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Hyperparathyroidism in Childhood

A Case Followed up for 15 Years

By

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A female patient 14 years of age was admitted in 1952. The complaints had started 18 months before and consisted in orthopaedic changes and a hazelnut-sized node to the right of the trachea. The laboratory findings, X-rays, biopsy from the ulna, further the elimination of the possibility of a secondary hyperparathyroidism allowed to diagnose primary hyperparathyroidism (Recklinghausen's disease). A chief-cell parathyroid adenoma was then removed. X-rays revealed a process of regeneration after the lapse of six months; Ca content of the bones increased, the cysts disappeared, and the deformities also improved. Now, 15 years later the deformities and dwarfism persist, but the patient has no complaints. The observed changes in calcium metabolism are discussed in detail.

Primary hyperparathyroidism (generalized cystic fibrous osteitis, Recklinghausen's disease) is a rare condition in childhood. Nolan et al. [18] collected 23 such cases from the literature up to 1960; Fanconi and Mieth [6] found reports on further 15 cases between 1955 and 1967 to which they added a case of their own so that literature now contains a total of 39 verified cases of children's hyperparathyroidism. Our observation of a case continued for 15 years was thought to contribute some new points to a better understanding of Recklinghausen's disease in childhood. Gerlóczy and Farkas [12] were the first to report in 1953 on a case of compensatory hyperparathyroidism found in the newborn child of a mother suffering from hypoparathyroidism (idiopathic tetany); the second case was described in 1966 by Aceto et al. [1], the third and fourth in 1968 by Bronsky et al. [4].

Report of a Case

K. T., a girl of 14 years, was first seen in 1952. The family history was noncontributory. The complaints had begun 18 months before admission; she had been easily fatigued and developed a waddling gate. Weakness of bones had been diagnosed, but vitamin D treatment elicited no response. She had then fallen off a sledge, developed costalgia and became completely abasic. The girl had then been hospitalized in two instances, but the condition failed to improve on vitamin D treatment and pituitary transplantation. She had suffered a fracture of the left leg a month before admission.

The underdeveloped and malnourished child disclosed many recent and earlier dislocated fractures involving the metaphysis, neck and diaphysis of the femur; both legs; both metaphyses of the humerus; the distal metaphyses of the forearm bones, the ribs and the sixth thoracic vertebra. Therefore, the lower and upper extremities as well as the vertebral column showed a variety of deformities (Fig. 1).

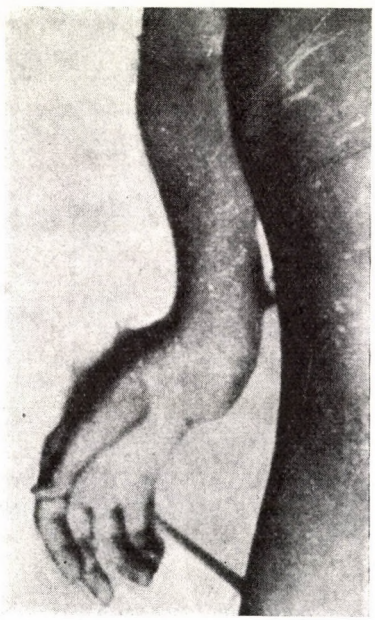

FIG. 1. Madelung-type deformity of right forearm and hand

When admitted, the patient had a plaster cast on the left lower extremity, while the right leg was free in maximum flexion. Wailing defensively, she held this extremity closely pressed to her trunk. X-ray examination under anaesthesia revealed a recent proximal and distal double fracture of the right femur at the diaphyseal border. These were fixed by a plaster cast covering the entire leg and pelvis.

X-rays showed a high degree of calcium deficiency in all bones. At certain points, their shadow was hardly distinguishable from the surrounding soft tissues. The distal metaphysis of both forearm bones was fractured with a dorsal dislocation of about 45°. Their cortex was uneven and thin, that of the phalanges showed erosions with occasional fine accompanying shadows; one or two small cysts were seen in the cortex and the spongiosa (Fig. 2). The cranial bones were thickened, the diploe widened; the outer table was invisible and its shadow was confluent with that of the diploe; the inner table was

