The term »primary hyperparathyroidism« signifies a condition characterized by the production of a greater amount of parathyroid hormone than is needed. An abnormally large production of parathyroid hormone is also encountered in secondary hyperparathyroidism, but here it is of compensatory character and may result from a diet deficient in calcium from pregnancy, lactation, rickets, osteomalacia and chronic nephritis (Albright & Reifenstein, 1948).

In 1947 Norris published a review of altogether 323 cases of parathyroid adenoma gathered from the literature from the period of 1903—1946. A great majority of these cases have been reported within the past 10—15 years, but this is not to be taken to indicate that the disease has become more frequent. It is merely due to the fact that many cases which previously would have been misinterpreted are now recognized.

*) Read before the Danish Society of Internal Medicine on January 26, 1951.
Four cases we have had an opportunity of observing suggested to us that the actual frequency of this lesion is still considerably higher than indicated by the number of cases diagnosed.

Primary hyperparathyroidism is readily misinterpreted because the clinical picture of the disease is very polymorphous, and the symptoms are not very characteristic. Hence, as a rule, the correct diagnosis is not made until late in the course of the disease. Thus in the large material collected by Norris, the patients have had symptoms of their lesion on an average for 5—6 years before its true nature was realized, and only in rare cases was the diagnosis made within the first two years of the illness. This fact jeopardizes the prognosis, as the lesion often causes a permanent impairment of the kidneys, which later leads to severe renal insufficiency and hypertension.

Before reporting our own four cases, it will be appropriate to recapitulate the main features of the lesion.

PATHOGENESIS

Primary hyperparathyroidism is nearly always due to an adenoma. Still, Rogers & Keating (1947) have gathered from the literature a total of 22 cases with diffuse hyperplasia of the entire glandular apparatus.

As a rule there is only one adenoma, but in about 6 per cent of the cases reported so far two or more adenomas were found. It is a peculiar fact that the adenoma usually originates from one of the lower parathyroid glands. In about 10—15 per cent of the cases it originates from some aberrant glandular tissue located most often in the superior mediastinum. The size of the adenomas is highly variable; the smallest that has been removed weighed 0.4 gm., the largest 120 gm. The adenoma is palpable only in about 10 per cent of the cases.

Norris' material comprises three times as many women as men, while Rienhoff (1950) found a different sex distribution, namely: 14 men and 12 women. This may possible be due to the fact that Rienhoff's material came from a surgical clinic, in
which systematic search was made for hyperparathyroidism as the cause of renal calculi, and the renal complications in hyperparathyroidism appear to be more frequent in men.

The hyperproduction of parathyroid hormone may cause decalcification of the bone, and the calcium output by the kidneys is increased.

SYMPTOMATOLOGY

The symptoms may be divided into:

1. **Osseous symptoms**: Generalized decalcification, osteitis, fibrosa cystica, bone deformities, fractures, bone tenderness and pains.
2. **Kidney symptoms**: Nephrolithiasis, nephrocalcinosis, polyuria, polydipsia, isosthenuria, azotemia.
3. **Gastro-intestinal symptoms**: Vomiting, anorexia, abdominal pains, constipation, gastric or duodenal ulcer.
4. **General symptoms**: Weakness, fatigue, apathy, weight loss.
5. **Metabolic changes**: Hypercalcemia, hypophosphatemia, hypercalcuria, increase of the alkaline phosphatase level.

Various »types« of the disease have been found dependent on the predominant symptoms, *e.g.*, the renal and the osseous types. As a rule, however, such types are not clear-cut.

In older cases the *osseous form* may produce massive skeletal changes with large osseous cysts and, sometimes, spontaneous fracture. In most of the published material up to the present the osseous changes occur very frequently, undoubtedly because these changes led to the recognition of the disease.

Our knowledge of the *renal form* of primary hyperparathyroidism is based on the classical work published by Albright *et al.* (1934). This form may very easily fail to be recognized especially if the bone symptoms are absent or only slightly marked. The incidence of this form in the various materials is highly variable. Thus only 5 per cent of the patients in Norris' material showed evidence of nephrolithiasis and/or nephrocalcinosis, while the rest of the patients pre-
sented either bone changes alone or bone changes + calcium deposits in the urinary tract. In contrast to this, 50—60 per cent of the patients in the material reported by Castleman & Mallory (1935) and by Cope (1934) showed urinary calculi without any demonstrable change in the bones.

