Parathyroid adenomas associated with the malabsorption syndrome and chronic renal disease

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Synopsis The pathology of the parathyroid glands in two cases in which hyperparathyroidism was associated with chronic renal disease and 10 in which the association was with the malabsorption syndrome is described. It is concluded that whereas in chronic renal disease the development of an autonomous adenoma may be preceded by anatomical secondary diffuse hyperplasia such a stage is not proven when the adenomas develop against a background of the malabsorption syndrome. The importance of this latter association is stressed.

Primary hyperparathyroidism is a condition in which hyperplasia and benign or malignant neoplasia developing without known cause lead to hypercalcaemia and varied clinical manifestations, the most common being renal calculi and osteitis fibrosa. Clinical cure with the development of normal blood chemistry follows removal of the excess of parathyroid tissue unless irreversible changes have developed in the kidneys or other tissues.

Secondary hyperparathyroidism is the term generally restricted to those cases in which hyperplasia of all four parathyroid glands (albeit of uneven degree in the various glands) is associated with renal failure, osteomalacia, or rickets, and is thought to be a compensatory hyperplasia induced by hypocalcaemia. Whether other triggers can initiate this compensatory hyperplasia is at present unknown.

Tertiary hyperparathyroidism is a term used by Davies, Dent, and Watson (1968) to describe cases in which a presumed secondary hyperparathyroidism has evolved to the development of an autonomous adenoma in one gland with consequent hypercalcaemia and associated clinical changes which are reversed by the removal of the tumour. In the 12 cases they describe there was clinical evidence of a condition thought to be associated with secondary hyperparathyroidism, namely, renal disease in two, and the malabsorption syndrome, usually with osteomalacia, in ten. In several of these blood calcium arose from normal levels while under observation, but the clinching evidence of a marked hypocalcaemic period was seen in only one before operation.

In this paper the pathology of the parathyroids in these 12 cases is presented. The thesis is developed that in 11 there is no anatomi cal evidence for a secondary diffuse hyperplasia preceding the adenomas. The importance of the association of parathyroid adenomas with the malabsorption syndrome is stressed and the possible mode of their evolution is briefly discussed.

The main clinical details are presented in Table I. The case numbers are those in the University College Hospital series of operated hyperparathyroid patients. The changes in the parathyroids from operative specimens are summarized in Table II. It should be mentioned that it is the practice of Mr D. R. Davies to confirm the histological state of all four parathyroids at operation if possible, and to remove such tissue as is thought to be necessary to cure the patient; 10 of these cases had a single adenoma resected, one had two adenomas removed, and one had an adenoma and two hyperplastic glands removed. It is usually possible to decide from the tissue removed whether the non-adenomatous parathyroids are normal or hyperplastic, but if the amount of tissue provided is small it is only possible to.
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Table I Details of patients with tertiary hyperparathyroidism

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Name &amp; Sex</th>
<th>Year of Operation</th>
<th>Calcium (mg/100 ml)</th>
<th>Phosphatase (KA units)</th>
<th>Evidence of Bone Disease</th>
<th>Operative Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>E.S.</td>
<td>1951</td>
<td>14-5</td>
<td>2.5</td>
<td>None</td>
<td>Radiograph</td>
</tr>
<tr>
<td>11</td>
<td>L.D.</td>
<td>1955</td>
<td>11-4</td>
<td>2.0</td>
<td>Radiograph</td>
<td>Radiograph</td>
</tr>
<tr>
<td>57</td>
<td>M.B.</td>
<td>1960</td>
<td>10-0 (1024)</td>
<td>3-9</td>
<td>None</td>
<td>Radiograph</td>
</tr>
<tr>
<td>59</td>
<td>A.R.</td>
<td>1960</td>
<td>12-7</td>
<td>2.0</td>
<td>Radiograph</td>
<td>Radiograph</td>
</tr>
<tr>
<td>91</td>
<td>H.M.</td>
<td>1963</td>
<td>10-9 (1028)</td>
<td>2.2</td>
<td>None</td>
<td>Radiograph</td>
</tr>
<tr>
<td>107</td>
<td>A.G.</td>
<td>1964</td>
<td>9-6 (1028)</td>
<td>1.8</td>
<td>Radiograph</td>
<td>None</td>
</tr>
<tr>
<td>138</td>
<td>H.C.</td>
<td>1965</td>
<td>10-4 (1025-6)</td>
<td>2.8</td>
<td>Biopsy</td>
<td>Radiograph</td>
</tr>
<tr>
<td>144</td>
<td>A.T.</td>
<td>1965</td>
<td>11-5 (1025-6)</td>
<td>1.9</td>
<td>Biopsy</td>
<td>Radiograph</td>
</tr>
<tr>
<td>146</td>
<td>M.N.</td>
<td>1965</td>
<td>9-3 (1021)</td>
<td>2.0</td>
<td>Biopsy</td>
<td>Radiograph</td>
</tr>
<tr>
<td>147</td>
<td>G.J.</td>
<td>1966</td>
<td>9-6 (1025-6)</td>
<td>1.4</td>
<td>Biopsy</td>
<td>Radiograph</td>
</tr>
<tr>
<td>158</td>
<td>D.S.</td>
<td>1966</td>
<td>9-7 (1024)</td>
<td>2.5</td>
<td>Biopsy</td>
<td>Radiograph</td>
</tr>
<tr>
<td>185</td>
<td>V.G.</td>
<td>1967</td>
<td>11-3 (1024)</td>
<td>2.2</td>
<td>Biopsy</td>
<td>None</td>
</tr>
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</table>

