A series of eighteen patients are described with this syndrome in whom there was no real evidence of renal impairment.

The importance of the condition lies in the fact that after a negative gastro-enterological investigation it can be, and often is, overlooked until uraemic symptoms supervene.

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HYPERPARATHYROIDISM WITH NORMAL SERUM CALCIUM

BY

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Osteitis fibrosa cystica was first described by von Recklinghausen in 1891, but the first clear demonstration that a parathyroid adenoma was the cause came in 1925, when Mandl cured a man crippled with the disease by the removal of such a tumour. Since then our knowledge of the disease, its clinical, radiographic, and biochemical features, has steadily increased, though as recently as 1950 Rienhoff estimated that there were only 597 proved cases in the world's literature or known to him personally. Thus the disease is rare enough to warrant a record of every case, especially when there are any unusual findings, and since treatment is so effective.

Case Report

A spinster tea-packer aged 33 first consulted her doctor in February, 1951, because of "rheumatism" in the legs and back for five months. Before this her health had been good; she had lived an active life and had played tennis during the previous summer. The aching pain had started in her right thigh rather suddenly in September, 1950, and had spread in several weeks to involve the lower back, thighs, and knees. The pain was made worse by movement, but did not prevent sleep. She noticed increasing weakness in the legs, so that walking, especially starting off, became difficult: a waddling gait developed. These disabilities caused her to stop her work at Christmas, 1950. The symptoms became increasingly severe; some aching and weakness developed in the right shoulder, and a painful lump appeared below the manubrium sterni. She had noticed some frequency of micturition, which disturbed her twice each night.

She was referred to the medical out-patient department, where the most striking abnormality was her gait as she entered the room. It resembled the waddling of a duck, and was thought to be due to muscular weakness, especially of the hip abductors. She was of stocky build, and had a marked thoracic kyphosis, which, though present since childhood, she thought had become more pronounced. The bones were not tender, and passive movement of the limbs was full and pain-free. There was definite muscular weakness of the abductors, flexors, and extensors of the hip-joints, but no wasting and no reflex or sensory changes. Examination of the neck, lungs, heart, and abdomen was normal. The blood pressure was 130/90 and weight 8 st. 9 lb. (54.9 kg.). There was a tender bony lump in the sternum between the third

costal cartilages. X-ray examination of the pelvis revealed a generalized osteoporosis, so she was admitted for investigation with a tentative diagnosis of hyperparathyroidism.

Investigations.—In order to confirm the clinical diagnosis and to exclude in particular multiple myelomatosis and polyostotic fibrous dysplasia (Albright's disease) extensive investigations were made. Skeletal x-ray films revealed generalized osteoporosis, with a "moth-eaten" appearance in the skull (Fig. 1), and early fibrocystic areas, especially in the pelvis and right upper humerus. There was a fracture of the body of the sternum, and a loss of the lamina dura of the teeth. No calcification was seen in the renal tract. Four pre-operative serum calcium estimations (10.8, 10.32, 9.8, and 9.7 mg. per 100 ml.) during three months were within the normal range: the method used was that described by Trevan and Bainbridge (1926). Two out of the three plasma phosphorus estimations (1.7, 2.2, and 1.8 mg. per 100 ml.) were, however, below normal limits. The serum alkaline phosphatase was 92.4, 94.4, and 98.0 King-Armstrong units per 100 ml. at monthly intervals. The blood urea (34 mg. per 100 ml.) and urea clearance were normal, as were the serum proteins (total, 6.7 g.; albumin, 4.16 g. per 100 ml.). An eight-day calcium balance showed that on an intake of 97 mg. daily her average urinary excretion was 322 mg. and faecal excretion 162 mg., a daily negative balance of 387 mg. The combination of low plasma phosphorus and a negative calcium balance, even in the presence of normal serum calcium, made the diagnosis almost certain.

A sternal bone biopsy showed osteoclastic destruction of bone trabeculae associated with proliferation of fibrous tissue. There was very little evidence of new bone formation and there was no mosaic pattern in the islets. The appearances were those of osteitis fibrosa cystica.

A blood count showed: red cells, 4,300,000 per c.mm.; Hb, 11.9 g. (80%); colour index, 0.9; E.S.R. 4 mm. (Wintrobe corrected); white-cell count, normal. There were no casts, cells, or albumin in the urine.

Operation.—On June 11, 1951, Mr. E. G. Muir explored the neck through the usual collar incision. A normal parathyroid gland was identified on the left side, but a small parathyroid adenoma was found attached to the right lower pole of the thyroid. It was removed by dividing the short pedicle. The adenoma was deep red in colour with a smooth surface; it measured 1.8 by 1 by 0.8 cm. and weighed 0.9 g. Microscopical examination showed parathyroid tissue composed almost entirely of "wasserhelle" cells.