As the osseous changes and the calcium concretions in the kidneys and urinary passages may appear alone or together, it is to be expected that these changes may also be absent in some cases. Two of the patients to be reported in our paper belong to this type, but otherwise — according to Abrams et al. (1949) — so far only one case of this kind has been described (Albright & Reifenstein, 1948). The clinical picture presented by such patients will show predominantly polyuria and isosthenuria, eventually associated with dyspeptic and general symptoms, and these symptoms may readily be misinterpreted as chronic nephritis or diabetes insipidus. The diagnostic difficulties are further increased by the fact that the blood changes typical of hyperparathyroidism may be completely or partially absent when the kidney function is involved, the renal insufficiency gives rise to phosphate retention with increase of the serum phosphorus to normal or hypernormal values and decrease of the hypercalcemia to about normal values; likewise the hypercalcuria may also disappear.

In the case of one patient mentioned by Schwensen & Eiken (1933), the lesion was interpreted as nephrosclerosis for a period of 18 months until spontaneous fracture led to the correct diagnosis. Several similar cases are found in the literature.

The clinical picture of the disease may show predominantly not only osseous and renal symptoms but also dyspeptic symptoms — vomiting, pain and constipation — thus giving rise to erroneous diagnoses as peptic ulcer, nervous dyspepsia, etc. Strange to say, there appears to be some connection between gastric ulcer and hyperparathyroidism (Rogers, 1947) — and this should be kept in mind, as an ulcer diet with an abundant supply of calcium may aggravate the symptoms.

As a rule, hyperparathyroidism usually takes a very chronic course. Still, acute hyperparathyroidism, analogous to the
thyrotoxic crisis, is encountered now and then. The clinical picture of this condition is characterized by persistent attacks of vomiting, abdominal pains, weakness, moderate fever, tachycardia, high serum Ca value, and marked impairment of the kidney function, with oliguria and azotemia. The intoxication may appear as an acute intoxication proper or as an acute aggravation of chronic hyperparathyroidism. The few cases of this kind described so far have nearly all been fatal and often the correct diagnosis was first made at autopsy. Besides the presence of a parathyroid adenoma, the typical autopsy findings are calcium deposits in various organs (especially in the kidneys, gastric mucosa and lungs) and multiple venous thromboses. The clinical picture has been described thoroughly by Mellgren (1943) and by Waife (1949).

Recently Blixenkrone-Møller (1950) has reported a case of acute hyperparathyroidism in a woman, 58 years old, who had shown symptoms only for a few days before admission to hospital. The clinical picture was characterized by repeated attacks of vomiting and marked fatigue; no osseous changes or nephrocalcinosis were found, and there was no hypercalcemia. An almond-sized adenoma was removed at operation. As long as the serum calcium level was increased, a hypokassemia was found — which could not be explained merely by the vomiting.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

If primary hyperparathyroidism is suspected, the diagnosis should be confirmed by the characteristic blood findings together with possible osseous changes and calcium deposits in the urinary tract. A single normal value for serum calcium is not sufficient to exclude the possibility of hyperparathyroidism. Thus for instance the serum calcium values are liable to spontaneous variation. In hypoproteinemia the serum calcium level will be lowered and may in hyperparathyroidism reach normal or even subnormal levels. Furthermore, as mentioned above, secondary renal insufficiency may bring about a fall in serum calcium to a normal value because of phos-
phate retention. It is essential to repeat the analysis, particularly the presence of other symptoms suggestive or hyperparathyroidism — e.g., marked tiredness, emaciation, constipation or repeated vomiting.

The calcium output in the urine should be examined in dubious cases after about one week on a low calcium diet, as naturally the calcium content of the food influences the calcium output.

A number of other diseases may be associated with decalcification of the skeleton. This applies, for instance, to osteomalacia, Cushing's disease, osteogenesis imperfecta, myelomatosis, Boeck's sarcoid, metastases of malignant tumors in bones and hypervitaminosis D. But none of these morbid conditions presents the combination of hypercalcemia and hypophosphatemia typical of hyperparathyroidism.

A couple of years ago the combination of nephrocalcinosis, halisteresis, acidosis and hyperchloremia was set up as a special syndrome; and it may readily be mistaken for primary hyperparathyroidism. The clinical picture of this syndrome has recently been described thoroughly by Lundbæk (1951) under the designation of »anacidogenesis renalis«.

Finally, it may be added that in 1949 Burnett, Commons, Albright & Howard described 6 patients with peptic ulcer symptoms in whom hypercalcemia, hypophosphatemia and nephrocalcinosis was considered to be caused by the intake of large amounts of milk and alkali over several years.

