PRIMARY HYPERPARATHYROIDISM
OBSERVATIONS IN A SERIES OF 50 CASES

By

John Hellström

Hyperparathyroidism was formerly rarely diagnosed, the diagnosis usually not being made until extensive skeletal changes of the osteitis fibrosa generalisata type were present. In recent years, however, the number of cases diagnosed has appreciably increased, thanks mainly to the more widespread knowledge that renal calcification and calculi are among the most common and striking symptoms of hyperparathyroidism. This is well illustrated by my own series; 60 per cent of the cases have been diagnosed since 1950, while the remaining 40 per cent were distributed over the period 1930–1949 with 1 to 2 cases a year. Although hyperparathyroidism is now diagnosed more often than before, only a few hospitals have large series of cases and the majority of publications are based on observations from occasional cases or a small series. The disease appears in so many varying forms, however, that only by studying a sufficiently large series can conclusions of universal applicability be drawn as to symptomatology, pathogenesis, therapy, and prognosis. My own material, consisting of a relatively large series of 50 cases, appears to me to offer an opportunity of elucidating these questions. Part of the series has been published before, but since the last occasion in 1952 another 19 cases have been added; these confirm and complement my earlier observations.

THE GENERAL CHARACTER AND COMPOSITION OF THE MATERIAL

The series consists of 50 cases in which the diagnosis of hyperparathyroidism was made on the following grounds:
Parathyroidectomy + biopsy 45
Autopsy + biopsy 1
Symptoms, laboratory findings – particularly hypercalcaemia, course 3
Skeletal radiology + skeletal biopsy 1

Of the 50 cases 33 were women and 17 men. The youngest patient was a 16 year old girl, the oldest a 62 year old woman. The average age of the patients was 46, roughly the same for men and women.

Of the women, 23 were doing domestic work. The others were in factories, offices, hospitals, and schools. 23 were married and 10 unmarried. There were 4 nulliparas in the first category, and 8 in the second.

Among the men there were 8 manual labourers, craftsmen and the like, 3 office employees, 4 business men and 2 university teachers. Seventeen patients were from Stockholm, 6 from Southern, 20 from Central, and 4 from Northern Sweden; 2 patients were resident in Finland and 1 was a refugee from Latvia.

In my series the distribution of the two most striking lesions of hyperparathyroidism, in the skeleton usually as osteitis fibrosa generalisata, and in the kidneys in the form of calcification or true concretions, was as follows:

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal changes only</td>
<td>13</td>
</tr>
<tr>
<td>Renal changes only</td>
<td>27</td>
</tr>
<tr>
<td>Both skeletal and renal changes</td>
<td>10</td>
</tr>
</tbody>
</table>

All these changes were demonstrable radiologically, a fact which does not rule out the possible presence of radiologically imperceptible histological changes of a similar nature in both the skeleton and kidneys.

It is noteworthy that radiologically demonstrable changes in the kidneys alone were present in 54 per cent of cases, while skeletal changes only were found in but 26 per cent. The total number of cases in which renal changes were observed amounts to 74 per cent, which illustrates the increasing importance of calcification and concretions in the kidneys in the diagnosis of hyperparathyroidism, as pointed out in the introduction. My observations are in complete agreement with those made at the Massachusetts General Hospital and the Mayo Clinic. At the Mayo Clinic 15–20 cases of hyperparathyroidism are diagnosed annually; these can, according to Black (1953) be »attributed almost entirely to a more careful screening of patients with urinary lithiasis for hypercalcemia«.

SYMPTOMS IN THE HISTORIES

It is generally known that patients with hyperparathyroidism often have symptoms for long periods before the diagnosis is made. Any calculation of their duration is, however, rendered uncertain by the frequently uncharacteristic and
Insidious nature of the symptoms. It may be difficult to decide whether a symptom in the patient’s history should be associated with hyperparathyroidism or not. With these qualifications, the duration of the symptoms in my series was as follows:

< 1 year in 6 cases; 1–3 years in 13 cases; 3–5 years in 7 cases; 5–10 years in 9 cases; 10–15 years in 5 cases; 15–20 years in 7 cases; > 20 years in 4 cases.

The average duration of the symptoms is 8 years.

The character of the symptoms has varied widely; in some cases one symptom predominated, in others the complex of symptoms seen varied a good deal. A list of the symptoms is given below, irrespective of whether they were present alone or combined with others:

<table>
<thead>
<tr>
<th>Skeletal symptoms</th>
<th>Renal symptoms</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone and joint pain</td>
<td>Infection in the urinary tract</td>
<td>Headache</td>
</tr>
<tr>
<td>Fractures</td>
<td>Polyuria - polydipsia</td>
<td>General fatigue</td>
</tr>
<tr>
<td>Giant cell tumour</td>
<td>Hypertension</td>
<td>Endocrinous disorders</td>
</tr>
<tr>
<td></td>
<td>Abdominal and intestinal disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

As was to be expected, skeletal and renal symptoms predominated. In the first category there were, almost without exception, skeletal changes, usually of the generalized osteitis fibrosa type.

The cases with so-called giant cell tumours are of particular interest (Table 1). In 5 cases these tumours were localized to the jaws and were for varying periods regarded and treated as local disease processes, until they were seen to be symptoms of generalized osteitis fibrosa. This also applies to the 2 cases in which a giant cell tumour was diagnosed in the scapula and clavicle respectively. In the second case, the patient had had renal calculi for more than 10 years and was treated with nephrectomy. In November 1951 a small, tender swelling developed on her right leg. An impression in the tibia corresponding to the tumour could be seen radiologically. This was removed and found to be a giant cell tumour. Further examination revealed the presence of hyperparathyroidism. It was remarkable that the only radiologically demonstrable skeletal changes were in the cranium, in the form of slight decalcification.

Of the 9 cases with fractures in the history there were 7 in which the trauma had been so slight as to justify the use of the term spontaneous fracture. In 7 cases radiological examination of the fracture led directly to the discovery
### Table 1.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Localisation</th>
<th>Diagnosis of giant cell tumour</th>
<th>Diagnosis of generalized osteitis fibrosa</th>
<th>Parathyroidectomy</th>
<th>Treatment of giant cell tumour prior to diagnosis of hyperparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Lower jaw</td>
<td>1924</td>
<td>1931</td>
<td>Not applicable</td>
<td>Operation + radio therapy</td>
</tr>
<tr>
<td>4</td>
<td>Lower jaw</td>
<td>1925</td>
<td>1930</td>
<td>1934</td>
<td>Operation</td>
</tr>
<tr>
<td>3</td>
<td>Upper jaw</td>
<td>1931</td>
<td>1933</td>
<td>1933</td>
<td>Operation + radio therapy</td>
</tr>
<tr>
<td>16</td>
<td>Lower jaw</td>
<td>1948</td>
<td>1948</td>
<td>1950</td>
<td>Operation + radio therapy</td>
</tr>
<tr>
<td>17</td>
<td>Upper jaw</td>
<td>1948</td>
<td>1948</td>
<td>1950</td>
<td>Biopsy + radio therapy</td>
</tr>
<tr>
<td>18</td>
<td>Neck of scapula</td>
<td>1949</td>
<td>1949</td>
<td>1950</td>
<td>Radio therapy</td>
</tr>
<tr>
<td>35</td>
<td>Clavicle</td>
<td>1949</td>
<td>1951</td>
<td>1951</td>
<td>Biopsy + radio therapy</td>
</tr>
<tr>
<td>28</td>
<td>Tibia</td>
<td>1950</td>
<td>1950</td>
<td>1951</td>
<td>Operation</td>
</tr>
</tbody>
</table>

of general skeletal lesions; in 2 cases these were, however, at first regarded as tumour metastases. In 2 cases it was not until 2 and 10 years respectively after the fracture that general skeletal changes were found to be present and the diagnosis of hyperparathyroidism made.

With regard to renal symptoms, it is understandable that renal colic predominated and was present in more than half of the whole series. Symptoms of urinary tract infection usually accompanied calculus symptoms, but in some cases they appeared later, in others much earlier.

In 3 cases there was marked polyuria, hypothenuria, and polydipsia before any radiologically demonstrable calcification appeared in the kidneys.

