosphorus values (5.6-7.8 mg./100 ml.). The serum alkaline phosphatase varied from between 19.2 units and 39.6 units. The 24-hour urinary calcium

* Now at Auckland Hospital, Auckland, New Zealand.

FIG. 1a.—Pelvis and hips of Gail P. (July 26, 1955). Note the metaphyseal rarefaction and deformity. The femoral shafts are well formed and straight as if the bone disorder is of relatively recent origin.

excretion was 30.4 mg./24 hr.; CO_2 combining power 25 mEq/l.; serum cholesterol 137 mg./100 ml. The amino acid excretion in her urine was considered not to be above normal. She was also found to have a normal fat balance, normal glucose tolerance test, and a normal intravenous pyelogram. The urea clearance was 79% of average normal. Radiographs of the hands showed subperiosteal resorption of the phalanges (Fig. 1c). She was treated with a 1,000-calorie diet and as a result lost weight. She continued to have no pain, was able to dispense with her crutches, and to walk without a waddle.

On Admission to University College Hospital. The patient was referred by Dr. Jolly to one of us (C.E.D.) at University College Hospital at the suggestion of Dr. Alex Russell, who also thought her bone radiographs showed hyperparathyroid changes. She was admitted in April 1956, at the age of 8 years. She had been well recently apart from an episode of pins and needles in both hands and feet which she had noticed on waking in the morning three weeks before admission. Her thumbs were held across the palms and could be pulled out only with difficulty. This attack passed off within an hour. She had had no other definite attacks of carpal spasm, but she was prone to 'pins and needles'.

Her appetite was good. Bowels were regular and she had no urinary symptoms.

Apart from her illness which had caused her admissions to hospital in Plymouth, the only feature of interest was that she had fractured her left wrist after falling off a scooter two years previously. This fracture had healed normally.

The child's parents are healthy and unrelated. Both have normal body proportions. The father is 6 ft. 1 in. (185 cm.) in stature and has plasma Ca 9.2 and P 3.5 mg./100 ml., phosphatase 10 K.-A. units. The mother is 5 ft. 8 in. tall (173 cm.) and has plasma Ca 10.7 and P 3.6 mg./100 ml. and phosphatase 13.5 K.-A. units. One brother of 6 years who was well and of normal body proportion was tall (4 ft. 8½ in. (143 cm.)) for his age (plasma Ca 9.7, P 4.9 mg./100 ml., phosphatase 8 K.-A. units).

Examination at the time of admission on April 17, 1956, revealed a healthy-looking plump girl of average intelligence (I.Q. 102). Her height lay just above the 90th percentile (53½ in. (136 cm.)); span 54 in. (137 cm.); pubis to heel 27 in. (68.5 cm.). There was 1 in. (2.54 cm.) shortening of the left leg above the knee. No bony tenderness was present. The Chvostek sign was positive on two occasions only. The cardiovascular system was normal, the blood pressure being 95/55 mm. Hg. The

FIG. 1b.

FIG. 1c.

FIG. 1b.—Left knee (July 5, 1955). There is density of the metaphysis and no trace whatever of a rachitic change. This means that the changes in 1a cannot be due to rickets but are fully consistent in their distribution with hyperparathyroidism. This appearance of the knees remained in all later films.

FIG. 1c.—Hands (November 24, 1955). Typical subperiosteal erosions pathognomonic of hyperparathyroidism. No rachitic changes.

respiratory, alimentary and central nervous systems appeared normal.