CASE REPORTS

Case 1 — Renal hyperparathyroidism.

This patient was a man, aged 27, who in the spring of 1947 had been troubled with a little nausea, periodical vomiting, slight thirst and tiredness. Four months later he suddenly got worse, with violent attacks of vomiting and abdominal pains, together with marked tiredness. He was admitted to a medical clinic with the diagnosis of acute gastritis and he stayed there for five months. The clinical diagnosis was: Chronic nephritis; duodenal ulcer. During the first three months in this clinic he had many attacks of vomiting and lost 9 kg. in weight. The following observations were made: The
diuresis was usually about 2—3 liters, sometimes even over 5 liters, with colipyuria for a short period. Addis' concentration test: D. 1000/sp. gr. 1004. In spite of the large diuresis the urine was usually turbid, and on microscopy it was found to contain numerous crystals. There was no albumine in the urine. Blood pressure: 125/80. Blood urea: 46—26—32 mg. per cent. Urography, cystoscopy, roentgenography of the lungs: no abnormality. Roentgenography of the stomach once showed evidence of a duodenal ulcer. The patient was treated twice with an ulcer diet, and sulphonamide was given for the colipyuria. After 3 months' stay in hospital the state of the patient suddenly improved for no demonstrable reason, the vomiting ceased, and he gained 11 kg. in weight. When discharged he was feeling well.

Three weeks later he had a slight rise in temperature together with cough, and was admitted to the Frederiksberg Hospital in January 1948, with the diagnosis: Gastric ulcer; chronic nephritis; pulmonary hypostasis. The presence of primary atypical pneumonia was demonstrated; this lesion subsided in a couple of weeks.

Attention was attracted to the peculiar »chronic nephritis« without albuminuria and hypertension, but with polyuria and iso-sthenuria. Hyperparathyroidism was suspected and hypercalcemia (12.2 mg. per cent) was found. During the following month the serum calcium increased to 13.2 mg. per cent and the calcium output in the urine increased to 550 mg. per 24 hours (Table 1). The alkaline phosphatase level was also high, but this might conceivably have been due to the pneumonia from which the patient just recovered. Roentgenography of the entire skeletal system and of the urinary passages showed normal findings.

When discharged from hospital, the patient was feeling well — apart from a slight sensation of thirst and polyuria.

During the following 6 months the patient was reexamined several times. Table 1 shows that there was a gradual increase in the serum calcium level, that hypophosphatemia appeared, and that the calcium output in the urine reached a level as high as 1659 mg./24 hours.

On examination of the kidney function*) six months after discharge the following findings were reported:

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<th>Test</th>
<th>Value</th>
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<tr>
<td>Urea</td>
<td>70</td>
</tr>
<tr>
<td>Diodrast</td>
<td>64</td>
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<tr>
<td>Diodrast T. M.</td>
<td>74</td>
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<tr>
<td>Addis-Shevsky test: specific gravity 1011.</td>
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</tr>
</tbody>
</table>

The diuresis between 2.5—3.5 liters.

*) Obligingly performed by Dr. Tage Hilden.
The patient was inconvenienced a little by a sensation of thirst and slight pains over the loins. Otherwise he was feeling well and able to work.

Table 1.

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum Ca (mg. %)</th>
<th>Serum P (mg. %)</th>
<th>Urine Ca (mg. per 24 hrs)</th>
<th>Alkaline phosphatase (2-7 units)</th>
<th>Diuresis (1-1.5 liters)</th>
<th>Sp. gr. (1020-1030)</th>
<th>Maximum clearance (60-90 ml)</th>
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<tr>
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<td>9/3</td>
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<td>31/10-50</td>
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</table>

Roentgenography in August 1948 and on January 10, 1949 still showed abnormality of the skeleton and the urinary tract.

On January 18 an operation was performed and a beansized adenoma, corresponding to the right lower parathyroid gland, was removed. The other parathyroids were not enlarged.

Histological examination (W. Kjaer): The roundish specimen, with
a maximal diameter of 13 mm., consists of uniform, rather large, roundish cells with light protoplasm, which here and there is slightly vacuolized. No eosinophilia. The nuclei are uniform as to their chromatin density; no mitotic figures are seen. The cells are arranged preponderantly in solid masses and cords; the scanty connective tissue stroma is reticular. Small follicles are seen here and there. There are several areas of hemorrhage. The peripheral demarcation of the specimen is sharp.