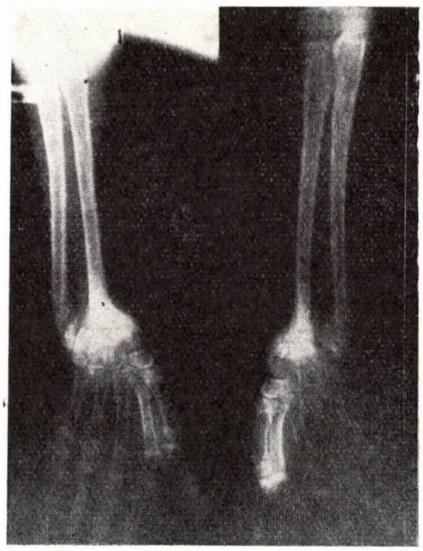

FIG. 2. Dislocated fracture of ulna and radius. Loose and partly eroded phalangeal cortex

considerably loosened. The amount of calcium in the bones of the cranial base and in the mandible seemed to be normal (Fig. 3). The upper portion of the thorax was narrow, and its shape approximately triangular owing to the outward bulge of the lower ribs. The midribs were fractured, the body of the sixth thoracic vertebra was flat (Fig. 4).

The pelvis was laterally compressed and of heart shape; the acetabulum and the joint cavity were obscured by the shadow of the adjacent soft tissues. The

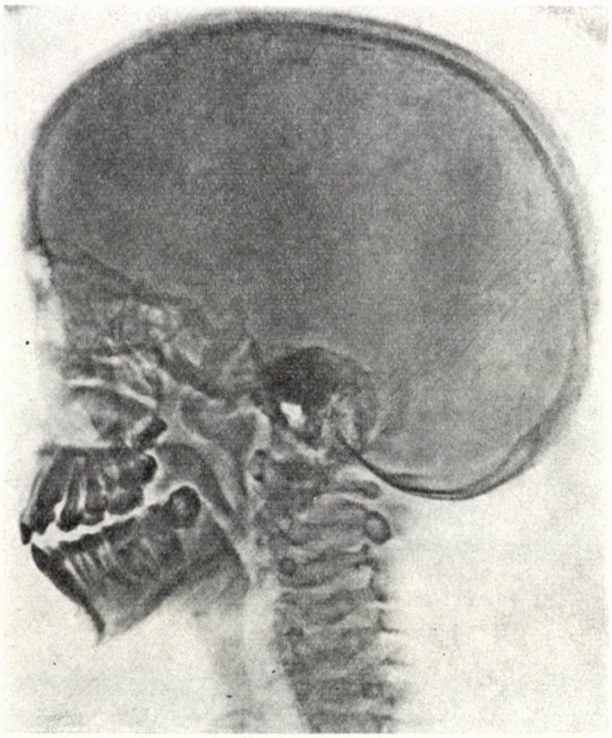

FIG. 3. Massive cranial bones, broad diploë, blurred contours, especially of outer table. Calcium content of the base almost normal

proximal part of the femurs was fractured involving dislocations of 90°. The contours of the little pelvis were hardly distinguishable (Fig. 5).

	Se. Ca	Se. P
	mg per 100 ml	
0' 8 ml Ca intravenously	15.2	2.3
5' 8 ml Ca intravenously	13.6	2.3
1^h	15.4	2.6
5' 8 ml Ca intravenously		
1^h	16.0	2.4
2^h	11.2	2.2
	14.4	3.3

Sulkovitch's test was ++++; urinary output of Ca variable; NPN, urine concentration and dilution were normal.

Repeated Ca and P determinations yielded a maximum value of 15.6 mg per 100 ml for serum calcium and one of 2.5 mg per 100 ml for serum phosphorus.

Double Ca loading gave the following results.

Hypercalcaemia and hypophosphataemia as well as the results of calcium loading pointed to Recklinghausen's disease and this the more so as an adenoma was palpable to the right of the trachea. To ensure the diagnosis, two longitudinal pieces were excised from the ulna of the left forearm which showed likeness to Madelung's deformity.

The specimens consisted of coarsely fibrous connective tissue containing trabeculae. Marked signs of lacunar reabsorption (Howship's foveolae) were observed at numerous points of the bony trabeculae many of which were split into laminae. No mosaic structure was observed. The