Among symptoms from organs other than the skeleton and the kidneys we find hypertension disorders in 10 cases. This is not surprising as hyperparathyroidism, as will be shown later, is very frequently accompanied by hypertension.

In the group of abdominal and intestinal disorders there are 7 cases of duodenal ulcer (Table 2). There were 5 men and 2 women in this group. I have noted the relatively high incidence of ulcers, 14 per cent. Like certain authors, including Rogers (1946), Black & Akerman (1947), Berlin (1949) and Schmidt & Faber (1952), I have observed the combination of ulcer and hyperparathyroid-
Table 2.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age when ulcer diagnosed</th>
<th>Ulcer before hyperparath.</th>
<th>Ulcer after hyperparath.</th>
<th>Main symptom of hyperparathyroidism</th>
<th>Localisation of ulcer</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>M</td>
<td>22</td>
<td>10 years</td>
<td></td>
<td>Gen. osteit. fibr.</td>
<td>Duodenum</td>
<td>+</td>
</tr>
<tr>
<td>35</td>
<td>M</td>
<td>31</td>
<td>4 &quot;</td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>-</td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>48</td>
<td>&lt;3 &quot;</td>
<td>12 years 24 &quot;</td>
<td>Renal calc.</td>
<td>&quot;</td>
<td>-</td>
</tr>
<tr>
<td>39</td>
<td>M</td>
<td>29</td>
<td>2 &quot;</td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>-</td>
</tr>
<tr>
<td>42</td>
<td>M</td>
<td>&lt;48</td>
<td></td>
<td>10 &quot;</td>
<td>Gen. osteit. fibr.</td>
<td>&quot;</td>
<td>-</td>
</tr>
<tr>
<td>40</td>
<td>F</td>
<td>47</td>
<td></td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>-</td>
</tr>
<tr>
<td>47</td>
<td>F</td>
<td>47</td>
<td></td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>-</td>
</tr>
</tbody>
</table>

ism and believe there is some connection between them. In every case the ulcer was duodenal. The age and sex of the patients was as is usually found in this disease. In 5 cases the ulcer symptoms preceded hyperparathyroidism, in 2 cases the reverse occurred. Ulcers were present in cases with skeletal changes only, or kidney changes only, roughly in proportion to the distribution of these lesions in the whole series. It is worthy of note that ulcers were diagnosed in only two women out of 33, whereas they were present in 5 of 17 men, or 5 times as often. My series certainly contains a strikingly high incidence of duodenal ulcers among the male patients suffering from hyperparathyroidism, but no conclusions can be drawn about the possible connection between these two conditions.

It was remarkable that so many of the patients suffered from severe headaches. An analysis of the 8 cases in which headaches occurred shows that in 3 cases they were probably due to a coexistent hypertension. In these 3 cases there were only renal changes. In the remaining 5 cases it has not been possible to find any explanation for the headaches. In every case they were severe and prolonged, and had been present for long periods before the diagnosis of hyperparathyroidism was made. In 3 of these cases generalized osteitis fibrosa was present, in 2 only renal lesions.

General fatigue was the predominant symptom in 5 cases. Several other patients complained of fatigue, probably caused by the anaemia which frequently accompanies hyperparathyroidism or hypotonia of the muscles owing to the hypercalcemia. Hypertension and lesions of the kidney may also be contributory causes of fatigue. On the other hand, a large number of patients were in excellent general condition and had an undiminished capacity for work despite hyperparathyroidism of long duration.

For several reasons it would be of interest to try and discover how often hyperparathyroidism is accompanied by other endocrine disorders. I shall re-
turn to this subject later: at present I only wish to mention the endocrine disorders found in the histories.

Dysmenorrhea was reported in only 3 cases. As mentioned before, there were 3 nulliparas among the 23 women who were married. In only 2 cases can it be presumed with certainty that hyperparathyroidism was aggravated by pregnancy.

Diabetes was present in 1 patient.

Symptoms of hyperthyroidism were found in 2, possibly 3, cases. 2 of the patients had goiter and a marked rise in basal metabolism together with hyperparathyroidism. The 3rd patient had, 20 years before the diagnosis was made, had goiter with toxic symptoms which subsided after treatment. When hyperparathyroidism was diagnosed she had a thyroid adenoma and a normal basal metabolism.

**Diagnosis**

Hyperparathyroidism is diagnosed in the first place by the presence of hypercalcaemia. Although hypercalcaemia may be present in a number of conditions other than hyperparathyroidism, this condition should always be suspected in the presence of hypercalcaemia. However, it is less well known that hyperparathyroidism may also be present when there is an insignificant rise in the blood calcium level, or even when this is normal: such cases may be either very advanced and with a high degree of renal damage and phosphate retention, or of an early and mild type. Other factors, such as a deficiency of vitamin D, low serum albumin, and technical errors in the laboratory, may result in a low blood calcium level. Finally, spontaneous remissions can certainly occur and cause the calcium content of the blood to be temporarily within normal limits. It is, therefore, important that even slight rises in the blood calcium level be observed, and frequent determinations made. In an earlier paper I discussed the diagnostic value of a fractional determination of the blood calcium in doubtful cases. There is much to suggest that in hyperparathyroidism the diffusible fraction of the blood calcium is raised to a higher degree than that of the non-diffusible fraction. The results of these investigations will be published elsewhere; here I should merely like to mention the fact that it is still too early to give any opinion as to the possible value of fractional determinations of the blood calcium level in the diagnosis of hyperparathyroidism.

A low figure for the phosphorus content of the blood, and a high one for the calcium in the urine, is strongly suggestive of hyperparathyroidism but not pathognomonic, and is greatly dependent on the state of the kidneys. In only a certain number of the patients in my series were hypercalcaemia, hypophosphataemia, and hypercalcinuria coexistent. Taking into account the lowest value
observed for the phosphorus content of the blood, the figures in the cases examined were as follows: $< 2$ mg. per cent in 7 cases, 2–3 mg. per cent in 24 cases, 3–4 mg. per cent in 8, 4–5 mg. per cent in 8, and $> 5$ mg. per cent in 1 case.

A low blood phosphorus level should arouse suspicion of hyperparathyroidism; a normal or raised figure does not rule out this possibility. As in the case of blood calcium, repeated determinations should be made.

Figures for the calcium in the urine show even wider variations. The following excretion per 24 hours was noted:

$< 100$ mg. in 9 cases; 100–200 mg. in 10 cases; 200–400 mg. in 9 cases; 400–600 mg. in 4 cases; $> 800$ mg. in 4 cases.

Thus, in more than half the cases examined the urinary calcium was within normal limits, and excessively high in only 8 cases. No complete examination of the total calcium balance was made; in the majority of cases it seems hardly likely that it is of greater value in the diagnosis of primary hyperparathyroidism than is the determination of the urinary calcium alone. The same applies to Hamilton's test for increased amounts of parathyroid hormones in the blood. A negative reaction to this test does not rule out hyperparathyroidism, and in those cases with a positive reaction there are usually such definite signs of hyperparathyroidism that the test is superfluous. A rise in blood phosphatase is present in diffuse bone decalcification and in generalized osteitis fibrosa, but is not pathognomonic of hyperparathyroidism. The hyposthenuria which nearly always accompanies hyperparathyroidism is of importance in the diagnosis and will be treated in more detail in the following.

Radiological examination is of great value in demonstrating changes in the kidneys and bones. In the kidneys multiple, small, often granular, renal calcifications are regarded as particularly characteristic of hyperparathyroidism. Such calcification may, however, also be present in nephrocalcinosis without any signs of hyperparathyroidism; on the other hand, there may be concretions similar in appearance to common renal calculi in this condition. Urography may give some information by showing a decreased contrast content, a sign equivalent to hyposthenuria.

In radiological examination of the skeleton findings of multiple, cystic decalcification are, in the majority of cases, indicative of the presence of generalized osteitis fibrosa and hyperparathyroidism. There is, however, the danger that, as illustrated by my series, only that part of the skeleton in which symptoms are present is examined radiologically, and a so-called giant cell tumour diagnosed. A complete radiological examination of the skeleton should always be made when such lesions are found. Multiple, cystic changes in the skeleton may, however, be present in conditions other than hyperparathyroidism, such as myeloma and fibrous dysplasia. The differential diagnosis between this condition and hyperparathyroidism may be difficult radiologically. As a
sign in differential diagnosis Pugh (1951) mentions the subperiosteal bone resorption, particularly in the phalangeal bones of the hand, which is believed to occur only in hyperparathyroidism and renal osteodystrophy and not in fibrous dysplasia or osteoporosis. However, in several of our cases subperiosteal bone resorption was absent, despite the presence of radiologically demonstrable skeletal changes. The radiological differential diagnosis of osteitis deformans Paget is not usually difficult, but at least one of my cases was diagnosed as such for a long time before it was discovered that the patient was suffering from hyperparathyroidism.