*Microscopic diagnosis:* Parathyroid adenoma.

On the day following the operation the patient was already feeling much better, and now realized how tired he had been before the operation. The serum calcium value and the diuresis returned to normal levels in 4—5 days. For the prevention of tetany, the patient was given vitamin D for the first five days after the operation. At no time did he present any evidence of tetany.

On re-examination, 2 months and 1½ years after the operation, the patient was feeling perfectly well. The values for serum calcium, serum phosphorus and alkaline phosphatase were normal. Diuresis about 1 liter; sp. gr. of the morning urine 1024.

*Case 2 — Renal hyperparathyroidism.*

The patient was a man, aged 42, in whom the presence of hyperparathyroidism was demonstrated during his admission to the Bispebjerg Hospital in 1949.

Previously he had been admitted 3 times to different clinics on account of symptoms that undoubtedly could be referred to as insidious hyperparathyroidism.

First admission in 1941. Diagnosis: Melena; recurrent pyelitis. For about 6 months he had a sensation of epigastric oppression and pyrosis. On the day of admission, melena appeared. During his stay in hospital he had two attacks of fever, accompanied by pain in the right kidney region and colipypuria. Diuresis varying between 1.5 and 2.5 liters; sp. gr. 1010—1015. Urography showed no abnormality, but cystoscopy revealed evidence of cystitis. Roentgenography of the stomach was not performed.

During the following couple of years he was feeling quite well — apart from periodical dyspepsia.

In 1945, admitted to a surgical clinic for lumbago. Now he complained of pains over the loins, but physical examination, urography and roentgenography of the vertebral column failed to reveal any abnormality. The urine contained no albumin; microscopically it showed crystals but no red or white blood cells. The diuresis was about 2 liters; sp. gr. 1008—1010.

Two years later the patient was admitted to a medical clinic
Table 2.

<table>
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<th>Date</th>
<th>Serum Ca mg. %</th>
<th>Serum P mg. %</th>
<th>Urine Ca mg. per 24 hrs.</th>
<th>Alkaline phosphatase 2-7 units</th>
<th>Diuresis 1-1.5 liters</th>
<th>Sp. gr. 1020-1030</th>
<th>Blood urea 20-40 mg. %</th>
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<td>1013</td>
<td>20</td>
<td>73</td>
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</table>

where dyspepsia of uncertain type was diagnosed. At that time he had been troubled for about six months with nausea, epigastric oppression and regurgitation of food; and he had lost 6 kg. in weight. The urine contained no albumin; microscopically it showed a few leucocytes. Ewald test meal showed normochylia. Roentgenography of the stomach: gastritis(?). Urography and gastroscopy: no abnormality. Diuresis was usually about 1.5 liters, though on three days it exceeded 2.5 liters; sp. gr. about 1010, once 1020.

During the next two years he was frequently suffering with dyspeptic, ulcer-like, phenomena, worst in the spring and autumn. He felt tired. He had constipation, pains over the loins, polydipsia, polyuria and nycturia.

In 1949 admitted to the Bispebjerg Hospital with the diagnosis of nephritis(?).


After this, thorough tests were made regularly with a view to the diagnosis of hyperparathyroidism (Table 2).
This diagnosis was confirmed by the demonstration of hypercalcemia and hypercalcuria. On the other hand, no definite hypophosphatemia was found, nor any distinct increase in the alkaline phosphatase level. Urography and roentgenography of the skeleton showed no abnormality. No palpable parathyroid adenoma.

On 24/5 operation was performed removal of an adenoma (hazelnut size) corresponding to the lower right parathyroid gland.

Histological examination (Dr. B. Vimtrup) showed a somewhat varying structure of the tumor but there could be no doubt that it originated from the parathyroid. The usual histological evidence of malignancy was not observed. Microscopic diagnosis: Parathyroid adenoma.

The postoperative course was uncomplicated, without any manifest or latent tetany, in spite of the fact that the patient was given neither calcium nor vitamin D. The diuresis decreased immediately after the operation to about 1.5 liters, and the sp. gr. rose to 1012—1016. (For other data, see table 2).

Three months after the operation the patient was feeling perfectly well; the pains over the loins, the dyspeptic phenomena, the fatigue and polyuria had disappeared completely. The Addis-Shevsky test showed a sp. gr. of 1020. On re-examination, 1½ years later, the patient was still feeling perfectly well; the serum calcium value was at the upper normal limit; serum phosphorus, alkaline phosphatase level and urea clearance: all normal. Sp. gr. of the urine: 1013.