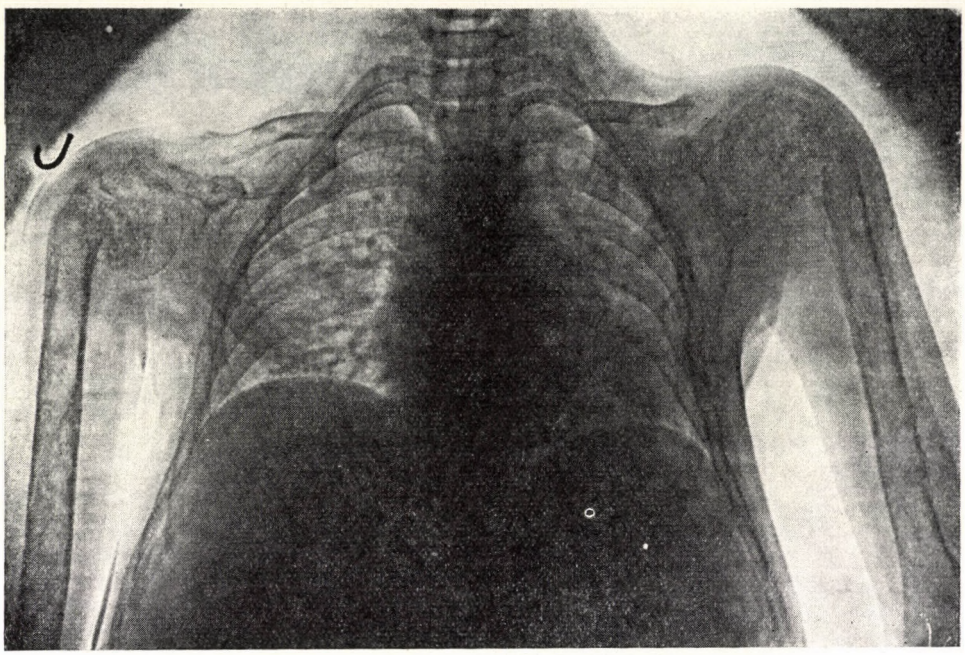

FIG. 4. Calcium-deficient bones. Surgical head of both humeri fractured. The heads of the humeri are almost radiolucent. Deformed, downwards broadening thorax

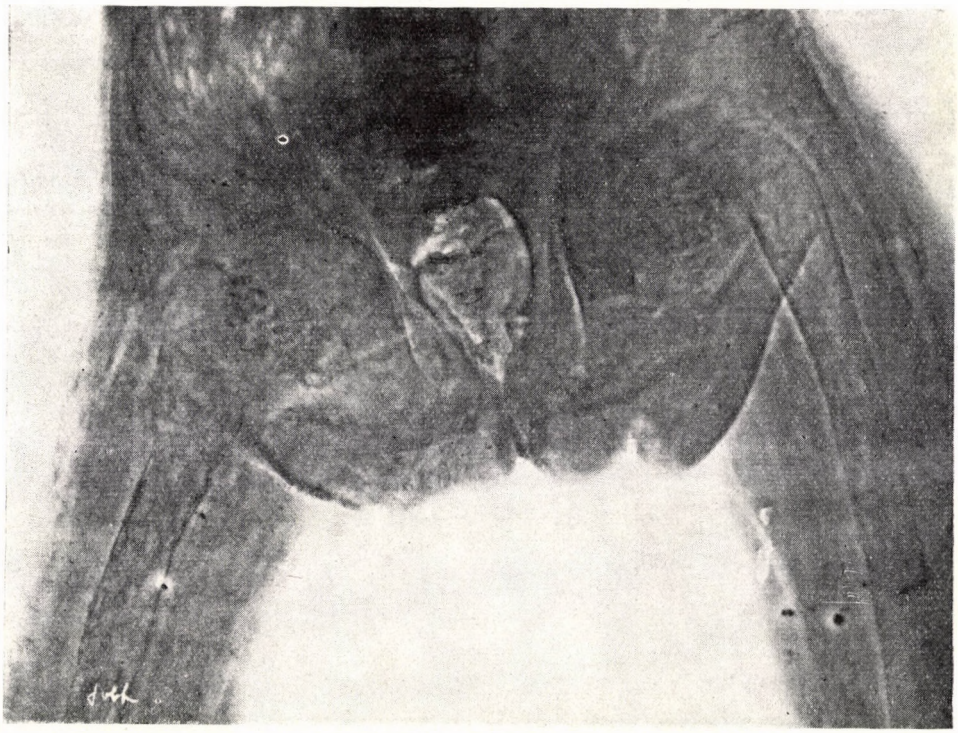

FIG. 5. The pelvic bones are hardly distinguishable from the surrounding soft tissues. Impressed acetabula. The femoral heads are hardly visible. The neck of both femora is fractured with marked dislocation. Sacrum, pubic bone, ischium hardly identifiable

Haversian canals were considerably distended, and the formation of perforating channels was seen. Recklinghausen's grid-iron configuration was clearly visible. There were occasional islets of cartilage which displayed signs of regression. The bone marrow was replaced by richly capillarized fibrous connective tissue with osteoclasts; haemopoietic elements were absent. Certain areas of the specimen contained osteoid islets in which no trace of calcium could be detected. There were haemorrhages at numerous points, while at others deposits of haemosiderin were

