Upsala J Med Sci 79: 109–115, 1974

Familial Hyperparathyroidism

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ABSTRACT

A family with four members having verified hyperparathyroidism (HPT) and another three with hypercalcemia is reported. Of the four patients with verified HPT two had adenoma and two hyperplasia of the parathyroid glands. The statistical analysis of the cases with borderline serum calcium is discussed, as well as difficulties in the histopathologic differentiation between adenoma and hyperplasia.

In recent years the polyendocrine syndrome with hyperparathyroidism (HPT) as one of its components has received considerable attention (1, 2). The syndrome has also been called multiple adenomatosis, and Wermer (1) has pointed out the possibility that the parathyroid glands may be the endocrine organ that is first involved.

It has been suggested, further (3, 4, 5), that familial HPT, familial pheochromocytoma, Zollinger–Ellison syndrome (6) and ulcerogenic tumours in the pancreas with diarrhoea all represent variants of endocrine adenomatosis.

Another family with familial HPT will be described in this paper. In addition to HPT and repeated attacks of renal calculi, other symptoms that have occurred among its members are peptic ulcer, localized osteitis fibrosa cystica and mental depression. Of 24 persons examined in the family, 4 had verified HPT and a further 3 showed hypercalcaemia, in two cases concurrent with duodenal ulcer. One of these latter 3 patients was investigated for HPT with a negative result. The other 2 did not wish to undergo further investigation so far (Fig. 1).

The 4 patients with verified HPT from this family are reported in detail.

CASE 1 (B. K. 290520)

A 44-year-old man with a 3-year history of recurrent duodenal ulcer and attacks of renal colic with passage of renal calculi.

Serum calcium was 5.9 mEq/l, serum phosphorus 0.7 mg% and serum creatinine 1.7 mg%. His severe symptoms of duodenal ulcer, with hypersecretion and greatly increased acidity (on provocation with continuous histamine infusion his acid secretion at a dose of 2.5 μg/min was 718 mEq/min and at a dose of 40 μg/min 1.502 mEq/min) gave rise to suspicion of Zollinger–Ellison syndrome. No tumour of the pancreas was found at angiography. In August 1968 a Billroth II operation was performed because of pyloric stenosis. Pancreatic exploration revealed no abnormality. In October 1968 the parathyroid glands were explored. The lower right gland was enlarged and was extirpated; it was yellow-brown and weighed about 300 mg. The upper right gland was also enlarged, but to a lesser extent. Approximately half of this gland (weight 40 mg) was removed. The other two parathyroid glands were found to be of normal size.

The immediate postoperative course was uneventful, and the serum calcium values were then about 4.6 mEq/l. The serum calcium level gradually increased during the following 3 years, however, and at follow-up in 1971 a value of 5.5 mEq/l was noted, but the patient had no subjective symptoms. The calcium values varied between 5.2 and 5.5 at repeated examinations 1971 to 1974.

Microscopic observations

The following methods were applied to the parathyroid glands of all 4 patients: The glands were fixed in 10% formalin, dehydrated and embedded in paraffin. They were sectioned throughout into series of 5 consecutive 4–5 μm thick sections with intervals of 150 μm between each series. The sections in the different series were stained with hematoxylin and eosin; van Gieson stain, periodic acid-Schiff (PAS) with or without prior diastase digestion, and with the Grimelius silver nitrate technique (7).