Investigations revealed a low plasma calcium (7.6 mg./100 ml.), raised plasma phosphorus (8.8 mg./100 ml.), raised serum alkaline phosphatase (40 King-Armstrong units). Plasma Na 135 mEq/l., K 4.4 mEq/l., HCO_3 17.9 mEq/l., urea 24 mg./100 ml. Total serum protein 7.1 g./100 ml. (albumin 4.4, globulin 2.7). Urine: acid reaction, no protein, normal on microscopy. Renal function on routine ward testing: maximum urea concentration 2.1%, maximum urine concentration SG 1,024, maximum urine dilution SG 1,003 (with normal excretion of water load), maximum urea clearance 74% (uncorrected for age), standard urea clearance 57% (uncorrected for age); fat balance: 96.7% of fat was absorbed on an intake of 60 g./day. Amino acid chromatogram of urine was normal. Radiographs revealed subperiosteal erosions of the phalanges of the hands, spottness of the skull, and absence of the lamina dura of the teeth. The femoral necks showed compression deformities. Changes at the growing ends of the wrists and knees were only slight by comparison with those of the hips (Figs. 2a, 3a, 4a and 5). In view of the pathognomonic radiological changes we decided that a bone biopsy examination was not justifiable.

Treatment During First University College Hospital Admission. The preliminary biochemical investigations suggested that she had hypoparathyroidism. This diagnosis, however, did not explain her raised alkaline phosphatase. On the other hand her radiological findings were those of hyperparathyroidism, a diagnosis consistent with the raised alkaline phosphatase. These findings appeared contradictory and at that time unprecedented. It was decided to treat her hypocalcaemic tetany and to see if this also had an effect on her bone lesions.

The metabolic data obtained while in hospital are summarized in Fig. 6. She was given a constant diet with normal content of calcium, phosphorus and nitrogen, and after the usual equilibration period, six-day calcium and phosphorus balances were collected. During the two control periods she was shown to be in a positive calcium balance of about 170 mg. per day, nearly all her calcium excretion being in her stools. This was considered to be a little less than it should be for her age and to resemble that found in mild vitamin D deficiency for which, however, there was not a shred of other evidence. She was then given 0.25 mg. of vitamin D_3 and two further six-day periods collected, as a similar small dose had appeared to produce clinical improvement in the summer of 1955. The balance did not

FIG. 2a.

FIG. 2b.

FIG. 2c.

FIG. 2a.—The fingers (April 18, 1956). Subperiosteal erosions, terminal tuft erosions and early cyst formation, all typical of hyperparathyroidism.

FIG. 2b.—Fingers (September 17, 1956) showing a considerable degree of healing.

FIG. 2c.—Fingers (January 5, 1960). These are quite normal and typical of all her later films.

change on this dose, nor were there any changes in the plasma levels of calcium and phosphorus. The dose of vitamin D_3 was, therefore, raised to 5 mg. a day. On this dose for four six-day periods she slowly went into a positive calcium balance of about 400 mg. daily, the excretion still being almost entirely in the stools. During this latter treatment her plasma calcium rose to normal and there was a fall of about 1 mg./100 ml. in the phosphorus level. Phosphatase was slowly falling from 40 to 30 units during this time. Phosphorus balance throughout was about half the calcium balance indicating that new bone formation was occurring. There was no radiological change visible during the whole of her stay in hospital. She was sent home on the same dose of vitamin D_3 . From the fourth balance period and during all her follow-up the vitamin D_3 given was prepared from pure crystalline cholecalciferol in capsules regularly assayed for potency, as we had evidence that the tablet form previously given was not fully stable.

Subsequent Follow-up. Her subsequent progress is summarized in Fig. 7.

She was readmitted to U.C.H. for a second time from September 15 to 26, 1956. At that time she was well and had been getting around normally at school. In spite of her previous period in hospital her schoolmistress reported that she had quickly caught up with the other girls in her lessons. Investigations at this time revealed: plasma Ca 9.5 mg./100 ml., plasma P 6.7 mg./100 ml., alkaline phosphatase 28 units/100 ml.; plasma HCO_3 21.4 mEq/l. She was able to concentrate her urine to SG 1,022 overnight and to dilute to SG 1,001 after ingestion of water. The radiographs showed a definite lessening of the hyperparathyroid changes (Fig. 2b). It was decided that she had shown a response to the vitamin D_3 in the hoped-for direction, both hypo- and hyperparathyroidism signs simultaneously improving with the one treatment. She was changed from a dose of 5 mg. vitamin D_3 daily to a dose of 3 mg. daily.