Table II State of parathyroids at operation in present series

<table>
<thead>
<tr>
<th>Case No.</th>
<th>State of Parathyroids at Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>9-5 g adenoma</td>
</tr>
<tr>
<td>11</td>
<td>150 mg and 1 g adenomas, 2 normal</td>
</tr>
<tr>
<td>57</td>
<td>1-8 g adenoma, 1 normal, 2 doubtful</td>
</tr>
<tr>
<td>59</td>
<td>4-5 g adenoma, 3 normal</td>
</tr>
<tr>
<td>91</td>
<td>1-5 g adenoma, 3 normal</td>
</tr>
<tr>
<td>107</td>
<td>1-2 g adenoma, hyperplastic</td>
</tr>
<tr>
<td>138</td>
<td>800 mg adenoma, 2 normal</td>
</tr>
<tr>
<td>144</td>
<td>2-4 g adenoma, 2 normal</td>
</tr>
<tr>
<td>146</td>
<td>500 mg adenoma, 3 normal</td>
</tr>
<tr>
<td>147</td>
<td>3-1 g adenoma, 2 normal</td>
</tr>
<tr>
<td>158</td>
<td>2 g adenoma, 2 normal</td>
</tr>
<tr>
<td>185</td>
<td>1 g adenoma, 2 normal</td>
</tr>
</tbody>
</table>

Table II State of parathyroids at operation in present series

determine whether it is indeed of parathyroid origin. In such instances the biopsy is removed from a small parathyroid gland and the presumption is that it is normal rather than hyperplastic.

More detailed pathology is given for patients 11, 57, and 59 who died four, five, and seven years respectively after removal of the tumour, and for cases 91 and 107.

Case 11

This woman had two operations for hyperparathyroidism in 1955. At the first, an adenoma (150 mg) was removed and two normal parathyroids were biopsied. At the second, an adenoma (1 g) with a rim of narrow normal parathyroid tissue was removed. There was no evidence of recurrence of hyperparathyroidism after the second operation, but the patient died in 1960 with fairly widespread reticulum-celled sarcoma which involved the mesenteric glands conspicuously. Steatorrhoea had persisted during her period under observation and it is possible that there is a relationship between this condition and the development of reticulum-celled sarcoma involving the bowel. No parathyroid tissue was identified in the neck or elsewhere. (Details of the early history are recorded by Davies, Dent, and Willcox, 1956.)

Salient Point

The stimulus led to the formation of two adenomas without diffuse hyperplasia of the parathyroid tissue.

Case 57

This woman had been a patient at another hospital from 1936 onwards. Her many complaints included sinusitis on several occasions and an important episode in 1954 when she had an attack of renal disease diagnosed as B. coli pyelonephritis in which the blood urea level rose to 320 mg% but fell to 62 mg% on her discharge a month later. It was 88 mg% a year later during an admission in which the diagnosis was acute potassium depletion as a consequence of purgation. At this time electrolyte disturbance was profound and included temporary hypocalcaemia (Houghton and Pears, 1958). In 1956 she had bone pain, x-ray evidence of osteitis fibrosa, a serum calcium level of 10-2 mg/100 ml
and a blood urea level of 53 mg%. She was referred to Professor Dent and admitted to University College Hospital in March 1954 when she was 57 years old. Dent (1962) has documented the difficulty of deciding whether this patient's severe bone disease was a manifestation of secondary or primary hyperparathyroidism at that time because of the normal serum calcium level and the dramatic response of her symptoms to dihydrotachysterol without marked elevation of the serum calcium. However, symptoms eventually recurred and in 1960 the ionized calcium level was consistently raised even when she was off dihydrotachysterol.