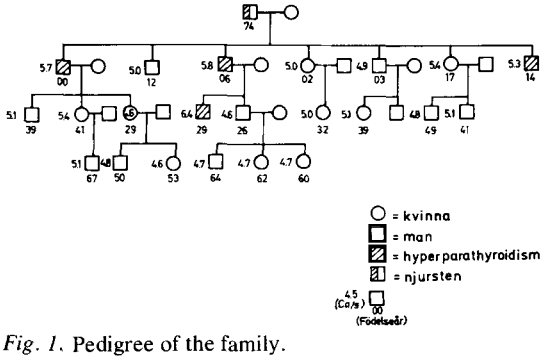
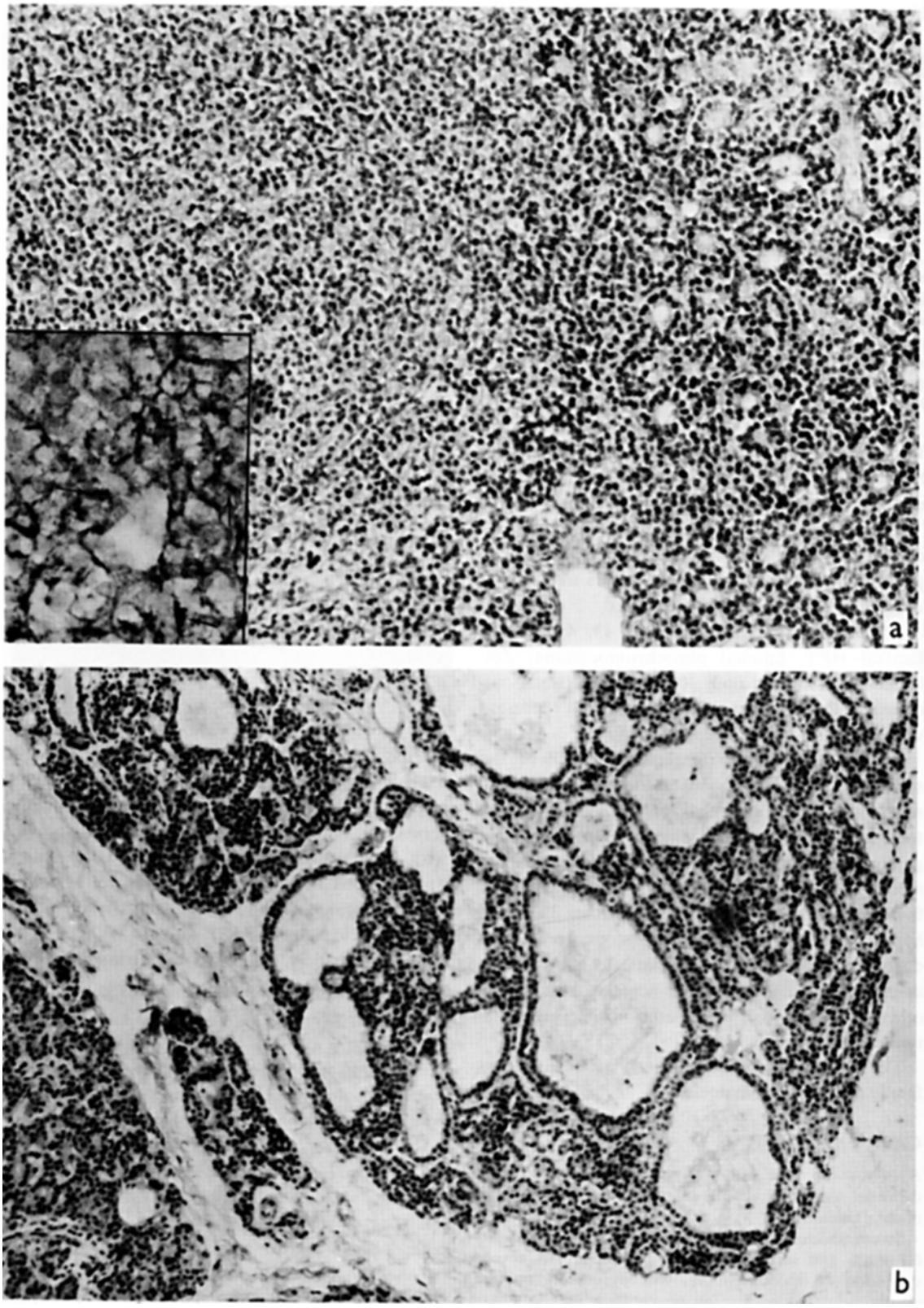