FIG. 3a.

FIG. 3b.

FIG. 3a.—Wrist (January 4, 1956). There are parathyroid erosions on both outer edges of the ends of the ulna and radius. There is no rickets.
 FIG. 3b.—Wrist (January 5, 1960). Typical appearance of healed bones during later follow-up.

We were prepared to take the risk of overdosage to ensure as rapid healing of her hips as possible. She was followed subsequently with short admissions to hospital every three to six months. In March 1957 (10 months after starting treatment), although asymptomatic, she was found to have a high normal plasma calcium (11.1 mg./100 ml.), high urinary calcium (325 mg./24 hrs) and high normal plasma urea (42 mg./100 ml.). A repeat plasma calcium estimation showed: total calcium 10.7 mg./100 ml., ionized calcium 5.9 mg./100 ml., un-ionized ultrafiltrable calcium 1.2 mg./100 ml. As her ionized calcium was not as dangerously high as might have been implied from her total plasma calcium level, it was decided not to change her treatment. We were still anxious to secure as rapid healing as possible of the femoral neck lesions.

In July 1957 (14 months after starting treatment) she developed slight thirst and nocturia. Investigations at this time showed that she was suffering from vitamin D intoxication. Plasma calcium (1) 14.7 mg./100 ml.; plasma calcium (2) 14.2 mg./100 ml. (total ultrafiltrable calcium 8.9 mg./100 ml., ionized calcium 7.8 mg./100 ml.); plasma phosphorus 5.1 mg./100 ml.; alkaline

phosphatase 14 King-Armstrong units; 24-hour urinary calcium 404 mg.; plasma urea 78 mg./100 ml., HCO_3 24.5 mEq/l.; Hb 68%; absolute indices normal. A clean specimen of urine showed a trace of protein, numerous pus cells and fairly numerous hyaline casts. Radiographs of her hands showed almost complete disappearance of the parathyroid changes; the hips, however, were not yet fully reformed.

Her vitamin D was stopped for one month and then resumed at a dose of 1 mg./day. Her symptoms which were minimal soon subsided.

She was readmitted three months later (i.e. 17½ months after starting treatment) at which time she was symptom free and had no abnormal physical signs. Her plasma calcium was still raised (11.4 mg./100 ml.) suggesting a mild vitamin D intoxication, but a normal plasma urea (33 mg./100 ml.) and a slightly raised alkaline phosphatase level (25 K.-A. units) did not support this. It was decided not to change her dose of vitamin D but to watch her carefully.

In February 1958 (21 months after starting treatment) she was well with no abnormal signs. Her height continued to follow the 90 percentile. She had recovered

FIG. 4a.—Right hip (January 4, 1956). Gross disorganization of femoral neck with deformity. While this superficially resembles rickets there is no gap visible in the region of the epiphyseal plate and the erosions are probably purely metaphyseal as in hyperparathyroidism.

from her previous slight overdose of vitamin D. Urine was normal on microscopy and sterile on culture. Radiographs of her hands were almost normal.

From then on her progress was fairly uneventful. In January 1959 it was decided to reduce the dose of vitamin D₃ to 0.5 mg. daily in view of the rather high plasma calcium level of 10.8 mg./100 ml. and a rise in her urinary calcium level. Three and a half months after the reduction of the dose of vitamin D₃, slight periosteal erosions of the phalanges reappeared on the radiographs of her hands. This was associated with a 24-hour urinary output of calcium of 53 mg., and because of this it was considered that she was probably now underdosed. However, it was decided not to increase her dose of vitamin D₃ but to review the situation four months later. During these subsequent four months her subperiosteal lesions healed again and no increase in the dose of vitamin D₃ was therefore necessary.

In August 1959 she developed consolidation in the right lower zone and this was associated with a pneumococcal urinary infection. These infections cleared with a course of penicillin and sulphadimidine.

In May 1961 and January 1962 slight recurrence of hyperparathyroid changes in the radiographs of her hands occurred, but as the alkaline phosphatase had not risen above 25 units no change in dose of vitamin D₃ was advised.