In April 1960 a parathyroid adenoma (1.8 g) was removed which had a rim of normal gland at one edge. The other three parathyroids were identified, confirmed histologically, and being of normal size, were left in situ. One of the biopsies from these showed normal tissue, the acini being well separated by fat (Fig. 1); the other two showed compact glandular tissue with some fat between acini. It is with such biopsies that one is uncertain whether the tissue is normal or slightly hyperplastic. The adenoma was chief-celled, some areas had larger nuclei than others, and in a single section through the whole adenoma four mitoses were identified (Fig. 2).

In the first few years after operation the patient's condition was improved, but she gradually developed progressive renal failure and died in 1965, the blood urea level rising to 255 mg% in 1964 and 350 mg% in 1965. The blood pressure rose to 220/120 mm Hg in 1964, but dropped to normal levels a few months later before she died.

At necropsy the three residual parathyroid glands were conspicuous hyperplastic, the kidneys contracted (the left 90 g, the right 80 g) with fine surface granularity and a few larger scars, but no calyceal deformity. Microscopical examination of the kidneys showed extensive tubular damage, dilated and hypertrophied tubules, some glomeruli altered and atrophied by ischaemia, and others showing changes consistent with chronic glomerulo-nephritis. There was conspicuous hypertrophy of the intima of medium-sized arteries. On the whole, it was thought that the changes were more suggestive of chronic glomerulonephritis than of chronic pyelonephritis.

SALIENT POINTS

The renal pathology in this case is difficult to unravel, but the salient points as regards function were the transient episode of uraemia in 1954 and the gradual development of uraemia between 1960 and 1965. The parathyroid adenoma removed in 1960 was unusual in that mitotic activity was present. The bulk of the evidence indicates that the remaining parathyroids were not hyperplastic at this time (one normal, two

Fig. 1 Case 57: biopsy of normal parathyroid. Haematoxylin and eosin × 92.

Fig. 2 Case 57: mitosis in anaphase in chief-celled parathyroid adenoma. Haematoxylin and eosin × 560.
with fat in compact tissue from glands of normal size, and normal gland at the periphery of the adenoma) but became hyperplastic during the development of uraemia between 1960 and 1965.

**Case 59**

This man was first admitted to University College Hospital in 1953 at the age of 41 with anaemia. This was thought to be partly due to deficiency of ascorbic acid in his diet and he responded to therapy. A few years later he began to suffer from bone pain and to lose height. This was followed by muscular weakness and more severe bone pain which led to extensive investigation when raised plasma calcium, lowered plasma phosphorus, and raised plasma alkaline phosphatase levels, and a skeletal radiograph showing typical changes of hyperparathyroidism led to an exploration of the neck. A parathyroid adenoma weighing 4.5 g was removed and three normal parathyroids were identified and confirmed by biopsy. At this time there was a question of changes of osteomalacia being present in the bones as well as osteitis fibrosa. Furthermore, the blood urea level was slightly raised. During the following years the bone symptoms improved considerably, but the patient continued to have some degree of steatorrhoea although a fat balance study gave an equivocal result and an intestinal biopsy in 1966 was normal. He gradually became increasingly uraemic and died with a blood urea level of 350 mg% in 1967 at the age of 55. Postmortem examination was limited and it was not possible to dissect the neck properly, but no residual parathyroid tissue was identified. Both kidneys showed extensive polycystic disease as well as the effects of calcium deposition in the remaining parenchyma. The lumbar vertebrae showed areas of cystic change in the centres and more dense bone adjacent to the intervertebral discs. Microscopic examination showed extensive nephrocalcinosis with gross tubular atrophy in the residual renal parenchyma as well as some glomerular lesions. Some degree of osteomalacia was present in the lumbar vertebrae, but no residual osteitis fibrosa.

**SALIENT POINTS**

At the time of removal of the adenoma the impairment of renal function was slight and there was no evidence of hyperplasia of the other parathyroids. It is probable that some degree of malabsorption of an uncertain nature was present in this patient and that the osteomalacia was a consequence.