Finally, arteriography was carried out in some cases to elucidate the possible diagnosis of an enlarged parathyroid gland. This examination, which can hardly be said to have afforded any definite information, will be described in detail by Seldinger of the Roentgen Diagnostic Department of this hospital.

PATHOLOGY

Opinions differ as to classification of the pathologico-anatomical changes in the parathyroids and their functional relation. Castleman (1952), who probably has the widest experience of these matters, uses the following divisions:

Primary hyperparathyroidism
Adenoma, single or multiple.
Primary hyperplasia and hypertrophy involving all four glands.

Secondary hyperthyroidism
Hyperplasia involving all four gland.

Non-functional enlargements
Oxyphil »adenomas«.
Cysta.
Carcinoma, primary and metastic.

A similar classification is employed by Woolner, Keating & Black (1952), but these authors include a group of 5 cases of »multiple tumours of the endocrine glands, including the parathyroid, the pancreatic islets and the pituitary«. They report that some cases in this group presented the picture called nodular hyperplasia by Bergstrand (1941), and say that »the line between true neoplasm and hyperplasia of a nodular type cannot be drawn sharply«.

Nowadays it is generally accepted that there is only one fundamental type of cell in the parathyroids, i. e. the chief cells, and that other cells, wasserhelle and oxyphil, develop from the chief cells and represent functional influences,
the former towards increased, the latter towards decreased, function. In this way the transitional forms between the different cells are also accounted for. The general view is that in primary hyperplasia of all the parathyroid glands, also termed diffuse hyperplasia, only wasserhelle cells are present and that their size and arrangement may vary. The so-called adenomas may be formed of any of the cell types, either from one type only or from several in varying interrelation. Further, primary hyperplasia and adenomas differ in that there is no remaining normal parathyroid tissue present in the first condition, whilst some may be present in the second condition.

In my series the parathyroids were examined macroscopically and microscopically in 46 cases; 45 times in connection with surgical interference, twice also at autopsy, and in 1 case only at autopsy. This examination, combined with the results of parathyroidectomy, led to the finding of an adenomatous enlargement, an «adenoma», in 39 cases, and of primary hyperplasia in 7 cases. The incidence of such cases, 14 per cent, is somewhat higher than is usually found in a large series; the figure for the material at the Massachusetts General Hospitals is 11 per cent, and at the Mayo Clinic 8.5 per cent.

In only 2 of the cases with primary hyperplasia could all the glands be examined, two of them in 4 cases, and only one gland in 1 case. The macroscopic and microscopic appearance and the blood calcium level after parathyroidectomy seem, however, to justify the diagnosis of primary hyperplasia, although there is some doubt in 2 of the cases. In one of these, No. 2, two glands were removed surgically, one being nearly as large as a hen's egg and one the size of a walnut, both consisting entirely of wasserhelle cells. Symptoms of hyperparathyroidism still remained, however, and at autopsy 12 years later a further two glands were found; these were of a different histological appearance in that they contained chief cells as well as wasserhelle cells. I have discussed this case in a previous paper and expressed the opinion that the renal damage which caused the patient's death could also have been the cause of the different histological appearance. Autopsy of this case also revealed an enlargement of the hypophysis, adrenal glands and pancreatic islets. This case may correspond to the Mayo Clinic's group of multiple tumours of endocrine glands, which include the parathyroid, pancreatic islets and pituitary.

The other doubtful case, No. 8, was described in an earlier paper as «nodular enlargement of one or more glands with adenomatous nodules in a changed parenchyma». In this case two parathyroid glands were removed surgically, with a combined weight of 53 g. Both were lobulated in appearance and were formed of solid follicles consisting of large wasserhelle cells, and transitional cells in patches. There were no remnants of normal parathyroid tissue. Hence, it seems probable that primary hyperplasia was present.

In 38 cases of adenomatous enlargement only one gland was involved, in one case 2 glands. The distribution was as follows: right upper 2, right lower 11,
left upper 10, left lower 13, right 2, left 1. There is, thus, a marked predominance of the left side and the lower glands. In one case the adenoma lay in the anterior, and in 2 cases on the border of the posterior mediastinum. The size varied. In 15 cases the greatest diameter was 1 cm. at the most, in 11 cases 2 cm., in 11 cases 3 cm., and in 2 cases it was more than 3 cm. As information on the weight is incomplete, these measurements have been used to classify the adenomas into a size groups, Nos. I-IV.

Histologically one can distinguish 2 main types, one of uniform structure and the other of a more or less marked nodular structure. In an earlier publication of part of the series Hellström & Wahlgren (1945) tried to differentiate these two types, but in the present paper they have been placed in a common group, i.e. adenomatous enlargement or «adenoma». Professor Wilton, who has examined the majority of excised parathyroid glands at Karolinska Sjukhuset, has in recent years discarded the word adenoma and used instead the term hyperplastic parathyroid gland, possibly with signs of hypersecretion. The presence in particular of so-called wasserhelle cells has been taken to be such a sign. The cases have been divided into 4 groups according to the content of wasserhelle cells in glands with adenomatous hyperplasia:

| I. Almost exclusively wasserhelle cells (+ + +) | 4 |
| II. Predominantly wasserhelle cells (+ +) | 5 |
| III. Lesser amounts of wasserhelle cells (+) | 16 |
| IV. No wasserhelle cells (—) | 14 |

The classification is, of course, inconclusive, as transitional forms between chief and wasserhelle cells were also found in a number of cases, and no examination of the glands was made by serial section. However, one has a distinct impression that the amounts of wasserhelle cells vary widely in different glands. The question then arises as to whether this exerts any influence on the degree of severity of hyperparathyroidism; this problem will be discussed in the following.

**THE RELATIONSHIP BETWEEN PATHOLOGICAL-ANATOMICAL CHANGES IN THE PARATHYROID GLANDS AND THE CLINICAL SYMPTOMS OF HYPER-PARATHYROIDISM**

In discussing this subject one must try to make it clear whether the clinical signs and symptoms of hyperparathyroidism differ in cases with primary hyperplasia of all glands and those with adenomatous enlargement, and whether they also vary within the second group.
As enlargement of the parathyroids is usually most marked in primary hyperplasia, and as it consists exclusively of wasserhelle «hypersecretion» cells, one should à priori expect more severe symptoms and evolution in cases of primary hyperplasia than in those of adenomatous enlargement. It would be of particular interest if one could find out whether any relation could be established between the nature of the parathyroid enlargement and the two most striking clinical symptoms, i.e. skeletal and renal changes. The series at the Massachusetts General Hospital tends to suggest this; Castleman & Cope (1951) found renal calculi in all 11 cases of primary hyperplasia, and slight skeletal decalcification in only 2. In my series, too, the 7 cases of primary hyperplasia had renal calculi, though 2 of the patients also had skeletal changes of the generalized osteitis fibrosa type. It is remarkable that 4 cases had symptoms of hyperparathyroidism in the form of renal calculi for more than 15 years before any skeletal changes could be shown radiologically. It would thus appear, that in primary hyperplasia one usually only finds renal changes, and that this is not dependent on the shorter course of the disease. As generalized osteitis fibrosa must be regarded as a more serious symptom – if parathyroidectomy is not performed – than the renal stones one can hardly say that the symptoms of primary hyperplasia are more severe than those of adenomatous enlargement of the parathyroids. It should also be borne in mind that the prognosis after parathyroidectomy is considerably better for the skeletal than for the renal changes.

The blood calcium level does not differ greatly between cases of primary hyperplasia and those with adenoma. The average value in the former was slightly higher, 14.6 mg. per cent, than in the latter, 14 mg. per cent; all the values were above 13 mg. per cent, whereas in 10 patients with adenoma values above this figure were never noted. Nor is there any great difference in renal damage and raised blood pressure between primary hyperplasia and adenoma, although the mildest degrees of these symptoms were found among the cases with adenoma.