She continues (December 1962) to be in good health on a dose of 0.5 mg. vitamin D₃ daily.

A typical body photograph is shown in Fig. 8. Typical follow-up radiographs are shown in Figs. 2c, 3b and 4b. Her summarized growth curve during the whole period is shown in Fig. 9. It is noted that she began on a high percentile for height and kept approximately to this line throughout. We think this provides further strong evidence against the possibility of her having rickets,

FIG. 4b.—Right hip (January 4, 1960). There has been excellent healing with some correction of the deformity, in spite of her being ambulant most of the time.

which always causes slow growth of long bones. It also excludes the possibility of any occult serious disease such as steatorrhoea or renal failure.

We were most interested to plot 24-hour urinary P output against total plasma P levels during the whole of her treatment. We do not show the details here as our interpretation is based on unpublished data and requires further checking. As far as it goes we can briefly say that there was clear evidence of abnormally high PO_4 reabsorption by the renal tubule when she was in the untreated state. When fully controlled with vitamin D_3 the PO_4 reabsorption approximately halved, then being in the normal range. This renal tubular response is quite typical for hypoparathyroidism given any form of vitamin D.

Discussion

The case history has summarized our evidence for the existence in this child of a syndrome involving at the same time aspects of both hypo- and of hyper-

parathyroidism in the absence of any other disease. Our interpretation is we believe strongly confirmed by the evidence of our follow-up during which treatment has been given by vitamin D alone. The response to vitamin D of her hypoparathyroid changes was typical of that of a patient with either idiopathic or post-operative hypoparathyroidism (Figs. 1 and 2). At the same time the bone changes as shown on radiographs (Figs. 2a-c), and the plasma alkaline phosphatase levels (Fig. 7) also became normal, as will always happen in the case of a patient with hyperparathyroidism secondary to renal disease (Dent *et al.*, 1961) or to steatorrhoea (Davies, Dent and Willcox, 1956) and perhaps also in primary hyperparathyroidism with bone disease (Dent, 1962). We believe the case is, therefore, made for the existence of a paradoxical state of affairs such as is indicated in the title of this paper,

FIG. 5.—Lower incisors (April 23, 1956). No lamina dura is present, as is found in hyperparathyroidism.

which name for this disease we submit without qualms as it is meaningful and is easy to remember, and as the stage has already been set in Boston, U.S.A., for unusual nomenclature in this field (e.g. pseudo-pseudo-hypoparathyroidism.) Our review of the literature has shown no similar patients to ours. The nearest are the patients described by Kolb and Steinbach (1962) who showed similar 'hypo-hyperparathyroidism' in two patients who, however, also showed developmental changes similar to those described in pseudo-hypoparathyroidism. They were also unable to trace previous descriptions of similar cases. We are most grateful to Dr. Kolb who gave us a full account of his early researches in 1956, well before their publication in final form. The response to treatment in his patients was probably similar to our patient except that most of the time probenecid, a low phosphate diet and calcium gluconate as well as a form of vitamin D were being given, so the improvement he obtained is less easy to attribute to one factor only. Apart from our and his patients a similar paradoxical situation can probably also occur in renal failure and in steatorrhoea (our own unpublished

FIG. 6.—Balance data on patient during her first attendance. Intake is measured downward from the zero line, output upward from this. A space between the zero line and the top of the hatched areas represents a positive balance. It is noted that vitamin D₃ in 5 mg. doses caused the usual slow fall in faecal Ca excretion. P balance also became more positive to about half the Ca figure.

data). In the latter case plasma changes similar to those in hypoparathyroidism are well described as an occasional finding (Salvesen and Bøe, 1953; Jackson, 1957); hyper-, however, as shown by the bone radiographs is much more common (Davies *et al.*, 1956). The difficulty in the combined hypo-hyperparathyroid cases with renal and malabsorptive aetiology is in determining the time relations. The course of the disease is often of fluctuating severity and it is possible to argue that the 'hypo-hyperparathyroidism', if present, could be due to, say, a recent hypofunction supervening on a long-term hyperfunction whose corresponding bone changes are in course of reversal but that some time will elapse before they show signs of this. This argument cannot apply to our patient whose history strongly suggests simultaneous development of both hypo- and hyperparathyroidism during the first year of her disease and whose subsequent improvement coincided in time exactly as expected with the administration of the vitamin D.