Fig. 1. Pedigree of the family.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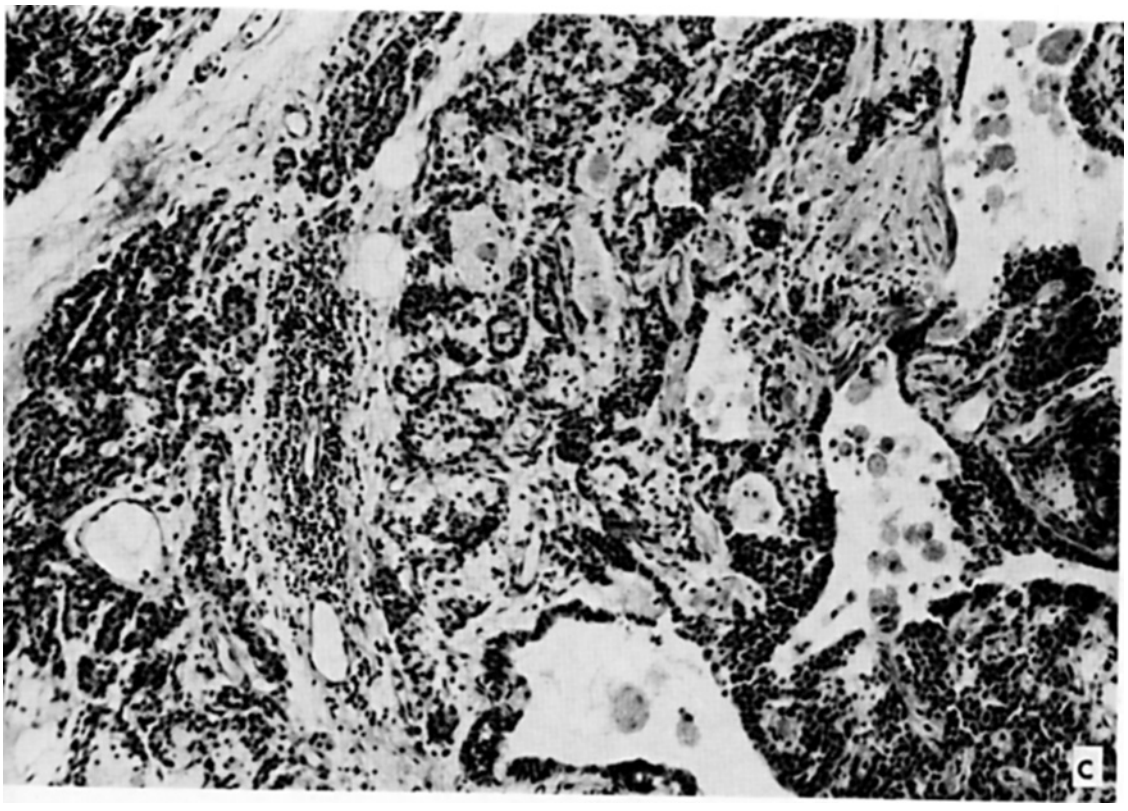

Fig. 2 (a–c) Parathyroid glands from case 1. (*a*) the larger gland. (*b, c*) The partially resected smaller gland.

(*a*) The parenchymal cells, dark and light chief cells, are arranged in solid masses. Some acini are also seen. v. Gieson stain. ×130. Inset: Argyrophil cells containing cytoplasmic silver (black) granules (arrows). The Grimelius silver stain. ×650.

(*b*) Mainly dark chief cells arranged in strands and groups. Some cystically dilated acini containing macrophages are seen. v. Gieson stain. ×130.

(*c*) Part of the gland with fibrosis and inflammatory cells (mainly lymphocytes). To the right some dilated acini containing macrophages are seen. Hematoxylin-eosin. ×130.

Both of the investigated parathyroid glands from case 1 were enclosed in a thin capsule of connective tissue. No glandular tissue, either normal or atrophic, was seen outside the capsule.