There are some data in the literature on the question of whether there is any relationship between the size and histological structure of the parathyroid adenoma and the clinical symptoms. Woolner, Keating & Black (1952) found the large adenomas in cases with marked skeletal lesions and high blood calcium levels. Castleman & Mallory (1935) and Cope (1943) also state that there is relation between the size of the adenoma and the blood calcium level. The higher the blood calcium level, the larger the adenoma. On the other hand, these authors could find no correlation between the histological appearance and the clinical picture. Rienhoff (1950) found that wasserhelle cells were predominant in cases with renal complications, whereas in the presence of skeletal changes the other cells, mainly chief cells, were in the majority.

In my series an investigation has been made into the relationship between
the size and histological appearance of the adenoma on the one hand, and the duration, character and degree of the symptoms on the other.

I have not been able to establish any connection between the size of the adenoma and the duration of the symptoms. Large adenomas have been found in patients with short histories and vice versa.

The cases with small adenomas showed a preponderance of renal changes only, and cases with large adenomas of skeletal changes only. In 11 cases with only skeletal changes the adenoma belonged to size groups III–IV, 70 per cent, whereas of 20 cases with only renal changes 3 cases or 15 per cent were in this size group.

If the level of the blood calcium is taken as a measure of the degree of hyperparathyroidism, which may be justifiable, then there appears to be some correspondence between the size of the adenoma and the rise in blood calcium. Of 23 cases in which no blood calcium value exceeding 14 mg. per cent was noted, the adenoma belonged to size groups I and II in 19 cases, or about 83 per cent, whereas in the 15 cases which showed blood calcium values over 14 mg. per cent the adenoma belonged to groups I and II in only 53 per cent. In view of what has been said above about variations in blood calcium it is, however, not surprising that even in cases of large adenoma one may find relatively low blood calcium values. It is more remarkable that the blood calcium value can be high in cases with a small adenoma, e.g. in one of my cases exceeding 17 mg. per cent.

If the histological appearance of the adenoma, instead of its size, is compared with the duration, character and degree of the symptoms, the following is found:

No relationship has been established between the duration of the symptoms and the number of wasserhelle cells. It is noteworthy that in a large number of cases with long histories wasserhelle cells were absent.

There is nothing to suggest with certainty that the number of wasserhelle cells in the adenoma has any influence on the interrelation of skeletal and renal changes. It is noteworthy, however, that in the 4 cases in which the adenoma was almost entirely formed of wasserhelle cells renal changes only were present in 3, and in the 4th case these lesions were coexistent with skeletal changes; further, the incidence of adenomas without wasserhelle cells was twice as high in the cases with skeletal changes only as in those with renal changes only.

There is no correlation between high blood calcium values and a high content of wasserhelle cells, rather the opposite. In fact, among the cases with blood calcium values over 14 mg. per cent there are only 2 adenomas with a high wasserhelle cell content, and 13 with only insignificant amounts or none at all.

Finally, if one compares the size of the adenomas with the wasserhelle cell content, a relatively large number of cases with a high content of wasserhelle
cells had adenomas belonging to the small size groups I–II, rather than to the large size groups III–IV.

To summarize one can say that an analysis of my series has shown the following: the duration of the symptoms has not been dependent on the size of the adenoma, nor on its content of wasserhelle cells. In cases with renal changes, small adenomas with a high content of wasserhelle cells predominated; in those with skeletal changes, large adenomas with a low content of wasserhelle cells were in the majority. High blood calcium values were more frequently found in cases with large adenomas and a low wasserhelle cell content. The number of these cells was relatively larger in cases with small rather than large adenomas.

**RENAI N FUnC TION IN HYPERPArATHYROIDISM**

In previous papers I have shown that in almost all my cases at the time some renal damage was present, the most characteristic feature being the kidneys' incapacity of concentrating the urine. The 19 cases of later date confirm this in most respects, even though these cases include a relatively larger number of patients with less severe renal damage. In the 45 cases in which we have data of a determination of the specific gravity of the urine in concentration test prior to parathyroidectomy, the highest value have been the following: less than 1.014 in 28 cases, 1.014–1.017 in 9 cases, 1.020–1.022 in 5 cases and 1.024–1.026 in 3 cases. No discrepancy between cases with radiological changes in the kidneys alone and those with changes only in the skeleton, or between cases with primary hyperplasia and those with adenoma, has been observed. Nor is there any demonstrable difference attributable to the degree of parathyroid enlargement and wasserhelle cell content. It is remarkable that, despite marked hyposthenuria, the non-protein nitrogen was usually normal. Filtration, too – determined by creatinine clearance test – may, despite the presence of hyposthenuria, be normal or only slightly decreased. Albumin was absent in 40 per cent.

The cause of renal damage in hyperparathyroidism is not yet established. As I have stated in earlier papers (1950, 1953) the primary cause appears to be a structural or functional tubular damage resulting from increased calcium and phosphorus excretion, a toxic process via the parathyroid hormone, or both these factors. According to Albright & Reifenstein (1948) hyposthenuria in hyperparathyroidism may be caused by structural tubular damage or a functional disorder resulting from the high parathyroid hormone level. The renal damage is, certainly, very similar to that brought about in both animal experiments and clinically by an overdose of vitamin D. This leads to hypercalcaemia and a marked increase in calcium excretion.
through the kidneys with damage to the tubular epithelium which is shown by a decreased concentration capacity in the kidneys. In cases not too advanced the renal changes appear to be reversible if the vitamin D is stopped in time. In cases of longer duration, however, irreversible changes appear in both the tubuli and glomeruli, especially in the form of calcification, the renal damage develops, and the relative renal insufficiency turns into an absolute insufficiency with rising non-protein nitrogen.

In early cases of hyperparathyroidism, too, one may see that the renal damage may cease to exist or improve if hyperparathyroidism is arrested by the complete removal of the hyper-functioning parathyroid tissue. Case 34 in my series illustrates this.

The patient was a 16 year old girl who had had symptoms of renal calculi for 4 months. Radiological examination disclosed multiple, small stones in both kidneys. The calcium content of the blood was appreciably raised, 13–15 mg. per cent, the excretion of calcium in the urine rose to 520 mg./24 hours. The non-protein nitrogen was 26 mg. per cent, the specific gravity of the urine in the concentration test was at the most 1.013.

<table>
<thead>
<tr>
<th>Time</th>
<th>Conc. test before operation</th>
<th>Conc. test after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>volume</td>
<td>spec. gravity</td>
</tr>
<tr>
<td>7 a.m.</td>
<td>1200 (night)</td>
<td>1.010</td>
</tr>
<tr>
<td>9 a.m.</td>
<td>200</td>
<td>1.013</td>
</tr>
<tr>
<td>11 a.m.</td>
<td>250</td>
<td>1.013</td>
</tr>
<tr>
<td>1 p.m.</td>
<td>250</td>
<td>1.013</td>
</tr>
<tr>
<td>3 p.m.</td>
<td>200</td>
<td>1.013</td>
</tr>
</tbody>
</table>

A parathyroid gland the size of a bean was removed at the operation; histologically it consisted mainly of chief cells, but also some oxyphil and wasserhelle cells. After parathyroidectomy the blood calcium fell to normal values, and 4 days after the operation the calcium in the urine was 150 mg. per cent. A week after parathyroidectomy a concentration test showed a specific gravity of up to 1.030. The filtration rate (creatinine) was 160 ml./min.

Another young patient, a 17 year old boy with bilateral renal calculi and a single bone cyst, also showed appreciable improvement after parathyroidectomy. The highest figure for specific gravity in a concentration test before the operation was 1.018, and 2 weeks after the operation 1.027.