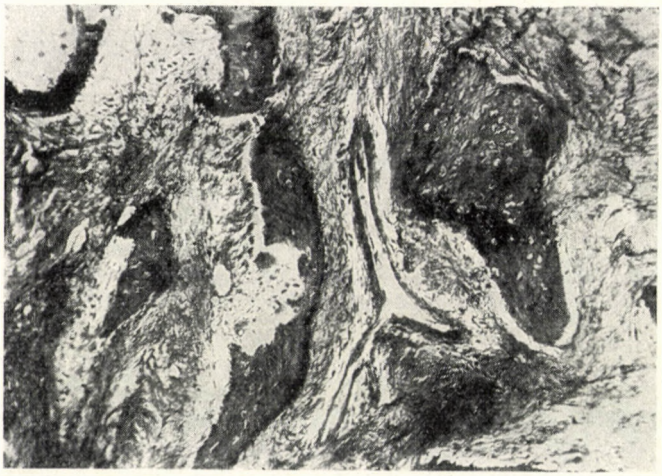

FIG. 6. Trabeculae split up into laminae and showing marked signs of lacunar resorption. Dilated Haversian canals. Note Recklinghausen's lattice pattern. The bone marrow is replaced by richly capillarized fibrous tissue. Several osteoid islets and haemorrhages with haemosiderin deposits can be seen

observed (Fig. 6). The histological picture, together with the clinical symptoms and the radiological findings, left no doubt that the case was one of Recklinghausen's disease. Accordingly, we resorted to surgical management.

Surgery. From Kocher's incision the thyroid lobe of small apple size was exposed and a hazelnut-sized mass was removed from behind it. (The frozen section showed it to be a lymph node.) Next, from the right thyroid lobe a cherry-sized growth was removed which the histological examination made in the course of the operation showed to represent an intracapsular parathyroid adenoma.

The stroma contained larger and smaller groups of epithelioid cells. It was composed of narrow bundles of connective tissue with a few dilated capillaries. The cells were sharply outlined, their cytoplasm was pale, and on staining with haematoxylin-eosin they appeared almost empty. The nuclei were spherical or ovai, situated usually in the centre; their chromatin exhibited a rich plexiform structure. Certain considerably enlarged cells contained one or two nucleoli. A circumscribed fibrous capsule was observed at the border of the preparation. Fresh haemorrhages as well as haemosiderin deposits were visible in the central portion. All these features proved the tumour to be a water-clear chief cell adenoma (Fig. 7).

After histological examination the adenoma was immediately transplanted into an adult female patient suffering from parathyroid tetany. This patient who had

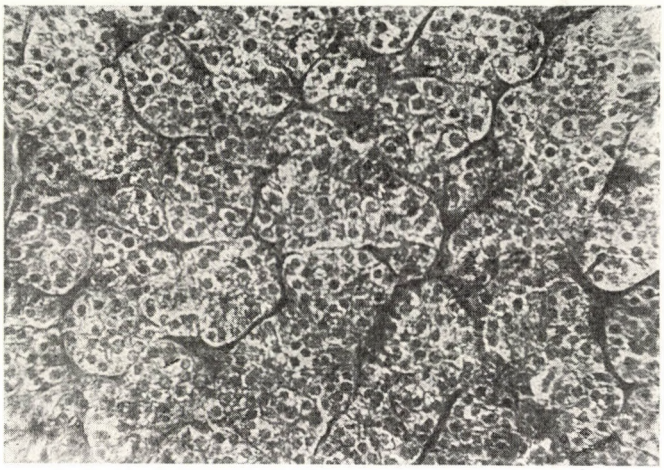

FIG. 7. Adenoma consisting of water-clear chief cells. Their cytoplasm is pale and, on staining with haematoxylin-eosin, appears to be almost empty

had spasms every other day, was relieved for the next three weeks, but relapsed thereafter.

Postoperative course (tetany, recalcification)

Immediately after the operation intravenous calcium was administered and this treatment was continued subsequently. Daily serum calcium determinations showed a gradual decrease. Hands and feet of the patient became numb on the 6th day. Since Chvostek's sign was positive, calcium was combined with dihydrotachysterol treatment. Accompanied by a classical episode of tetany, the Ca level suddenly dropped to 4.3 mg per 100 ml on the 7th postoperative day. Numbness became more pronounced, and the hands assumed a typical tetany position, witchings appeared in the facial and extremital muscles. The patient remained conscious, and the spasm subsided on the slow intravenous administration of 20 ml of calcium. The drop of the Ca level and the development of tetany were accompanied by a slight increase in serum P-level. Then, some 7 days after the operation, serum Ca reached 8.2 mg per 100 ml and Chvostek's sign was difficult to elicit. The young girl felt well, her complaints ceased; although she had no more episodes of tetany, a slight numbness, moderate hypocalcaemia and a positive Chvostek's sign persisted for another three months, the time apparently required for a complete regeneration of the parathyroid glands.