Both glands contained a sparse amount of fat tissue. In the larger, completely extirpated gland the parenchymal cells were arranged in a solid mass and here and there acini were found (Fig. 2*a*). In the partially resected gland areas with a nodular cell pattern were observed as well as more densely packed groups of cells. In the latter gland acini were also seen, some of which were cystically dilated (Fig. 2*b*). In both glands dark chief cells predominated, but some light chief cells were also seen, and in the partially resected gland small groups of oxyphil and transitional oxyphil cells were found.

The stroma was sparse in the larger gland and contained a few lymphocytes. In the smaller gland, on the other hand, an abundance of connective tissue strands was found in some places; here and there these strands had an oedematous loose appearance and contained some lymphocytes, plasma cells and macrophages, and hemosiderin (Fig. 2*c*). A little less than half of the parenchymal cells of the glands contained PAS-positive diastase-digestible substance, while 10–20% showed an argyrophil reaction (Fig. 2*a* inset). These silver particles may possibly represent secretion granules (17). (17).

CASE 2 (E. K. 060519)

A 63-year-old man, the father of case 1 and brother of cases 3 and 4. At the time the son was hospitalized

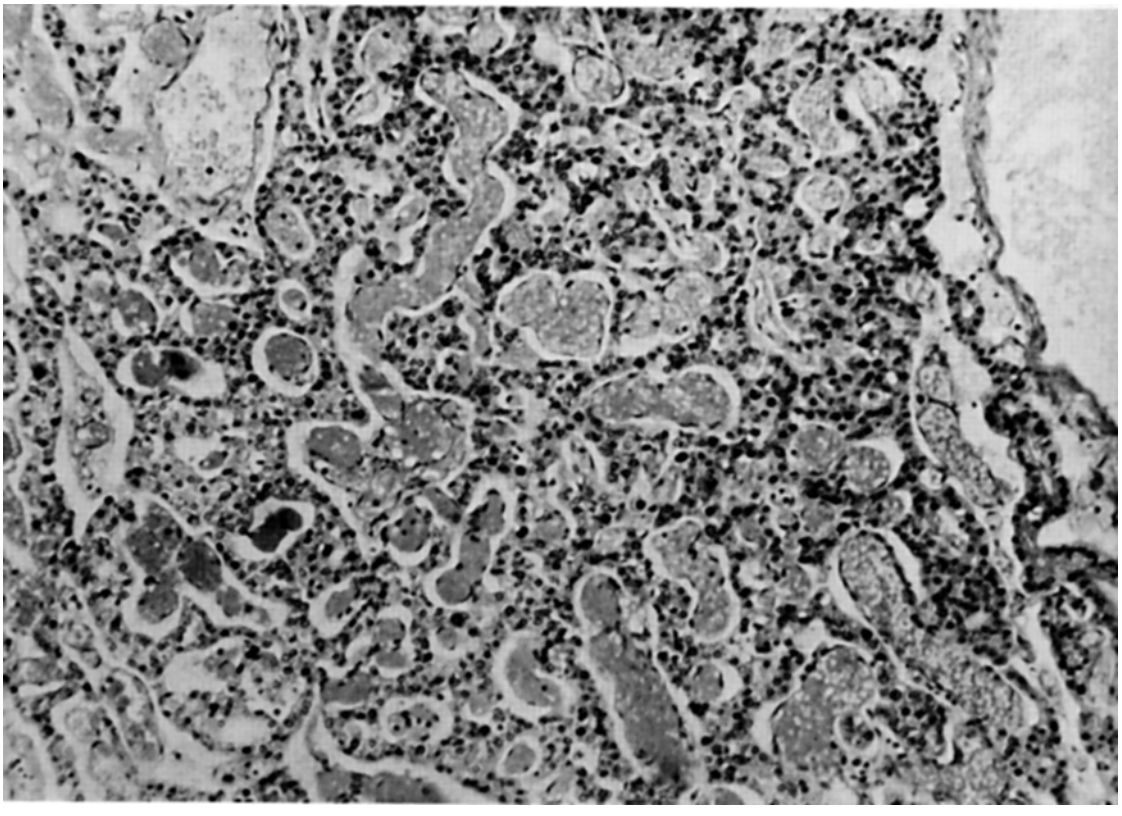

Fig. 3. The smaller parathyroid gland from case 3. The parenchymal cells, mainly dark chief cells, are arranged in a trabecular pattern. The stroma contains dilated capillaries. Hematoxylin-eosin. ×130.

in 1968 the father's serum calcium was also determined, and was 5.8 mEq/l. The patient had also had attacks of renal calculi on a few occasions in the 1930s and 1940s and again in 1962 and 1963.