**Case 91**

This woman was treated for the Plummer-Vinson syndrome and associated anaemia at University College Hospital from 1952 onwards. At that time there was evidence of steatorrhoea which became more convincing, although intermittent, in subsequent years. In 1961 she was found to have a daily fat excretion of 14.4 g; duodenal mucosa showed severe villous atrophy, and the plasma calcium level was 10.9 mg/100 ml. She improved on a gluten-free diet, but the plasma calcium level slowly rose to 12.6 mg/100 ml in June 1963. The bones were thought to show changes of osteoporosis with collapse of L3. In August 1963 she was diagnosed as having hyperparathyroidism with calculi in the right kidney, and at operation a chief-celled parathyroid adenoma weighing 1.5 g was removed and biopsies of three normal parathyroids were taken (Fig. 3). A mitosis was identified in the section of the adenoma which showed a distinct margin of normal parathyroid at the border (Figs 4 and 5). After the operation she had a transient period of hypocalcaemia from which she recovered and has since been reasonably well on a gluten-free diet. There has
been no evidence of recurrence of hyperparathyroidism.

**SALIENT POINTS**
This is a case with very good biopsies of three normal parathyroid glands, a rim of normal parathyroid around an active adenoma, and a short period of hypercalcaemia.

**Case 107**

This patient has been reported in detail by Glanville and Bloom (1965).

At the age of 31 this man developed osteomalacia which was shown to be a case of type II renal tubular osteomalacia, in which renal glycosuria is associated with phosphaturia. He became symptom-free after treatment with dihydrotachysterol for about five years when he developed pains in the lower limbs which followed a reduction in the dose of dihydrotachysterol because of hypercalcaemia. Investigation showed a recurrence of osteomalacia with a persistently raised alkaline phosphatase level and Looser zones on the radiographs. All the evidence indicated that the hypercalcaemia which persisted after stopping dihydrotachysterol was a manifestation of hyperparathyroidism. On exploration of the neck a chief-celled adenoma weighing 1.2 g (Figs. 6 and 7) and two hyperplastic glands were identified (Fig. 8); the adenoma was removed together with one gland and two-thirds of the other. No normal parathyroid was identified around the adenoma but some was present at the edge of one of the hyperplastic glands. The fourth parathyroid was not identified. There was symptomatic improvement, with reduction of the blood calcium levels which has persisted.

**SALIENT POINTS**
This is the only case in the series in which there is pathological evidence compatible with an adenoma arising against a background of hyperplastic parathyroid glands. Probably the stimulus to parathyroid hyperplasia had been persistent and relatively steady for many years. The nature of the stimulus in this case has not been defined clearly. It was not due to hypocalcaemia during the time of observation.

**Discussion**
The most important fact about these patients is that they develop parathyroid adenomas. The mechanism of this process is interesting, both from the clinical and the general angle.
The possible mechanisms appear to be several.

The metabolic situation in each case was such as to cause secondary parathyroid hyperplasia, and one of the hyperplastic glands became autonomous forming an adenoma. This reversed the biochemical trend with cessation of the stimulus to secondary hyperplasia and involution of the remaining parathyroid tissue. (This was the hypothesis of Davies et al., 1968.)

The metabolic situation in each case triggered a group of more sensitive cells in one gland causing a neoplasm which was at first conditioned but later became autonomous, without any intervening stage of diffuse secondary hyperplasia.

Sometimes the first mechanism operates and in other cases the second. In deciding between them, it is necessary to consider (a) the response of the parathyroid tissue where it was possible to follow this for some time; (b) the incidence of parathyroid hyperplasia in this series at the time of operation; and (c) the response of other endocrine tissues after reversal of a metabolic situation, eg, the effect of the iodine level of the blood on the thyroid.

Case 57 is the only one which enables us to answer question (a). The evidence as summarized at the end of the case history indicates that secondary hyperplasia was not present at the time of the operation but developed during the period of uraemia between 1960 and 1965. Before 1960 there was no prolonged period of uraemia, but the transient episode in 1954 may have been the initiating factor in the development of the adenoma removed in 1960. The onset of steadily progressive uraemia then led to secondary hyperplasia of the remaining three parathyroids. This suggests that a more sensitive group of parathyroid cells responded to an initial stimulus and the whole mass of parathyroid tissue to a later prolonged stimulus.