The patient was kept under observation, and admitted 9 more times until 1963. She was last examined in the outpatient department in October 1967.

Ten months after the operation we succeeded in making her stand up in a plaster cast, one month later this was replaced by a dynamic splint and walking trials were continued. The patient was able to make a number of steps by the 12th postoperative month; in the 19th month she was able to walk and after 24 months she moved, stood and walked without any aid (Fig. 8). X-rays of the skull taken at this time showed an inner table more sharply outlined along its whole length, while the outer table, accompanied by a pale accessory shadow, was beginning to assume a distinct form in the occipital region. X-rays of the hands showed structural readjustment of the bones. The cortex was thickened and the laminae of the spongiosa had become normal. The distal pha-

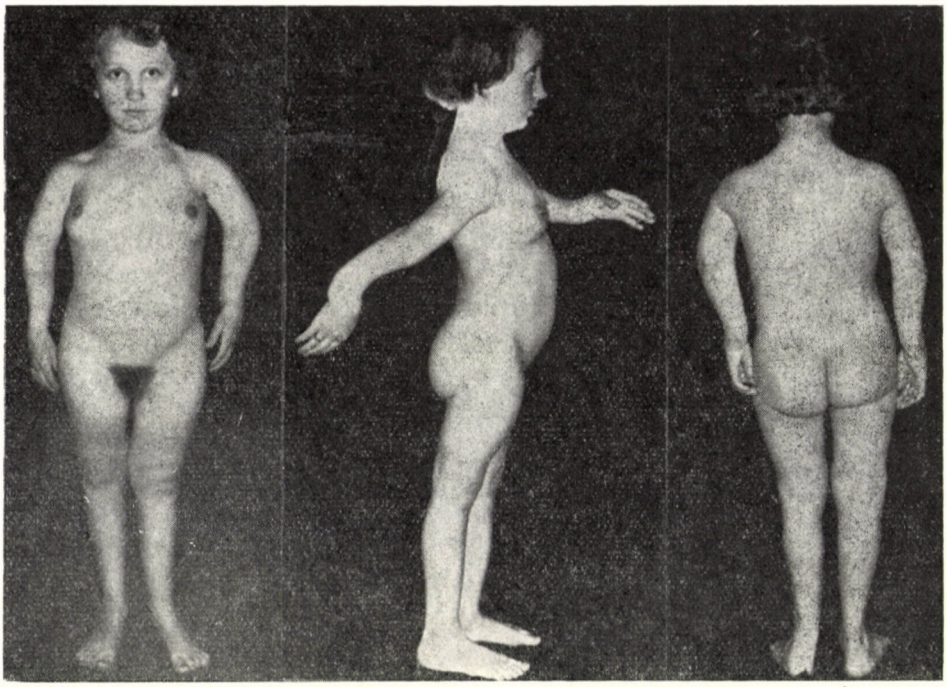

FIG. 8. Two years after the operation: the preoperatively existing deformities were no longer remediable at the time of puberty

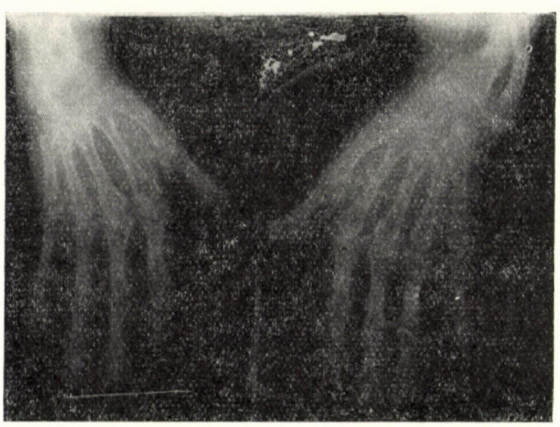

FIG. 9. Cortical erosions have disappeared. Smooth, sharp contours. Almost normal structure

langes were short; the erosions had disappeared (Fig. 9). The pelvis displayed a striking improvement of the impression (Fig. 10). Increased calcium contents made the contours and the structure of the bones perceptible. Although the amount of calcium was increased in the femurs, their structure was still irregular. Fractural dislocation appeared to be reduced in the neck of the right femur but was unchanged