A third case, No. 38, showed a great improvement in concentration capacity when hyperparathyroidism had been arrested by operation.
The patient was a 41 year old man with symptoms of both hyperthyroidism and hyperparathyroidism. He had a diffuse goiter, decalcification of bone, the basal metabolic rate was +75, blood calcium 16.0 mg. per cent, and blood phosphorus 2.9 mg. per cent. The calcium in the urine was 70 mg./24 hours. Non-protein nitrogen was 30 mg. per cent, but the clearance rate only 30 ml./min. The specific gravity of the urine in a concentration test was 1.007–1.013. After pre-operative iodine therapy the basal metabolic rate fell to +6, the blood phosphorus rose to 5.2 mg. per cent, and the calcium in the urine to 500 mg./24 hours, but the blood calcium remained unchanged at its high level. After sub-total thyroidectomy both the basal metabolic rate and the blood calcium showed normal values, recalcification of bone took place, and 7 years after the operation the kidneys could concentrate urine up to 1.030. The filtration rate had increased to 140 ml./min.

Finally, in case 16 the specific gravity of the daily volume of urine before the operation was 1.010, and 8 months after the operation 1.025, with a highest specific gravity of 1.034 in a concentration test.

Although the concentration capacity was not regained as completely as in these cases, the majority of cases have shown some improvement after parathyroidectomy. This applies particularly to cases in recent years. In several instances the improvement did not appear until long after parathyroidectomy. In a number of cases, however, no improvement was noted, and in several the renal damage progressed, with rising non-protein nitrogen and death from uraemia.

In addition to direct damage to the tubular epithelium, one must take into account the renal damage resulting from the blocking of the urinary canals by calcium deposits, the formation of true calculi, and the urinary infection which so frequently accompanies hyperparathyroidism. In my series an infection of this type was present in 53 per cent of cases. Finally, it is possible that the progressing hypertonia found in many cases of hyperparathyroidism, even after parathyroidectomy has been performed, is not only a result of the renal damage but may aggravate it.

**BLOOD PRESSURE IN HYPERPARATHYROIDISM**

In previous papers (1950, 1953) I have pointed out that the majority of patients in my series have had hypertension in varying degrees, and that it was somewhat transient to start with, later becoming more and more progressive. Several patients died of cerebral haemorrhage. It is difficult to decide what level of blood pressure should be regarded as indicative of hypertension. In my series a complete hypertonia examination was not generally made, but only frequent determinations of the blood pressure. If a permanent blood pressure of 160/100 is taken as the marginal level for hypertension, the distribution in my series was as follows:
No hypertension \hspace{1cm} 19  
Moderate hypertension, 160–200 mm. \hspace{1cm} 20  
Marked hypertension \hspace{1cm} > 200 mm. \hspace{1cm} 6  
Incomplete data \hspace{1cm} 5

Of the 18 cases in which the blood pressure was not raised at the time of parathyroidectomy, manifest hypertension developed later in 5 cases, the blood pressure was normal more than 4 years after the operation in 2, and in 11 cases the time elapsed since the operation is so short that one can draw no definite conclusions as to the state of the blood pressure. In 4 of the cases with no definite data about the blood pressure before parathyroidectomy, marked hypertension was present after the operation. Thus, hypertension present, before or after parathyroidectomy, in a total of 35 patients.

Of the 25 surviving cases in which hypertension was present before parathyroidectomy, blood pressure rose after the operation in 13 cases, fell in 7, was unchanged in 2 and was not examined after the patients left hospital in 3 cases. In only 1 case has the blood pressure returned to normal after having been high before the operation.

In determining the blood pressure, the age of the patient is, of course, of importance.

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt; 160</th>
<th>160–200</th>
<th>&gt; 200</th>
<th>Not determined</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31–40</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>41–50</td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>51–60</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As can be seen in Table 4, the majority of patients with only slight hypertension, or none at all, were under 40 years of age; but moderate or marked hyperten- 
sion was also present in an appreciable number of patients between the 
ages of 31–50 years.

As it may be of particular interest to analyse the cases with a high degree of hypertension, > 200, they have been given in a table which also gives the patients’ age, degree of renal damage, and information as to whether the high blood pressure had been noted before or after parathyroidectomy. In the Table 6 we see that severe manifest hypertension was also present in patients of middle age, in cases of advanced renal damage as well as in cases with so slight
a damage that is can hardly be supposed to have been the cause of hypertension – or at least not the primary cause. Further investigations are necessary, including the possibility that the adrenal glands are concerned in the production of the hypertension.

Table 5.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age</th>
<th>Blood pressure</th>
<th>Before or after parathyroidect.</th>
<th>Renal damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>F</td>
<td>38</td>
<td>225/130</td>
<td>Before</td>
<td>++ +</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>45</td>
<td>230/150</td>
<td>&quot;</td>
<td>++ +</td>
</tr>
<tr>
<td>33</td>
<td>M</td>
<td>56</td>
<td>215/130</td>
<td>&quot;</td>
<td>(+)</td>
</tr>
<tr>
<td>43</td>
<td>F</td>
<td>52</td>
<td>210/120</td>
<td>&quot;</td>
<td>—</td>
</tr>
<tr>
<td>27</td>
<td>F</td>
<td>49</td>
<td>225/150</td>
<td>&quot;</td>
<td>+</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>41</td>
<td>225/135</td>
<td>After</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>53</td>
<td>280/170</td>
<td>&quot;</td>
<td>—</td>
</tr>
<tr>
<td>38</td>
<td>M</td>
<td>48</td>
<td>220/160</td>
<td>&quot;</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>60</td>
<td>220</td>
<td>&quot;</td>
<td>++</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>37</td>
<td>205/140</td>
<td>&quot;</td>
<td>++ +</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>60</td>
<td>230/120</td>
<td>&quot;</td>
<td>++</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>60</td>
<td>220/140</td>
<td>&quot;</td>
<td>+</td>
</tr>
<tr>
<td>47</td>
<td>F</td>
<td>47</td>
<td>240/110</td>
<td>Before</td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>52</td>
<td>220/130</td>
<td>After</td>
<td>+</td>
</tr>
</tbody>
</table>

HYPERPARATHYROIDISM AND RENAL CALCULI

As was mentioned in the introduction, calcification and concretions in the kidneys are nowadays the most common basis for the diagnosis of hyperparathyroidism. From the point of view of practical surgery, the formation of concretions is of great significance, as operation for calculi in hyperparathyroidism are often followed by a relapse. In my series 29 operations for calculi were performed on 17 patients before the diagnosis of hyperparathyroidism was made and parathyroidectomy undertaken. 8 operations for calculi were performed after parathyroidectomy. Thus, in one patient 5 operations were performed during 1937–1951 before hyperparathyroidism was diagnosed. One should bear in mind the fact that this condition can be present not only when there are bilateral, multiple renal calculi, but also when there is a single oxalate stone. In one of my cases, in which the earliest symptoms were polyuria and polydipsia, one could follow the development of the stone from the size of a pin’s head in one kidney to large bilateral concretions in both kidneys. It is also noteworthy that the presence of other factors influencing the forma-
tion of concretions can delay the diagnosis of hyperparathyroidism. In 3 of my cases chronic staphylococcuria was present for many years, necessitating several operations for calculi, before hyperparathyroidism was diagnosed.

It is surely beyond doubt that hypercalcaemia, and increased excretion of calcium via the kidneys, is the primary cause of calculus formation in hyperparathyroidism, though other stone-forming factors may play a part. According to Meyer (1942) there is no increase in calcium concentration in the urine in hyperparathyroidism, but only in the daily volume of calcium. One can imagine the concretions developing in two different ways, either round a nucleus of the calcium deposited in the urinary canals, or on a foundation of epithelial and subepithelial calcification. The concretions usually consist mainly of calcium phosphate, but they may contain varying amounts of calcium oxalate or this salt only. A secondary infection in the urinary tract, particularly one with urea-splitting bacteria, can of course affect the chemical composition of the concretions.

COEXISTENT CHANGES IN THE PARATHYROID AND THYROID GLANDS

An investigation of the interrelation between parathyroid and thyroid glands in hyperparathyroidism is of practical importance and of theoretical interest. The approach may be topographical, pathologico-anatomical and functional or pathogenetic.

To the surgeon the topographical relation of the thyroid gland to the parathyroids is of great importance, primarily because of the danger of parathyroid damage with tetany in an operation for goiter. But the position of the parathyroids in relation to the thyroid is also important in parathyroidectomy for hyperparathyroidism. It may happen that in some cases a parathyroid adenoma is so completely embedded in the thyroid gland that it escapes notice in a normal dissection of the neck. This may be due to the fact that the parathyroid lies in a deep fold of the thyroid capsule, or is completely surrounded by thyroid tissue; this is usually not discovered until a histological examination is made. According to Black & Haynes (1949) this is found in 2–3 per cent of cases.