Case 3 — Parathyroid Poisoning.

Woman, aged 73, admitted June 1950 to the Frederiksberg Hospital with the diagnosis of fever and pneumonia(?).

The patient gave a past history of good health. Two days before admission she suddenly became ill with nausea, repeated vomiting, diarrhoea and rise in temperature to about 39° C.

On admission, the presence of bilateral pneumonia was ascertained. With penicillin therapy the temperature fell to a level around 37.5° C, during the following weeks subfebrile temperature. Pulse rate about 100. Diuresis at first 1.5 liters, later somewhat lower, with intermittent slight albuminuria and colpyuria. Blood pressure 140/80.

During the following weeks the patient gradually became more debilitated, she was troubled with nausea, and occasionally also vomiting. The blood urea concentration was increased (on 11/7: 97 mg. per cent).

On account of the uncharacteristic kidney lesion without hypertension, acute hyperparathyroidism was suspected, and tests were
performed with a particular view to this possibility. The outcome of these tests is recorded in table 3.

Thus some of the changes typical of primary hyperparathyroidism were demonstrated, namely: high serum calcium value, and low serum phosphorus level, but there was no hypercalcuria nor any increase in the alkaline phosphatase level. The blood urea concentration was 114 mg. per cent. The patient now showed evidence of dehydration and slight acidosis, and she was given subcutaneous infusions of saline and bicarbonate solution. This brought about a transitory increase in the diuresis, the blood urea value fell to 25 mg. per cent and the general condition of the patient improved.

Roentgenography of the skeleton and urinary tract showed no sign of ostitis fibrosa or nephrolithiasis.

On August 16, laboratory tests showed: serum potassium value 15.5 mg. per cent; serum sodium value 333 mg. per cent; total base value 157 m. equiv.; serum protein: albumin 3.2 per cent, globulin 3.7 per cent.

The patient was again getting rapidly worse, with a rise in blood urea, and the idea of operative intervention had to be given up. She died on August 24.

Autopsy (Dr. Thorborg) revealed a reddish-brown tumor (walnut-
size) in the lower part of the right lobe of the thyroid and a greyish-white tumor (pea-size) at the upper pole of the left lobe of the thyroid.

**Histological examination:** The larger, somewhat cadaverous, tumor was found to consist of close-packed, light parathyroid cells. The glandular parenchyma was found to be subdivided by delicate connective tissue into alveoli-like or larger lobulated sections. The smaller tumor was made up of better preserved hyperplastic characteristic parathyroid tissue.

There was no enlargement of the thyroid.

Both iliac veins and the lower part of the vena cava inf. were filled completely by large thrombi. A large thrombus had lodged in the right main branch of the pulmonary artery, and a walnut-sized infiltration was found in the right lung.

The kidneys were of medium size, with small cysts here and there on the surface, which was otherwise smooth. Microscopically the kidneys showed thickening and atheromatosis of the larger and middle-sized vessels, also scattered areas with hyalinization of the glomeruli and moderate round-cell infiltration. In the greater part of the kidneys, however, the glomeruli were well preserved, and no evidence of nephritis was found. In addition, there was a moderate degree of interstitial fibrosis, more marked in the pyramids between the straight tubules. The renal pelves, the ureters and the bladder showed no abnormality. The adrenals and hypophysis showed no definite pathological changes, macroscopic or microscopic. Histological examination of the various organs revealed no deposits of calcium salts.

**Case 4 — Osteitis fibrosa generalisata.**

A woman, 30 years old, who was admitted to the Frederiksberg Hospital in October 1950 with the diagnosis of heart lesion and kyphoscoliosis. The patient gave a past history of good health until 1944, when she was admitted to a medical clinic for toxemia of pregnancy (second month), and had been vomiting very often ever since conception. The urine contained leukocytes, but no albumin. Diuresis about 1—1.5 liters; sp. gr. 1002—1010. After interruption of pregnancy the patient was extremely exhausted with very frequent vomiting for about one month, she was given two blood transfusions, and in addition 18 liters of glucosesaline. The diuresis was 1—1½ liters, with sp. gr. of 1000—1020.

Since then the patient has not been well. Her chief complaint has been a most distressing fatigue, vomiting, polyuria, polydipsia, and indefinite pains in the arms and legs. These symptoms appeared with varying degrees of intensity, and there have been free intervals
of some months. In 1946 the patient was admitted to a psychiatric clinic after attempting suicide on account of mental depression due to her condition.