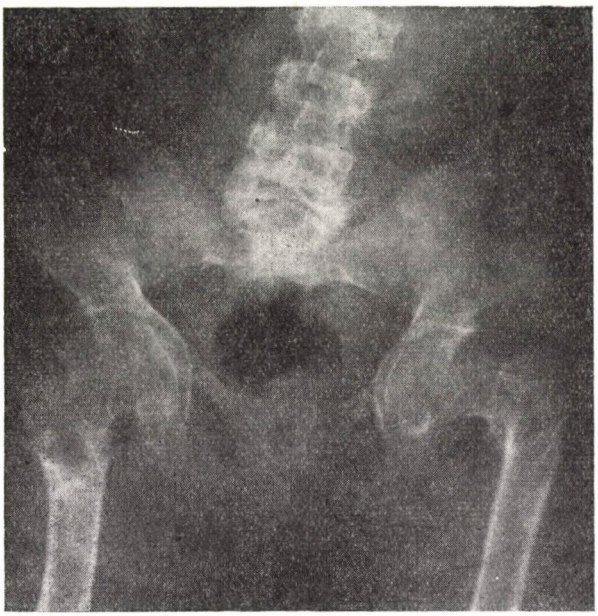

FIG. 10. The pelvis has grown in width, its lateral impression is less pronounced. The femora disclose no fractures, but the left femur is strongly bent. The pelvis contains an almost normal amount of calcium

on the left side. The thickness of the cortex was almost normal. The tibiae and ulnae were curved medially. The legs still contained insufficient amounts of calcium, the contour of the bones was blurred, and their cortex thin, the structure diffuse. As regards the thorax, its reversed funnel shape remained as before; the growth of the ribs was lagging; they hardly extended beyond the midline: their oval end faced the spectator. The body of the sixth thoracic vertebra had considerably grown in height but still measured only one third of the adjacent vertebrae (Fig. 11).

Ten years after the operation the 25-year-old patient, though still fatigable, had practically no complaints. X-rays showed the bony substance to have healed, whereas the deformities had remained essentially unchanged in the last 8 years. A moderate shortening of the left leg ensued as the fracture of the right femur had healed in the form of coxa valga, that of the left in the form of coxa vara. Accordingly, orthopaedic shoes were prescribed. The height of the patient was 127 cm at the age of 17, and she had not grown since. Body weight was 30 kg so that body length and weight were not out of proportion. Menarche occurred at 14 years of age.

Values of serum Ca and P were normal: 9.8 and 4.0 mg per 100 ml, respectively.

Double Ca loading

	Ca	P
	mg per 100 ml	
0'	9.5	2.5
15 ml Ca intravenously		
5'	11.6	2.5
60'	10.5	2.5
15 ml Ca intravenously		
5'	13.5	2.6
60'	10.6	3.0
120'	9.8	2.8
180'	10.6	2.5

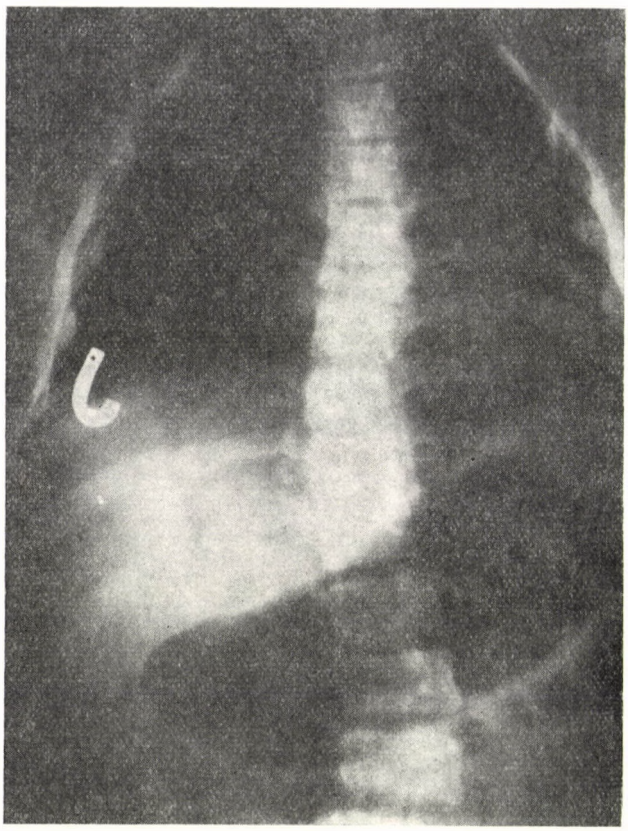

FIG. 11. The thoracic bones have regained most of their calcium contents. The sixth thoracic vertebra is less compressed; the ribs are short

Sulkovitch's test + ; NPN 25 mg per m. Urinary tests were negative. Normal neurological conditions, the EEG revealed no change, Chvostek's sign was negative bilaterally.