In my series there were 2 cases in which a parathyroid adenoma was embedded in the left thyroid lobe, and was not discovered until this was examined histologically. In one of these cases a previous operation at another hospital failed to disclose the presence of a parathyroid adenoma. The result is that one must either, as Black (1949–1951) has done, split the thyroid gland at the point at which an included parathyroid adenoma is suspected, or rather, as I have suggested, do a sub-total thyroidectomy if no parathyroid adenoma is found when exploring the organs of the neck. In yet another of my cases, No. 2, parathyroid tissue was included in the thyroid gland. This was a case of diffuse hyperplasia in which two large parathyroid glands had been removed sur-
gically; autopsy 12 years later disclosed the presence of 2 more enlarged glands and parathyroid tissue the size of a pin's head, built up of wasserhelle cells, and included in the thyroid gland.

From a pathologico-anatomical point of view it is of interest that thyroid changes not infrequently accompany parathyroid enlargement, usually in the form of an adenoma but also as a nodular or diffuse goiter. In my series this type of change in the thyroid gland was found in 19 of the 44 cases operated on or examined at post-mortem. I have not been able to find any systematic investigation of the incidence of thyroid adenomas in different age groups which would allow me to draw any conclusions as to whether the incidence of thyroid adenomas in my series of hyperparathyroidism cases is higher than in a normal series. They are, however, of importance in practice, as in an operation they may be mistaken for enlarged parathyroids.

From a functional and pathogenic point of view the concomitant hyperfunction of the thyroid and parathyroid glands is of great interest. Two such cases were found in my series.

In the first case, which has been described in detail in a previous paper, the patient was a 48 year old woman who had been treated with radiotherapy in 1925 for hyperthyroidism. The basal metabolic rate was +60, she had exophthalmos, on the left side there was a palpable tumour which was taken to be a goiter, and generalized osteitis fibrosa with a giant cell tumour in the lower jaw. The first diagnosis was osteosarcoma with metastases. She also had bone and joint pain, headaches, polyuria, and polydipsia. An appreciable improvement in all the symptoms resulted from radiotherapy, and the basal metabolic rate fell to +14. In 1931 it was +31, the serum calcium was 14 mg. per cent, and on the left side of the neck there was a tumour the size of a walnut. The diagnosis of hyperparathyroidism was then made and an operation suggested, but the patient did not wish it to be performed. Her death was caused by uraemia 18 months later. Autopsy showed the tumour in the neck to be a parathyroid adenoma. In the anterior lobe of the hypophysis there was a small basophil adenoma; the adrenal glands were enlarged, with a combined weight of 18.8 grammes.

The second case (partly described on page 44) was a 41 year old man who had had typical symptoms of hyperthyroidism for 6 months. He had exophthalmos and goiter, the basal metabolic rate was +75, and the blood cholesterol 169 mg. per cent. At the same time there were clear signs of hyperparathyroidism. The blood calcium level was 16-14 mg. per cent, blood phosphorus 2.9 mg. per cent, urine calcium 70 ml./24 hours, specific gravity of the urine 1.007-1.013, non-protein nitrogen 30 mg. per cent, and the inulin clearance rate was 36-41 ml./min. Blood pressure was 180/95. There was slight decalcification of bone, and no calcification in the kidneys. During pre-operative iodine therapy the basal metabolic rate fell to +6, but the blood calcium remained at its high level. The urine calcium rose to 500 ml./24 hours and diuresis also showed a marked increase. Sub-total thyroidectomy was performed. No enlarged parathyroid glands were observed. The histological examination revealed colloid goiter with, here and there, forms approaching so-called proliferating goiter. Unfortunately, no systematic examination was made for possible parathyroid tissue included in the thyroid gland. After the operation all the signs of both hyperthyroidism and hyperparathyroidism disappeared. The basal metabolic rate returned to normal and the patient put on 20 kg. in weight.
The blood calcium level fell gradually to normal values, although it was still 13 mg. per cent 10 days after the operation. The urine concentration rose to 1.030 and the creatinine clearance rate to 140 ml./min. The calcium content of bone became normal. 8 months after the operation the blood pressure was 190/80, but 7 years after this it had risen to 250/160.

The basal metabolism in 23 cases is given in the diagram below:

![Diagam](image)

Fig. 1.

With the exception of the two cases mentioned above, the basal metabolic rate was in general well within normal limits. In 2 cases it was slightly raised, in 2 low, – no other signs of hyperthyroidism or hypothyroidism were present.

Cases are described in the literature in which parathyroidectomy led to a change in the basal metabolic rate. In Heimbecker's (1950) case the basal metabolic rate before the operation was —16, but 5 weeks after the removal of a parathyroid adenoma it had risen to +26.

I made the same observation in a number of my cases.

One of these was a case of primary hyperplasia in which two enlarged parathyroid glands were removed by operation and two more discovered at autopsy 12 years later. The figures for the basal metabolic rate, blood calcium, and blood phosphorus are given in the table below.

<table>
<thead>
<tr>
<th>Date</th>
<th>Basal metabolic rate</th>
<th>Blood calcium</th>
<th>Blood phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov. 1930 before 1st operation</td>
<td>+ 9</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>Mar. 1931 after 1st operation</td>
<td>+10</td>
<td>13.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Apr. 1931 after 2nd operation</td>
<td>—22</td>
<td>10.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Dec. 1931 after 2nd operation</td>
<td>+13</td>
<td>17.5</td>
<td></td>
</tr>
<tr>
<td>1934</td>
<td></td>
<td>13.6–11.6</td>
<td></td>
</tr>
<tr>
<td>1940</td>
<td></td>
<td>11.5</td>
<td>4.5</td>
</tr>
<tr>
<td>1941</td>
<td>+ 6</td>
<td>12.5</td>
<td>5.0</td>
</tr>
</tbody>
</table>
As can be seen in the table, the basal metabolic rate fell after the second parathyroidectomy from +10 to −22, and at the same time blood calcium values fell from 13.7 mg. per cent down to 10.5 mg. per cent. But the patient still had hyperparathyroidism; the blood calcium rose again and the basal metabolic rate increased to values above the normal.

The post-mortem findings were 2 enlarged parathyroid glands, a small thyroid gland with medium-sized follicles and flat epithelium, enlargement of the anterior lobe of the hypophysis with an increase in both eosinophil and basophil cells, and appreciable hypertrophy of the adrenal cortex.

In the literature, several cases of coexistent hyperparathyroidism and hyperthyroidism are described. Miller & Evans (1942) report a case of toxic goiter with a basal metabolic rate of +36, blood calcium 17.2 mg. per cent, and blood phosphorus 2.5 mg. per cent. When a parathyroid adenoma had been removed, all signs of both hyperthyroidism and hyperparathyroidism disappeared. The authors state that they found 5 similar cases in the literature. Stanley & Fazekas (1949) describe a case of concomitant thyreotoxicosis and hyperparathyroidism in which all the symptoms disappeared after treatment with propyl-thiouracil. They do not consider that true hyperparathyroidism was present, as the symptoms subsided so rapidly after anti-thyroid therapy, but believe that the thyreo-toxicosis brought about an increased mobilisation of calcium from the skeleton and that the kidneys had been incapable of excreting the calcium owing to a decrease in function.

There are other observations which may be of importance in discussing a possible pathogenetic connection between parathyroid and thyroid glands, namely the coexistence, mentioned earlier, of changes in both the parathyroid and thyroid glands. The combination of goiter and parathyroid adenoma is of particular interest. Ponteva (1939) describes this in a 14 year old girl. She had a very large goiter, the basal metabolic rate was −2, and the blood calcium 16.2 mg. per cent. After sub-total thyroidectomy the blood calcium level was normal and the basal metabolism rose to +12. No parathyroid tissue was found in the biopsy specimen. Aarseth & Björko (1949) had a 29 year old male patient with hyperparathyroidism, generalized osteitis fibrosa, goiter and exophthalmos, but without a raised basal metabolic rate. After thyroideectomy and extirpation of a parathyroid adenoma the blood calcium fell to 3.6 mg. per cent, and 73 days after the operation it was still as low as 4.7 mg. per cent. Ten months after the operation it had risen to 11 mg. per cent, and an appreciable recalification of the skeleton had taken place.