In 1947 she was hospitalized for 3 months in a medical clinic because of emaciation. Here no abnormality was found on roentgenography of the heart and lungs, small and large intestines, stom-

Fig. 1.

ach and pancreas, abdomen or urinary tract; gastroscopy, gynecological, ophthalmological, and neurological examination showed no abnormality whatever. Weight: 47.2 → 42.8 kg., hemoglobin: 93 → 84 per cent. Ewald test meal: normochyliia. Serum potassium: 12.5 mg. per cent. Liver functional test: No abnormality. Diuresis, measured on the first three days: 2300, 2330, 1500 ml. Blood urea: 28 mg. per cent.

After her discharge from the hospital the patient was just as poorly as before; and 1½ years later she had also constant vague pains over the left loin and in the iliac fossa.

In January 1948 she was admitted to a private clinic because of nervous dyspepsia. Here the Ewald test meal showed normal values.
Microscopy of the urine: some leucocytes, no albumin. Diuresis varying, sometimes up to 2.5 liters; sp. gr. about 1010.

During the following three years her state of health remained invariably poor. On 28/10-50 the patient was admitted to the Frederiksborg Hospital. On admission she was undernourished, pale, tired, and deformed with marked kyphosis and bowing of the femora and tibiae. The chest was distorted (fig. 1).

The patient claimed that during the past 5—6 years her height had been gradually reduced from 168 to 160 cm.

X-ray examination revealed generalized decalcification. The vertebral column presented kyphoscoliosis; the bodies of the 7th and 8th thoracic vertebrae were wedge-like flattened (result of fracture?). Some of the long bones showed cysts. There was no deposit of calcium in the kidneys nor any concretion in the urinary tract.

Laboratory tests (table 4) showed hypercalcemia, hypophosphatemia, hypercalcuria, and a marked increase of alkaline phosphatase level. Diuresis: 1.5 to 2.5 liters; sp. gr. 1007—1012.

A detailed functional examination of the kidneys in the medical department III of the Kommune Hospital revealed the following results:

On urography, the pyelograms were found to be normal. No visible nephrocalcinosis.

<table>
<thead>
<tr>
<th></th>
<th>252 ml./min.</th>
<th>per 1.73 sq. m. surface</th>
<th>600 ml./min.</th>
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<tbody>
<tr>
<td>Para-aminohippuric acid clearance</td>
<td>33.8 mg./min.</td>
<td>»</td>
<td>75 mg./min.</td>
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<tr>
<td>Inulin clearance</td>
<td>64.5 ml./min.</td>
<td>»</td>
<td>120 ml./min.</td>
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<tr>
<td>Endogenous creatinine clearance</td>
<td>82.4 ml./min.</td>
<td>»</td>
<td>140 ml./min.</td>
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<tr>
<td>Urea clearance (max.)</td>
<td>47.1 ml./min.</td>
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<td>75 ml./min.</td>
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<tr>
<td>C_{In}:Tm_{PAH}</td>
<td>1.91</td>
<td></td>
<td>1.6</td>
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<tr>
<td>C_{In}:C_{PAH}</td>
<td>25.8</td>
<td></td>
<td>20</td>
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<tr>
<td>C_{PAH}:Tm_{PAH}</td>
<td>7.48</td>
<td></td>
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<tr>
<td>24-hour creatinine clearance</td>
<td>72 hours = 90 ml./min.</td>
<td>3</td>
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<tr>
<td>Concentration test (Addis)</td>
<td>1015 (390 ml.)/1014 (77 ml.)</td>
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</table>

Urine: + albumin (Kjeldahl: trace of protein); microscopy: a few leucocytes.
Table 4.

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum Ca</th>
<th>Serum P</th>
<th>Urine Ca</th>
<th>Alkaline phosphatase</th>
<th>Diuresis</th>
<th>Sp. gr.</th>
<th>Blood urea</th>
<th>Serum K</th>
<th>Alkaline-res.</th>
<th>Serum Cl</th>
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<td>1.2</td>
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<td>2400</td>
<td>1007</td>
<td>15.6</td>
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<td>15.0</td>
<td>2.1</td>
<td>325</td>
<td>54.6</td>
<td>1500</td>
<td>1012</td>
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**Conclusion from the results obtained** (Dr. Claus Brun):

The tests show a reduction in the kidney functions examined to about one-half of the normal capacity. The damage appears to involve equally both the glomerular and the tubular functions as well as the blood flow.