Since the possibility of pituitary hypofunction had been excluded by the 17-ketosteroids and double dextrose, adrenaline and insulin tolerance tests, the dwarfism was considered of parathyroid origin, and this the more so as the adenoma had been removed at the time of puberty.

The patient had grave psychic problems owing to her dwarfism and deformities [8]. She was aware of her misshapen build and crippled condition, and the inhibition of interpersonal (sexual) contacts. Neither at home nor at her place of work was she regarded as a grown-up person. She had a practically normal intelligence and a good combinative capacity. Her attention, mainly centred on her somatic condition, was in other respects diffuse and uneven. In affectivity the patient exhibited an extremely disturbed picture of puberty.

It was in the autumn of 1967, fifteen years after we had first seen her, and fourteen years after the operation that we last examined the patient who then was 29 years of age. She had a regular job, no serious complaints, and was having no treatment. The cranial bones were considerably thickened (Fig. 12); the lesser pel-

vis had become lower, the femora (the left femur in particular) were deformed. The curvature of the lower extremities appeared to be partly reduced. The X-ray aspects of the case will be published elsewhere [7].

The patient showed readiness for personal contacts; she was alive to realities, her critical faculty and orientation were adequate, her intelligence was above average, she suffered from anxiety due to sexual problems. The overall psychic picture was that of a gifted adult ready to form contacts, who had preserved the personality characters and disclosed good social adaptability.

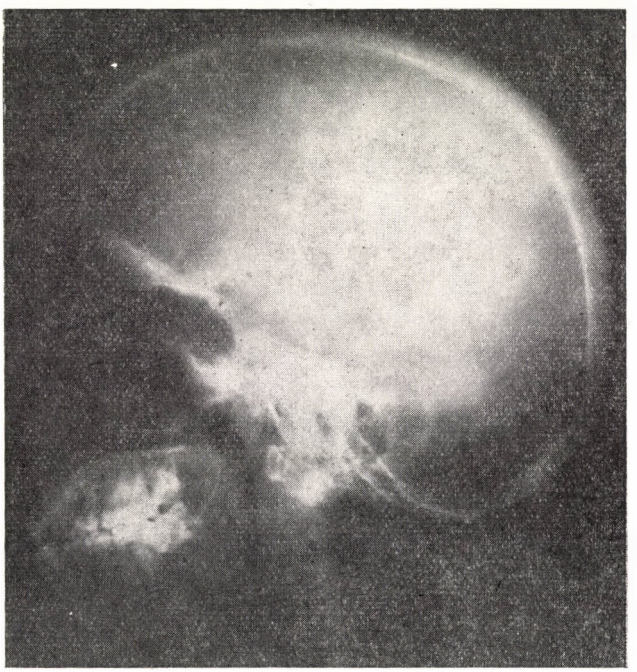

FIG. 12. Massive calvaria; sporadic patches of increased density

DISCUSSION

Generalised cystic fibrous osteitis is mostly due to an anatomical change of the parathyroid glands, one of which usually contains a hazelnut-sized or larger adenoma. In other cases, all parathyroid glands were hyperplastic. Our case was one of a water-clear chief-cell adenoma. Parathyroid hyperplasia is usually accompanied by the appearance of numerous water-clear chief cells, a particular active cell form. Parathyroid adenomas consisting of such cells give rise to Recklinghausen's disease.

The history and the pathogenetical data allowed certain conclusions to be drawn. First of all, it would have been possible to diagnose the case and start adequate therapy at a much earlier time. The Madelung-type forearm and the deformed wrist were infallible proofs of the fact that hyperparathyroidism had existed long

before the gait disturbances were observed. Correct diagnosis was belated, and the child was inadequately treated in the meantime. Surgical management succeeded in enabling the patient to stand and walk, but the late intervention could not correct the irreversible deformities; the disease had started in a latent form, and, by the time purposeful and successful therapy could be started, Recklinghausen's disease is, thus, the mirror image of the corresponding curve in tetany (HETÉNYI's calcaraemic reaction — 13, 14), since in tetany Ca loading is followed by a considerable rise of the level which returns to the initial value slowly. On the other hand, in Recklinghausen's disease the calcium curve shows a close similarity to that obtained in myositis ossificans.