Several experimental investigations of the relationship between the thyroid and parathyroid glands have been made. Malcolm et al. (1949), giving albino rats thiouracil and similar preparations for long periods, 6–18 months, produced hyperplasia of the parathyroid glands and skeletal changes of the generalized osteitis fibrosa type. Histologically, chief cells were transformed
into oxyphil and wasserhelle cells. Engfeldt & Hjertqvist (1952) fed rats on thyroxin and found an increase in the excretion of urine and phosphorus. The blood phosphorus rose, blood calcium fell, and the parathyroid glands showed histological signs of hyper-function. They believe that thyroxin stimulates the parathyroids indirectly via changes in the chemistry of the blood, and that a direct stimulation of the parathyroid glands is not possible as it would presuppose a low blood phosphorus level. The same results were obtained after the administration of thyrotrophic hormones as with thyroxin. On the other hand, experiments with methyl-thiouracil gave no definite results.

What genetic connection is there between a coexistent hyper-function of the thyroid and the parathyroid glands? There is, of course, the possibility of coincidence, though in view of the large number of cases described this appears unlikely. The disappearance of both hyperthyroidism and hyperparathyroidism after thyroidectomy might then be explained by the removal of hyper-functioning parathyroid tissue at the operation, even though such tissue was not found at the operation or in the biopsy specimen. In the case treated with radio therapy, mentioned earlier, it is possible that the treatment had an inhibitory effect on the function of both the thyroid and parathyroid glands.

Whether hyper-function of the thyroid gland could in some way exert a stimulating effect on the parathyroid glands and lead to hyperparathyroidism is, however, open to discussion. It seems to be suggested by Stanley & Fazekas' case, in which thiouracil led to the disappearance of both hyperthyroidism and hyperparathyroidism. Moreover, animal experiments appear to suggest that the thyroid gland can stimulate the parathyroids, though this occurs indirectly via changes in the chemistry of the blood. In these experiments, however, no rise in the blood calcium level occurred, and the parathyroid changes should probably be viewed as expressions of a so-called secondary compensatory hyperparathyroidism. If, in man, concomitant hyperthyroidism and hyperparathyroidism were dependent on stimulation of the parathyroid glands by the thyroid via changes in the chemistry of blood, it would be necessary to assume that over-compensation occurred in this way, leading to true hyperparathyroidism with hypercalcaemia. A third possibility is that the parathyroids stimulate the thyroid gland. Parathyroidectomy, without any concomitant interference with the thyroid gland, has led to the disappearance of both hyperparathyroidism and hyperthyroidism, Miller & Evans.

Furthermore, as illustrated by my series, both the blood calcium and the basal metabolic rate may fall after parathyroidectomy. Here there is, of course, the possibility of some local influence resulting from the operation, particularly circulatory disturbances, which may decrease the function of the thyroid gland; in addition, one must be cautious in judging the values obtained in so uncertain a method as the determination of the basal metabolic rate.

Even though there are several possible explanations of concomitant func-
tional and pathologico-anatomical lesions in the parathyroid and thyroid glands, it seems to me not unlikely that the hypophysis, which controls the activity of the thyroid gland, may either directly or indirectly play some part in the changes in the parathyroid glands.

**PROGNOSIS AND TREATMENT**

With the exception of the rare cases of acute hyperparathyroidism with severe and usually fatal course, so-called acute parathyroid poisoning, hyperparathyroidism is as a rule a chronic disease. Its symptoms and course may, however, vary widely; on the one hand with progressive skeletal destruction of the type of generalized osteitis fibrosa it may lead to spontaneous fractures and a high degree of disability, and on the other hand to uncharacteristic symptoms in different organs, and the kidneys in particular, but a good general condition and undiminished working capacity for many years. The long-term prognosis is, however, as a rule poor because of progressive renal lesions and hypertension. Temporary remissions are not unusual, and spontaneous healing not impossible. This was thought to have occurred in one of my cases. The patient was a man with histologically confirmed generalized osteitis fibrosa. It is possible that renal calculi develop as a result of a hyperparathyroidism, that later disappear spontaneously. As will be seen in the following, even when hyperparathyroidism has been arrested by operation, the prognosis is frequently doubtful or poor and is greatly dependent on the state of the kidneys at the time of the operation. It is, therefore, of primary importance that the diagnosis be made as early as possible.

We have as yet no specific internal treatment, though it is conceivable that one may be discovered in the future. Irradiation of the parathyroid glands should, of course, help to decrease their function by analogy with the irradiation in hyperthyroidism. As reported in a previous paper, intensive irradiation was used in 4 cases in my series, but this did not arrest the course of the disease. As valuable time is lost by the use of this method, during which the renal lesions in particular may progress, it should not be employed in hyperparathyroidism.

The only cure at present for hyperparathyroidism is an operation radically removing the hyper-functioning parathyroid tissue. When the hyper-function is restricted to a single parathyroid adenoma the operation is usually easy, but when it results from diffuse hyperplasia the radical operation is more difficult, not to say impossible. In this operation it is extremely difficult to find all the parathyroid tissue and remove sufficient to arrest hyperparathyroidism without leading to parathyroid insufficiency and tetany. Happily, diffuse hyperplasia occurs, as mentioned earlier, in only some 10 per cent of cases, and even partial parathyroidectomy leads in these cases to a more or less marked degree of improvement, though hyperparathyroidism is not fully arrested.
In cases of single adenoma there may also be appreciable difficulty, owing to their varying position and appearance. The adenomas which are most difficult to find are, of course, those lying in the mediastinum, occurring in 5 to 10 per cent of cases. Owing to its embryonic derivation from the same branchial cleft as the thymus, the originally cephalic parathyroid gland may accompany the thymus down into the mediastinum. Another difficulty is that, as mentioned earlier, parathyroid tissue may lie wholly completely within the thyroid gland. Thyroid adenomas and lymph glands may also be confused with parathyroid adenomas, and these may be very small. In my series there are 4 cases in which an operation performed at another hospital failed to disclose an adenoma which was found later at Karolinska Sjukhuset. A previous operation greatly complicates a renewed search for the adenoma. An operation for hyperparathyroidism should, therefore, not be carried out unless there is every reason to believe that this condition is really present and the surgeon has detailed knowledge of the varying positions of the parathyroid glands. It is also desirable that biopsies should be performed in connection with the operation.

The immediate result of parathyroidectomy is usually a rapid fall in the blood calcium to subnormal levels, and more or less marked signs of parathyroid insufficiency may appear. Calcium administered per os or intravenously, AT 10, vitamin D, and parathyroid hormones are, as a rule effective in checking the parathyroid insufficiency until the remaining parathyroid tissue has had time to regenerate and increase its function. In severe instances of skeletal decalcification there is calcium-hunger in the bones which must be satisfied before the blood calcium level can return to normal. In one case of this type the blood calcium fell to 4.5 mg. per cent and severe symptoms of tetany appeared. It was not until 3 months later that the blood calcium level reached normal values, though it was still necessary to give the patient vitamin D and calcium. It has been suggested that a small portion of the adenoma should be implanted, for instance, in the sterno-mastoid muscle in cases in which a marked post-operative fall in blood calcium is expected; this should later be removed if hyperparathyroidism does not disappear completely. This method was used in one of the cases discussed in this paper.

The series includes a post-operative death. The patient was a woman who for many years had had renal calculi which led to nephrectomy before the diagnosis of hyperparathyroidism was made. Hypertension 230/150 and advanced renal damage were present. In the operation a parathyroid adenoma slightly larger than a walnut was removed. The blood calcium level fell from the highest point of 17.5 mg. per cent before the operation to the lowest level of 5.6 mg. per cent, the non-protein nitrogen rose and the patient died 12 days after the operation. Autopsy disclosed acute pancreatitis in addition to marked changes in the remaining kidney. Albright & Reifenstein (1948) offer the advice that in cases of renal damage with a tendency to retention of phosphate one
should remove less parathyroid tissue than one would otherwise. In view of
this, sub-total parathyroidectomy should perhaps have been performed in the
case described here.