In answering question (b) it is convenient to refer to Table II which indicates that hyperplasia was not associated with any of these adenomas at operation except in case 107, in which the background of type II renal osteomalacia is associated with phosphaturia and not at any time with a low blood calcium level. The abnormal metabolism here in some way provided a steady stimulation to the parathyroid tissue over many years. This resulted in hyperplasia of most of the parathyroid tissue. (I may mention here that in diffuse hyperplasia the process sometimes leaves a little parathyroid tissue unaffected, as in this case.) With time the hyperplastic tissue in one parathyroid formed an adenoma. This did not lead to involution of the other parathyroids. Thus in this case the evidence is in favour of the first mechanism postulated but without subsequent involution of non-adenomatous parathyroid tissue. There are a few other cases recorded in the literature in which autonomous adenomas develop from a background of longstanding chronic uraemia and have shown diffuse hyperplasia in the rest of the parathyroid tissue (Massachusetts General Hospital Case Records, 1963; Golden, Canary, and Kerwin, 1965).

In the remaining cases in Table II there is no evidence that anatomical hyperplasia was associated with an adenoma at the time of operation. Of these case 57 had a renal background as discussed above, but no period of prolonged chronic uraemia before the operation in 1960. In case 59 the evidence suggests that the background was malabsorption before the operation.

In the remaining nine cases the background was undoubtedly malabsorption of some form with osteomalacia present in eight. It seems very unlikely to me that involution to normal would have occurred in all the non-adenomatous parathyroids in these cases if anatomical hyperplasia had indeed been present. It seems equally unlikely that a rim of normal parathyroid would be formed by involution around an adenoma as is clearly illustrated in Figure 5. It is also pertinent that although many argue that secondary hyperparathyroidism develops in osteomalacia...
associated with the malabsorption syndrome the anatomical evidence for secondary parathyroid hyperplasia is scanty. As Dent (1956) pointed out, the papers which describe secondary parathyroid hyperplasia in rickets and osteomalacia date back to the early years of this century before the classical descriptions of metabolic bone disease. I have never encountered secondary hyperplasia in necropsies on cases of the malabsorption syndrome and am unaware of any series describing it.

In considering (c)—other endocrine hyperplasias—the best documented is that of the thyroid. Here reversal of a metabolic situation may lead to involution of a hyperplastic tissue but the result is often a gland with areas of fibrosis, cholesterolosis, and residual nodules of hyperplastic tissue rather than a normal anatomical structure. In the adrenal cortex hypersecretion of hormones may be associated with diffuse hyperplasia, nodular hyperplasia, adenoma, and carcinoma. Thus, in an analysis of the adrenal cortex in 81 patients with Cushing's syndrome, Neville and Symington (1967) found bilateral hyperplasia in 69, adenomas in five, and carcinomas in seven cases. In association with the latter, tumours there was cortical atrophy of the non-neoplastic adrenal tissue. It is often assumed that this atrophy develops as a result of the tumour secretion but this is not proved. In any event there is no evidence that such adrenal neoplasms develop from hyperplastic glands. I cannot therefore support the first mechanism postulated by analogy from other endocrine tissues.

It is therefore suggested that in the abnormal metabolic situation of the malabsorption syndrome the second mechanism operates so that parathyroid adenomas arise from groups of cells more sensitive to stimulation, which become small areas of hyperplasia within an otherwise normal gland, then nodules, which could be regarded as conditioned neoplasms in that a feedback mechanism may still be operative, and then autonomous neoplasms. At this point the cells are altered so that they divide without a persistent stimulus and hypercalcaemia results. It is interesting that in the adenoma removed in case 91 a few mitoses were present. This is indicative of active, and probably relatively rapid growth (we have seen mitoses in only four of about 250 parathyroid adenomas and suggests an unusually effective stimulus, or an unusual group of responsive cells (case 57 also had mitoses). Whether the initial stimulus is a temporary hypocalcaemia or something unknown cannot be decided at present. The suggestions of Lloyd (1968) on parathyroid adenomas in relation to intermittent and constant stimuli are of interest.

The possibility that different mechanisms operate in the pathogenesis of parathyroid adenomas associated with the malabsorption syndrome and those initiated by prolonged chronic

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**Fig. 7** Case 107: chief-celled adenoma. Haematoxylin and eosin × 560.

**Fig. 8** Case 107: hyperplastic parathyroid. Haematoxylin and eosin × 140.
renal disease should open up the search for other factors in parathyroid metabolism. Keynes and Caird (1970) have suggested that in cases associated with steatorrhoea and osteomalacia the hyperparathyroidism is primary but masked initially by vitamin D deficiency. This view can be criticized because it gives no explanation for the association of hyperparathyroidism with the malabsorption syndrome. The use of the word 'primary' tends to dismiss the association; the words 'secondary' and 'tertiary' endevavour to fit the association into known concepts. It would appear wise to keep an open mind at present, and even to look for other factors than variation in the plasma calcium and phosphorus levels in parathyroid metabolism.

**References**


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