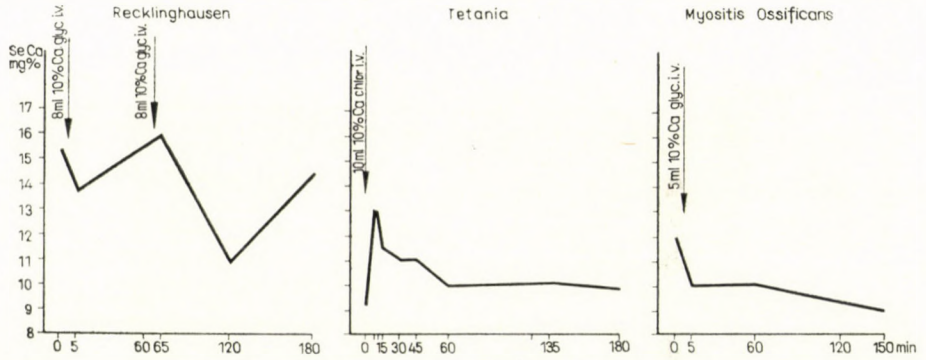

FIG. 13. Ca-loading curves in Recklinghausen's disease, tetany and myositis ossificans

irreparable disorders of growth and ossification had developed. Although the patient's locomotor capacity was fully restored, her deformities and low stature interfered with the normal development of her personality.

The radiographic changes were characteristic of hyperparathyroidism. As to Ca metabolism (Fig. 13), preoperative administration of calcium, instead of an elevation, resulted in a considerable decrease of the serum Ca level, and a second load was followed by another notable decrement.

The calcium tolerance curve in

The prompt fall of the Ca level following loading in cases of Recklinghausen's disease may have been due to the calcium avidity of the tissues, while the fact that the level soon increased again was ascribed to the tissues being unable to utilize calcium, and thus to return it to the blood stream [9, 10, 11].

In the knowledge of thyrocalcitonin, this explanation has to be amended. It is now known that the Ca level does not depend on a single hormone governed by a negative feed-back mechanism, but on two

hormones, the parathyroid hormone — PTH — which tends to elevate, and thyrocalcitonin — TCT — which tends to reduce, the Ca level [5]. PTH is activated by hypocalcaemia, TCT by hypercalcaemia [15, 17, 20, 21]. There is a certain interval between the actions of these hormones, PTH having a delayed but more permanent, TCT a prompt but transitory, effect. Besides, these hormones draw upon the body's was Ca depot (calcium pool) of which the circulating amount of Ca is but a small part, and it is the interaction of these two factors which warrants the delicate adjustment and stability of serum calcium.

Hypocalcaemia, by stimulating the parathyroid glands, induces PTH release which leads to osteolysis and phosphaturia. Hypercalcaemia, on the other hand, stimulating the parafollicular cells [16], induces TCT outflow which inhibits osteolysis and phosphaturia. By short-circuiting of these paths, there is also a direct interaction between hypercalcaemia and osteolysis.

We are, thus, able to offer the following interpretation concerning the fluctuations of the Ca level in the present case. As soon as the existing hypercalcaemia was further stepped up by the intravenous administration of calcium, TCT release began and the Ca level decreased. Since there was nothing to mobilize TCT after the operation when the patient had become normocalcaemic, the Ca curve, too, returned to normal.

On the other hand, in tetany the hypocalcaemia by means of a feedback mechanism elicits PTH release so that the administration of Ca raises its level considerably. Since the action of PTH lasts longer, the serum Ca level remains longer above the initial value.

The anomalous personality development was also instructive. Somatic retardation in puberty was associated with psychic retardation. The somatic treatment combined with psychotherapy succeeded in stopping the disturbance in personality development. The psychic condition of the patient resulted from problems connected with her deformities and not from the metabolic disturbances caused by the primary disease [3].

As regards the patient's stature, although the removal of the adenoma had put an end to the disease, the intervention, performed at the time of puberty, was no longer able to correct the dwarfism. The preoperatively existing deformities also persisted.

In 1951 we have reported on a case of a hyperparathyroid patient where the adenoma was transplanted into an individual suffering from tetany [2] and ensured a symptomless period of 7 months. This was the second attempt of this kind described in the literature [19]. In the present case, the parathyroid adenoma was transplanted into an adult female patient suffering from strumiprivous tetany. The condition improved only temporarily.

Primary hyperparathyroidism is rare in childhood; nevertheless, its possibility must always be taken into account since erroneous diagnoses may entail grave consequences.

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