With regard to late results, one should distinguish between cases of adenoma
and those with diffuse hyperplasia. In the 37 patients with adenoma, who are
still alive, the removal of the adenoma arrested hyperparathyroidism; this was
expressed by normal values for the blood calcium. The skeletal alterations
affected by the hyperparathyroidism have in all cases shown calcification and
more or less complete restitution radiologically and functionally. In cases with
calcification or concretions in the kidneys, no growth has taken place and no
recurrence followed operations for stones. The two most important symptoms
from the point of view of prognosis — the damaged renal function and hyper-
tonia — have been discussed in above. In early cases, before the renal damage
was manifest, some appreciable improvement generally appeared. In other
cases, however, the renal damage became permanent or progressed, and in 3
cases it led to death from uraemia. The same applies to hypertension. This
also frequently progresses, despite parathyroidectomy, leading to disability or
death from cerebral haemorrhage — as occurred in at least 2 cases in my series.
A long period of observation is necessary for the prognosis as, in spite of many
years of apparently good health, the patient may die of sequelae of hyperpar-
athyroidism. One of my patients was in excellent health for 13 years, only to
have both legs amputated as a result of arteriosclerosis; another patient lived
in seeming by good health for 10 years and then died of cerebral hemoorhage.
As more than 60 per cent of the cases were operated on in 1950 or later, it is
still too early to give any definite opinion as to prognosis.

In the 7 cases of primary hyperplasia the prognosis is more serious than in
those with a single adenoma, as it was not usually possible to arrest the hyper-
parathyroidism completely by parathyroidectomy; this has also been observed
elsewhere, e.g. at the Massachusetts General Hospital (Cope, 1943). In none of
the cases was there so immediate a return to normal blood calcium values as
after the removal of an adenoma. However, appreciable improvement has oc-
curred, even though the long-term prognosis has been poor. Two patients died
of uraemia, and two became severely disabled as a result of hypertension. One
case, not previously published, is of great interest.

The patient was a 50 year old man who since 1937 had had several operations for
renal calculi. In August 1952 hyperparathyroidism was diagnosed and an enlarged
parathyroid gland measuring 3 x 2 x 1 cm. extirpated. Histological examination
showed it to consist of wasserhelle cells. The blood calcium level fell but never reached
normal values. In January 1953 pyelolithotomy was performed because of acute indi-
cations. After the operation the patient’s temperature rose, cerebral symptoms developed
and he died within 4 weeks. Autopsy revealed a further two enlarged parathyroid
glands of the same histological appearance as that removed at operation. In addition,
a basophil adenoma the size of a walnut was found in the hypophysis.
There are, however, two cases in which the patients' general condition is surprisingly good despite a remaining hyperparathyroidism.

In one case the patient is a 63 year old woman with a long history of calculi. Nephrectomy was performed in 1928. An enlarged parathyroid gland was removed in 1939 and another in 1943, both of the primary hyperplasia type with only wasserhelle cells. The level of the blood calcium is still raised, though lower than before parathyroidectomy, there is marked isosthenuria, and calcification in the remaining kidney and pancreas. In spite of this the patient's general condition is fairly good and she is still working as a hospital nurse.

The other patient is a 47 year old man with bilateral renal calculi and hyperparathyroidism. In February 1952 two parathyroid glands of the primary hyperplasia type were extirpated. As the blood calcium remained at a high level explorative mediastinotomy was performed in May of the same year; this did not reveal the presence of any further parathyroid gland. The blood calcium is still at a slightly raised level, though lower than before parathyroidectomy, the blood phosphorus is low, and renal function decreased. The patient's general condition is, however, excellent, he feels well and has not had to interrupt his work as the supervisor of a post office.

PATHOGENESIS

Despite experimental investigations and clinical observations the problem of the true cause of hyperparathyroidism cannot yet be regarded as solved. In a previous paper I discussed the pathogenesis of hyperparathyroidism, now I only wish to mention factors which appear to support the different views.

It would appear that in every case in my series the patient had so-called primary hyperparathyroidism, not the secondary form which may occur in cases of renal damage associated with the retention of phosphate. The effect of extirpation of a single parathyroid adenoma, the definite return of the blood calcium to normal values and the more or less complete restitution of the symptoms resulting from hyperparathyroidism, strongly suggests that hyperfunction is in largely dependent on local autonomous factors in the parathyroid gland itself. Continuous stimulation from outside the parathyroids is not likely in these cases, although the possibility of some temporary stimulation having had some part in the development of the adenoma cannot be ruled out. In diffuse hyperplasia it seems most probable that some continuous stimulation is exerted from places outside the parathyroid gland. There are circumstances suggesting that this stimulation is effected via the hypophysis, but the existence of a hypophyseal parathyrotrophic hormone has not been established, nor is it known whether the stimulation takes place through changes in the calcium and phosphorus contents of the blood.
SUMMARY AND CONCLUSIONS

1. Nowadays hyperparathyroidism is diagnosed much more often than before, owing to the more widespread knowledge that this condition is common in patients with renal calculi. In the author’s series of cases of hyperparathyroidism cases more than 60 per cent had been diagnosed since 1950, while the remaining 40 per cent were distributed over the period 1930–1949. In 74 per cent of cases there was radiologically demonstrable calcification or true concretions. The great practical significance of this is illustrated by the fact that 29 operations for calculi were performed on 17 patients before hyperparathyroidism was diagnosed.

2. So-called giant cell tumours are often the symptoms of hyperparathyroidism which impel the patient to consult a physician. These were present in 8 of the author’s cases and had been treated locally before they were found to be accessory symptoms of a general skeletal disease.

3. An interesting, though not yet clarified, phenomenon is the high incidence of duodenal ulcer in patients with hyperparathyroidism; these ulcers were present in 7 cases in the author’s series.

4. In the diagnosis of hyperparathyroidism it is important to note that, under certain circumstances, the blood calcium level is not necessarily raised. Repeated determinations should be made. It is still too early to assess the diagnostic value of a fractional determination of the blood calcium, mainly owing to the uncertainty of the analysis methods.

5. The pathologico-anatomical basis of hyperparathyroidism is, in the majority of cases, an adenomatous transformation of only one parathyroid gland. In 14 per cent of the cases in the author’s series there was a primary hyperplasia of all the glands. A comparison of the pathologico-anatomical changes in the parathyroids and the clinical symptoms has been made and is considered to justify certain conclusions.

6. In almost every case of hyperparathyroidism renal damage is present, even if radiologically demonstrable renal changes are absent. The renal damage is probably primarily a tubular lesion, resulting mainly in a decrease in concentration capacity. In early cases the renal lesion may be of a more functional nature, disappearing after parathyroidectomy; in more advanced cases it becomes structural and regresses only partially after operation. In many cases the renal damage progresses even though the hyperparathyroidism process is arrested, leading finally to death from uraemia.

7. Hypertension is frequently present in hyperparathyroidism; in early cases it may be moderate and transitory, but severe and stationary in more advanced cases. Even though hyperparathyroidism has been arrested by operation, progressive hypertension may lead to death from haemorrhage.

8. Coexistent changes in the parathyroid and thyroid glands are common
and of practical importance and theoretical interest. In 2 of the author's cases a parathyroid adenoma was completely embedded in the thyroid gland. In 41 per cent of cases there were pathologico-anatomical changes in the thyroid gland, usually small adenomas, but also nodular or diffuse goiter. In 2 cases there was concomitant severe hyperparathyroidism and hyperthyroidism.

9. If hyperparathyroidism is not treated, the prognosis is doubtful. Spontaneous healing is possible. Radio-therapy only wastes valuable time. Primarily because of renal damage, hyperparathyroidism should be treated surgically as soon as the diagnosis is made. In cases of single adenoma the disturbed calcium metabolism as a rule returns rapidly and permanently to normal values, the patient usually becomes free of symptoms, but permanent renal damage and hypertonia in many cases result in the long-term prognosis being poor. In diffuse hyperplasia it is usually impossible to bring about complete regression of the hypercalcaemia, although there may be an appreciable improvement in the patient's general condition.

10. The pathogenesis of hyperparathyroidism is not yet established. It seems likely that the enlargement and hyper-function of the parathyroid glands is dependent on some temporary or continuous stimulation originating outside the glands. Possibly the hypophysis has some part in this, even if there is no parathyrotophic hormone and the stimulation may occur via changes in the calcium and phosphorus contents of the blood.

REFERENCES

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