Apart from the serum calcium value mentioned above, the serum phosphorus was 0.8 mg/100 ml, serum magnesium 1.7 mEq/l and maximum urinary calcium excretion 11.3 mEq/d. The tubular reabsorption of phosphate (TRP) during a calcium-phosphorus rich diet was reduced. Further, the phosphate clearance seemed to be slightly increased and was not reduced by calcium infusion according to Kyle.

Roentgenological examination of the bones of the hand revealed focal changes of the osteitis fibrosa cystica type.

At operation in January 1969 the left lower parathyroid gland was found to be somewhat larger than the other three glands. It weighed about 50 mg.

Postoperatively the serum calcium level fell to about 4.6–4.7 mEq/l. At follow-ups in 1969 and 1972 the serum calcium values were normal.

Microscopic observations

The extirpated gland was encapsulated and at one place small clumps of parenchymal cells were seen in and outside the capsule. The gland showed practically no fat tissue.

The parenchymal cells consisted mainly of dark and light chief cells arranged in a solid mass. A small number of oxyphil and transitional oxyphil cells were also observed. Slight nuclear polymorphism was seen.

About half of the parenchymal cells contained PAS-positive diastase-digestible substance and an approximately equal number showed an argyrophil reaction. The silver particles were usually localized to the peripheral parts of the cells.

There was some perivascular fibrosis, but otherwise the stroma was sparse.

CASE 3 (E. K. 000705)

A 68-year-old man admitted to hospital in 1968 with a diagnosis of cardiac infarction. He died during his first 24 hours in hospital. At autopsy[1] two enlarged parathyroid glands were found, weighing about 200 and 300 mg.

Earlier, however, HPT had been suspected and an elevated serum calcium value (5,7 mEq/l) had been noted.

Roentgenological examination of the bones of the hand revealed focal osteitis fibrosa cystica in the phalanges.

This patient had a history of recurrent duodenal ulcer, with attacks in 1934, 1956 and 1957. He was operated on for this condition in May 1957, but in 1966 further recurrence was verified roentgenologically.

Microscopic observations

Both glands were encapsulated. There was a small amount of fat tissue in the smaller gland, but practically none in the larger one. In and outside the capsule of the larger gland some small groups of parenchymal cells were seen.

The parenchymal cells were mainly arranged in a trabecular pattern and here and there acinar or pseudoacinar structures were seen. Dark chief cells dominated in both glands, but some diffusely scattered light chief cells were also observed (Fig. 3). In the smaller gland there were also a few oxyphil and transitional oxyphil cells with a nodular arrangement. In the larger gland slight nuclear polymorphism was noted.

The glands contained a sparse amount of connective tissue but were richly vascularized. In the stroma, especially around blood vessels, a few inflammatory cells, mainly lymphocytes, were found.

The acini contained PAS-positive colloid material which was not digestible with diastase. An argyrophil reaction was noted in 20–30% of the parenchymal cells. The silver granules were mainly localized to the part of the cell facing capillaries.

CASE 4 (A. K. 140525)

A 55-year-old man admitted to a mental hospital on several occasions (in 1946, 1948, 1952 and 1959) for depression. He had no symptoms of renal calculi or peptic ulcer.

His serum calcium values varied between 5.1 and 5.3 mEq/l. Further, he had slight hypercalcuria and a TRP reduction on infusion of Ca^{++} compared with the TRP during a calcium-phosphate rich diet (8). This TRP reduction was accompanied by an increase in the phosphate excretion index (9).