Our preferred interpretation is that the para-

FIG. 7.—Summarized biochemical data on patient, explained more fully in the text.

thyroid gland normally produces at least two hormones: one, that recently isolated by Rasmussen and Craig (1961), with an action on plasma calcium and phosphorus levels, and another, whose excess production manifests itself by the production of osteitis fibrosa and a rise in plasma alkaline phosphatase. In our patient it is supposed that no 'Rasmussen and Craig hormone' is being produced while excess production occurs of 'osteitis fibrosa hormone'. There are other possible interpretations. For instance, there could be an excess production of one hormone having all these actions in the presence of a circulating antagonist only of the plasma Ca and P actions, by whatever mechanism this may act. The theory preferred by Kolb and Steinbach (1962) to explain the changes found in their two rather similar cases was more along the lines of the Albright theory of renal tubular unres-

ponsiveness to the action of the one parathyroid hormone produced. This would produce a chronically raised plasma phosphorus level, and then possibly lower plasma calcium and stimulate the parathyroids to produce an excess of hormone leading to osteitis fibrosa, the bones, unlike the kidney, being normally responsive to the hormone. Kolb and Steinbach did indeed treat one of their patients for a while with probenecid and high calcium and low phosphorus diet only, so as to increase renal phosphorus excretion and to counteract such a possible vicious sequence at its origin. Plasma calcium and phosphorus values became normal under this régime, and they further claimed some improvement in the bone radiographs. They did not continue the treatment for more than three months, but then added vitamin D (as calciferol or AT 10), this combined therapy lasting the next

FIG. 8.—Gail P (May 23, 1961) age 13 years.

FIG. 9.—Growth curve: she showed no stunting at any stage nor was a spurt of growth induced by treatment. This is against her having even a mild rickets. The earliest height recorded was obtained from her school record. The chart was obtained from the Department of Child Health, Guy's Hospital, London. Her growth corresponds approximately to the 90 percentile.

five years. Naturally most of the healing of the osteitis fibrosa occurred during the latter period.

We clearly need further studies along these lines to elucidate the theoretical challenge posed by these various patients. Recent work by Copp, Cameron, Cheney, Davidson and Henze (1962), suggests that the parathyroid gland may produce a hypocalcaemic hormone as well as its better known one(s). They have not yet quoted studies of the effect if any of their new hormone on renal phosphorus handling, so it is still difficult to apply this new knowledge to our current clinical problems. Nor do we yet know if the pure Rasmussen-Craig parathyroid hormone produces osteitis fibrosa.

The recent paper by Frame, Fruchtman and Smith (1962), in which a patient is described with long-lasting hypocalcaemia and clear-cell hyperplasia of her parathyroids, also poses problems of similar perplexity to those in our patient.

Summary

A child is described who presented symptoms from

hyperparathyroid bone disease (osteitis fibrosa generalisata) simultaneous with those of mild tetany shown to be due to idiopathic hypoparathyroidism.

On treatment with vitamin D alone the bone lesions healed and her plasma calcium and phosphorus levels became normal. This improvement has been maintained till the present time (six years).

The patient is normal in height and in mental and physical development. Steatorrhoea and renal dysfunction were not present, nor were the physical features of pseudohypoparathyroidism. In these latter respects she is unlike some other patients described recently.

The coincidence of signs of hypo- and of hyperparathyroidism in the same patient who has no signs of disease in any other system presents us with a considerable theoretical problem.

We wish to thank the nurses, dietitians and biochemists in the Metabolic Ward for the full study of her calcium and phosphorus balances during her admission, and for their work during her subsequent follow-up.

We are also most grateful to Dr. H. Jolly for referring the patient to us.

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