Subsequent Course.—The patient was given 2 pints (1,140 ml.) of milk, 60 gr. (4 g.) of calcium lactate, and 10,000 units of calciferol daily from three days before operation until six months afterwards. The bone pain vanished immediately after operation, and muscle strength returned within a few weeks. Five days after operation latent tetany was detected by a positive Chvostek's sign; at that time the serum calcium was 7.9 mg. per 100 ml. The dose of calcium lactate was increased to 240 gr.

FIG. 1

FIG. 2

FIG. 1.—Skull. Moth-eaten osteoporosis. FIG. 2.—Skull. Six months after operation.

(16 g.) daily. The sign disappeared after two days, and thereafter convalescence was uneventful. Subsequent biochemical tests are recorded in Fig. 3. On the sixteenth day the daily urinary excretion of calcium had fallen to 40 mg. despite an intake of more than 3,900 mg. of calcium ion. Three months after operation radiographs of the bones showed much recalcification; the gait was normal and the patient symptom-free. Six months after operation radiographs were almost normal (Fig. 2), and the phosphatase had fallen to 14.7 units per 100 ml. All treatment was then stopped.

FIG. 3.—Serial estimations of serum alkaline phosphatase, serum calcium, and plasma phosphorus. Normal ranges are shown thus ———.

Discussion

This case is of special interest because of the very short duration of symptoms, the normal serum calcium, and the rapid and complete response to treatment. Most reported cases have had symptoms for more than two years before the diagnosis has been made (Norris, 1947). The importance of early diagnosis is seen in Rienhoff's own 27 patients, who were followed for several years; within a few years of operation 10 died from uraemia or hypertension following nephrocalcinosis. In general, the fatalities were among those with the longest histories before operation and those with renal damage.

Since the prognosis is so much improved by early diagnosis, the early symptoms of hyperparathyroidism merit emphasis. They are usually described as: (1) due to decalcification of the skeleton—aching bones, deformities, spontaneous fractures; (2) due to hypercalciuria—polyuria, thirst, renal pain; or (3) due to hypercalcaemia—anorexia, nausea, constipation, muscular weakness, increasing muscular fatigue, waddling gait.

Although this patient had the symptoms usually ascribed to hypercalcaemia, her serum calcium was in fact within normal limits. Four estimations were made in three months, by an experienced technician, at a time when the patient had marked symptoms from the disease. It is obvious that these symptoms may be caused by factors other than hypercalcaemia.

Gutman and his colleagues (1936), reviewing the serum calcium levels of 114 cases of hyperparathyroidism, found values below 11 mg. in five only and below 12 mg. in 23

only. They thought that normal serum calcium values could be explained in one of four different ways.

1. *Renal Failure.*—This commonly occurs in cases of long duration. It causes phosphate retention with secondary depression of the serum calcium level. This is well illustrated by Case 2 of Gutman *et al.*, in which renal failure occurred while the patient was in hospital, with a fall in calcium from 12.4 to 10.5 mg. along with a rise in phosphorus from 3.9 to 6.1 mg.

2. *Hypoproteinaemia.*—Normally about 50% of the total serum calcium is bound to protein; the remainder is ionic calcium, and it is this fraction which is raised in hyperparathyroidism. Coincidental hypoproteinaemia, with a low protein-bound fraction, may thus mask a pathologically high ionized calcium when the total serum calcium is normal.

3. *Insufficient Testing.*—Sometimes a normal value is found in an isolated test, but repeated estimations show the typical elevation. For instance, the initial estimation of Case 2 of Albright *et al.* (1934) showed a level of 10.4 mg.; on subsequent testing it was 12.3 mg.

4. *Short Duration of Symptoms, with Normal Kidneys.*—Under these circumstances the excess calcium mobilized from the bones can be excreted without accumulation in the blood: such is the explanation in the present case. The kidney-function tests were normal, as were the serum proteins; the disease was active as judged by the bone pain and negative calcium balance, yet the serum calcium was normal on four occasions during three months.

Summary

An example of hyperparathyroidism is described in which the duration of bone pain and weakness was only five months and the serum calcium was normal. The early symptoms of the disease are reviewed and emphasized. The normal serum calcium was thought to be due to effective excretion of calcium by the kidneys. A parathyroid adenoma was removed successfully and the patient's health restored.

I wish to thank Dr. Clifford Hoyle, under whose care the patient was admitted, for help with this paper; Mr. E. G. Muir, who did the operation; Dr. A. M. Rackow for the radiographs; Professor C. H. Gray for the biochemical investigations; and Dr. B. S. Cardell for the histology.

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The outstanding social problem of our age, particularly in northern towns, is unsatisfactory housing, says Dr. C. Metcalfe Brown, medical officer of health to the city of Manchester, in his annual report. "Notwithstanding the strenuous efforts of the housing department in providing new houses," he writes, "the housing position in the city is bad. Hundreds of cases annually seek the help of the health department for the alleviation of hardship caused by wretched housing conditions. The department takes all action within its power, but this action is severely limited by the controlling factor—namely, the grave shortage of new houses. Enormous distress is being caused to thousands of Manchester people because of the inadequacy of housing accommodation. The health, happiness, and integrity of family life cannot be achieved and maintained to the full unless housing is good."