Roentgenological examination of the bones of the hand revealed focal osteitis fibrosa cystica.

In 1969 a moderately enlarged parathyroid gland was extirpated. It weighed about 100 mg. The other glands appeared to be of normal size. The upper part of the mediastinum was also explored. In addition, partial resection of the left thyroid lobe was performed because of nodular changes.

Postoperatively the patient felt well and there have been no recurrences of his mental depression. The serum calcium values have not decreased, however, and between 1969 and 1972 they varied from 5.1 to 5.5 mEq/l.

Microscopic observations

The gland was enclosed in a connective tissue capsule except for an area where parenchymal cells had extended outwards into the surrounding fat tissue. The number of fat cells was reduced.

The parenchymal cells were mostly arranged in a solid mass, but in some places a nodular pattern was seen.

Dark chief cells predominated, but several light chief cells were also observed. In some noduli oxyphil and transitional oxyphil cells were seen.

Apart from strands of connective tissue around noduli, the stroma was sparse.

About half of the parenchymal cells contained PAS-positive diastase-digestible substance and about two-thirds showed an argyrophil reaction. There appeared to be a greater number of silver particles per cell in this gland than in the glands of cases 1–3. In the water-clear cells the silver particles were mainly localized to the peripheral part of the cell, while in the chief cells they were often more diffusely distributed.

DISCUSSION

Including Mandl's case in 1926 and the patients here described (10), 22 families with familial HPT have now been reported. Opinions have differed as to whether or not this disease should be regarded as a separate entity. Some authors have chosen to incorporate all cases of familial HPT under the concept of multiple adenomatosis or polyendocrine syndrome (1, 2). Others have distinguished a form of familial HPT without involvement of other endocrine systems (11, 12).

Concerning the clinical diagnostic test of primary HPT, the main weight is placed on the serum calcium level, while the serum phosphorus, urinary calcium, tubular reabsorption of phosphate, phosphate excretion index and urinary hydroxyproline have been regarded as complementary information.

[1] This autopsy was carried out at Karolinska Hospital, Stockholm, and the material was kindly placed at our disposal by Professor A. Ljungkvist.

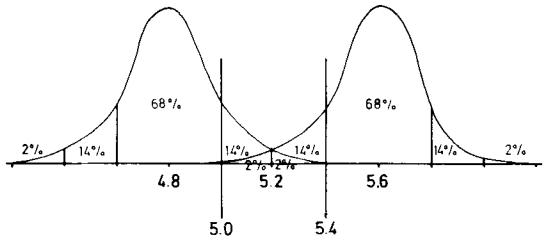

Fig. 4. Hypothetical statistical analysis of the cases with borderline serum calcium values.

Apart from these tests the clinical symptoms are obviously very enlightening. These may present in the form of repeated attacks of renal calculi, recurrent duodenal ulcer, pancreatitis, foci of osteitis fibrosa cystica, general muscular weakness and mental disturbances; in addition there is a history of a familial occurrence. In one of our patients the only clinical manifestation was mental depression. His serum calcium values were only occasionally and slightly elevated. This patient represents the well-known situation of "normocalcaemic" hyperparathyroidism (13). Since in this family there were several members with calcium values at or immediately above the upper normal limit, this may be worthy of a statistical comment.

The mean value for serum calcium in our laboratory is 4.8 mEq/l for healthy persons. The standard deviation is 0.2. As a variable, calcium in serum can be assumed to have a normal distribution. Let us assume, further, that in population of early HPT the mean serum calcium value is 5.6, and let us also assume that the serum calcium values are normally distributed around this mean value and that the standard deviation is the same as for the healthy population (see Fig. 4). We thus have two distributions which intersect at a value of 5.2 and which overlap one another in the range 5.0–5.4. If the distributions had the same population content, which we may suppose for the sake of reasoning, the probability will be fifty-fifty in the range 5.0–5.4 that a serum calcium value will identify a hyperparathyroidism or a healthy person. In the range 5.0–5.2 the probability is one to eight, i.e. 12.5%, that the serum calcium value will identify hyperparathyroidism. The corresponding probability in the range 5.2–5.4 is 87.5%.