*Renal biopsy,* a. m. Iversen & Brun, was performed.

*Histological examination* (Dr. Harald Gormsen): The biopsy specimen is about 13 mm. long, made up almost equally of cortex and medulla. Rather large calcium deposits are found in the cortex and particularly in the medulla; it is difficult to decide whether they are interstitial or intracanalicular. The cortex consists of about 15 glomeruli, of which only 3 appear to be intact. A couple of the others
are partially hyalinized and the fibrous tissue here shows a marked
diffuse infiltration with leucocytes and histiocytes, together with
just a few plasma cells. In addition, the cortex appears to have
undergone a slight degree of diffuse interstitial fibrosis. The de-
stroyed glomeruli are surrounded by atrophic tubules, but apart
from this the tubules appear to show no abnormality, and the lumina
of the proximal convoluted segment appear fairly wide throughout.

![Image](image.png)

*Fig. 2.*
Renal biopsy from case 4.

No casts are seen. In the medulla there is a marked increase in the
connective tissue, with rather lively infiltration with lymphocytes
and histiocytes. The few blood vessels seen in this specimen appear
to show no abnormality in the lumen — though a few small arteries
possibly show a slightly hyaline thickening of the walls (fig. 2).

*Phosphatase stain:* Distinctly positive in the lumina of nearly all
the preserved proximal convoluted tubules. Probably also a positive
reaction in a few loops of Henle, of which but very few are seen in
the specimen.

On December 15 an explorative operation was performed. No
adenoma was found. The upper left parathyroid, about the size of
a pea was removed, but on microscopic examination it was found
to consist of apparently normal parathyroid tissue.
After the operation the patient was rather poorly, the serum calcium value was between 15 and 18 mg. per cent, and a marked hypopotassemia developed (table 4) that could hardly be explained as due to the rather scanty vomiting. While the electrocardiogram had been normal on admission of the patient, it now showed distinct flattening of the T wave.

On subcutaneous of potassium-containing electrolyte solution, the state of the patient improved markedly.

Then, on 23/1-51 she was again submitted to an operation at which an adenoma was found (2 × 2.5 × 3 cm., weighing 12 gm.), corresponding to the left lower parathyroid.

Microscopic examination (Dr. V. Eskelund): Sections show solid tissue made up of relatively large cells with distinct cell borders and round nuclei varying somewhat as to their localization within the cell body. The nuclei are rather uniform in size, though now and then varying up to twice the usual size. The nuclei mostly show one nucleolus, though sometimes two. The form and size of the cells are somewhat variable. In most places the cells form solid masses or coarse trabeculae, surrounded by a stroma which is but very poorly vascularized and often somewhat hyalinized. Here and there degenerative changes are seen. The protoplasm of the cells shows mostly fine eosinophil granules, and only in a few groups of cells is the protoplasm clear and light. The tissues masses are encapsulated by lamellae of collagenic connective tissue.

Histological diagnosis: Parathyroid adenoma.

On the second day after the operation the diuresis was only 50 ml., the blood urea value rose to 92 mg. per cent, but after this the diuresis became normal. (Table 4). The serum calcium value fell gradually to a level as low as 4.6 mg. per cent — in spite of the administration of calcium and concentrated vitamin D preparation — and 6 weeks after the operation the patient had an attack of tetany. Treatment with parathyroid hormone was started, and the serum calcium level rose to about 9 mg. per cent.

The patient was discharged from the hospital three months after the operation, continued treatment with calcium and vitamin D being prescribed.

On re-examination, 3 months after discharge the patient was feeling much better, and she had gained 7.1 kg. in weight. Serum calcium value 8.3 mg. per cent; blood urea value 51 mg. per cent; and normal values for serum potassium, sodium, chlorine and bicarbonate. The urea clearance was still lowered to about one-half of the normal. 6 months after discharge (17/10) the serum calcium value was 9.6 mg. per cent, serum-phosphorus value: 4.2 mg. per cent, and the alkaline phosphatase level: 5.3, sp. gr.: 1010.
DISCUSSION

These four case reports illustrate quite clearly the varied clinical picture of primary hyperparathyroidism. Patients no. 1, 2 and 4 had presented symptoms which at previous admissions had led to the following diagnoses: chronic nephritis; duodenal ulcer; melena; pyelitis; cystitis; lumbago; dyspepsia: toxemia of pregnancy; emaciation; nervous dyspepsia; and kyphoscoliosis.