Even if the above probability figures do not completely correspond with reality, the reasoning is on the whole tenable. Clinical experience also supports the validity of the above assumption. Thus, patients with a serum calcium in the limit zone with values between 5.0 and 5.2, and presenting clinical symptoms or a familial accumulation of HPT, should not be excluded from complementary investigation.

The histo-pathological differential diagnosis between parathyroid adenoma and primary chief cell hyperplasia can be very difficult (4, 14, 15, 17, 18). One reason for this is the variation in the size of the glands that also can occur in the latter condition (14, 16). Even normal-sized glands can be hyperplastic due to an increase in number of the parenchymal cells at the cost of fat tissue (15). Gilmour & Martin found in studies of the parathyroid gland in an autopsy material that "normal" glands in adults contained between 33 and 51 volume percent of fat tissue. Similarly, some authors (4) have pointed out the difficulties that may be encountered in differentiating the normal glandular tissue adjacent to an adenoma from hyperplastic parenchymal cells that extend outwards into surrounding fat tissue.

In none of our four patients was the histopathological diagnosis of the parathyroid gland changes absolutely clear. In cases 2 and 4 only one gland was extirpated, but in each case it was larger than the remaining glands. In both cases the microscopic picture was pathological, with an almost complete absence of fat tissue. In both cases the dark chief cells predominated, and these were mostly arranged in solid masses. In case 2 the serum calcium values returned to normal after extirpation of an apparently normal-sized gland (50 mg), and there has been no recurrence of the HPT symptoms during the years since the operation. Probably this gland represents a small adenoma. The small groups of parenchymal cells which were observed in some places in and outside the capsule also support this diagnosis.

Extirpation of the gland in case 4 did not result in normalization of the serum calcium values. Despite the fact that this gland had a microscopic pattern corresponding to that of the above-mentioned gland from case 2, with all probability this was a case of primary chief cell hyperplasia.

In case 1 a clearly enlarged gland and part of a slightly enlarged gland were extirpated. The findings at exploration suggested a solitary adenoma. On histo-pathological investigation the smaller gland also showed a hyperplastic pattern. The

diagnosis was then changed to primary chief cell hyperplasia. Postoperatively the serum calcium values normalized, but since then there has been a gradual increase of the level, which further supports the diagnosis of hyperplasia.

In case 3 only two, clearly enlarged, parathyroid glands—with a nodular cell arrangement—were found at autopsy. We consider it probable, that the glands represented double adenomas and that the other two glands were small and were therefore overlooked at autopsy.

As demonstrated in the above cases, it can be difficult or impossible to make a definite histopathological diagnosis after examination of only *one* pathological gland. Exceptions, however, are those cases where a clearly enlarged gland is found which exhibits a distinct capsule with normal or atrophic parathyroid tissue outside it. Similarly, one can be satisfied with extirpation of only one gland if this gland is distinctly enlarged and the other glands are definitely localized and appear *strikingly small*. It is difficult to give a normal size, because of the different shapes of the glands, but as general guide $3–4 \times 3 \times 1\,^1/_2$ mm would seem reasonable. As up to about 50% of the gland volume can consist of fat tissue, the *strikingly small* glands mentioned above should comprise at the most half of the "normal" volume, in order that hyperplasia can be excluded with certainty. If the other glands do not appear strikingly small, but are normal or enlarged, then more than one gland should always be taken for histo-pathological examination or multiple biopsies made as is our present policy. If all the glands are enlarged at least three glands will be removed and the evaluation at the histo-pathologic examination will be easier to make.

As regards earlier cases of familial HPT, both primary chief cell hyperplasia and adenoma (4) have been found, as in our patients.

ACKNOWLEDGEMENT

This investigation was supported by the Swedish Medical Research Council, grants.

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Received February 6, 1974

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