The first two patients presented renal hyperparathyroidism, but X-ray examination failed to reveal any osseous decalcification, nephrocalcinosis or nephrolithiasis. Both these patients showed symptoms of renal insufficiency with polyuria, isosthenuria, and slight, inconstant, albuminuria, but no hypertension. In addition, they also had dyspeptic symptoms. Thus, during his first hospitalization, no. 1 had numerous attacks of vomiting --- undoubtedly signifying a parathyroid poisoning. X-ray examination revealed the presence of a duodenal ulcer, but after removal of a parathyroid adenoma his dyspeptic complaints subsided completely. No. 2, no doubt, also had a peptic ulcer as melena was seen at an early stage of the disease. In this patient, too, the dyspeptic complaints subsided after the operation. On re-examination, 1½ years after the operation, the kidney function had improved considerably in both patients.

The third patient presented the rare clinical picture of acute, fatal parathyrotoxicosis. The diagnosis was based on the presence of hypercalcemia and hypophosphatemia. No skeletal or renal changes were found by means of X-ray examination. The kidney function was markedly lowered, and this presumably explains the absence of hypercalcuria. Saline infusions brought about a fall in serum calcium value and improved the condition of the patient somewhat. After this, however, her condition got worse again, terminating fatally.

Autopsy revealed the presence of a parathyroid adenoma and the multiple venous thromboses characteristic of parathyroid intoxication. The absence of calcium deposits in the viscera is possibly attributable to the relatively low serum
phosphorus level (according to Albright & Reifenstein, the concurrence of hypercalcemia and hyperphosphatemia disposes to precipitation of calcium phosphate crystals). In patient no. 4 the disease appears to have persisted for about 7 years, manifesting itself first in the form of toxemia of pregnancy. Most likely the vomiting was not due to intoxication of pregnancy, as attacks of vomiting persisted for one month after an induced abortion. The later course of her illness was characterized by general and gastrointestinal symptoms, especially vomiting, and subsequently by gradual decalcification of the skeletal system. On the other hand, at no time had the patient shown evidence of nephrolithiasis, and the diuresis was not strikingly large. Nevertheless, the kidney function had become markedly involved; and, in spite of negative X-ray findings, the kidney biopsy showed deposits of calcium salts in the renal medulla as well as in the cortex. After an explorative operation, the state of the patient became worse. A decrease of the serum potassium level and a further increase of the hypercalcemia was observed, but without any constant inverse correlation. After removal of a walnut-sized parathyroid adenoma, a marked hypocalcemia developed.

While the prognosis in the first two cases is undoubtedly good, there can hardly be any doubt about a poor prognosis for this patient. Recent clinical experiences have shown that in such cases, in which the recognition of the hyperparathyroidism is not established until late in the course of the disease, the kidney lesion progresses and terminates in nephrosclerosis and hypertension. In the case of a patient described by one of us (Schmith, 1938) the result of the operative treatment was primarily good, but later on severe nephrosclerosis and cerebral hemorrhage developed. The general poor prognosis of patients who are treated operatively only at a late stage of the disease has recently been pointed out by Rienhoff (1950), and by Hellström (1951).
SUMMARY

After a review of the pathogenesis and symptomatology of primary hyperparathyroidism, a report is given of four cases in two of which the clinical picture consisted essentially of symptoms of renal insufficiency — polyuria and isosthenuria — but no nephrolithiasis, nephrocalcinosis or skeletal changes. The third patient was a case of acute and fatal parathyroid intoxication; the fourth patient a clinical picture of classical ostitis fibrosa generalisata. In the last case the kidney function was markedly lowered, and renal biopsy showed calcium deposits in the cortex as well as in the medulla, although this phenomenon was not noticeable on X-ray examination.

In three of the patients a parathyroid adenoma was removed operatively. In the patient with acute parathyrotoxicosis autopsy revealed a walnut-sized parathyroid adenoma and multiple venous thromboses, but no deposits of calcium in the kidneys, lungs and stomach.

In the case of patients presenting signs of renal insufficiency — the possibility of hyperparathyroidism should be kept in mind, especially in the absence of albuminuria and hypertension.

This also applies to patients with uncharacteristic refractory dyspeptic complaints, especially if vomiting is a predominant feature of the clinical picture.

The significance of an early recognition of the disease and operative treatment is pointed out.

REFERENCES

Cope, O.: Surgery 16, 273, 1944.