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PARATHYROID TUMOUR WITH VISCERAL METASTASES

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(PLATES XII-XVIII)

MANY examples of "tumours" of the parathyroid glands have been described but there are very few in which there is exact evidence of the kind of proliferation and the nature of the tissue. The distinction between some hyperplasias and benign tumours is admittedly difficult and the assumption that a particular form of tissue growth is a neoplasm is made all too easily. Similarly malignancy cannot always be determined either readily or accurately from histological appearances alone. Two criteria are necessary for the diagnosis of malignant change in these glands; (*a*) clinical and biochemical evidence that the cells are behaving as parathyroid tissue and (*b*) evidence that the tumour has recurred locally, with invasion of the surrounding tissue, or has produced indisputable secondary growths by metastasis.

A considerable number of tumours presumed to be parathyroid in origin were described by Guy in 1929. The diagnosis was based on morphology only. Though they may indeed have arisen in parathyroid tissue, proof of their exact nature or origin was absent. Thyroid, parathyroid and thymic tissues are often closely intermingled, and any of these could give rise to growths in the neck, while the similarity of various epithelial cells in different stages of activity makes deduction solely from morphology, particularly if this be atypical, most hazardous. Any anaplastic tumour may fail to show demonstrable functional activity of hormonal type and in such cases a specific origin cannot be asserted. Thus in the absence of biochemical or clinical confirmation of the true character of the growth, a parathyroid origin and nature may be discounted and even repudiated.

A mass of tissue may be the result of various processes and, especially in places where non-neoplastic proliferation is of rapid development, may reach such a size that its distinction from a true neoplasm is of great importance. Non-neoplastic proliferation of this kind is seen particularly in the ductless glands, and is well shown in the hyperplasias associated with hyperactivity of the thyroid gland.

Similar proliferation occurs, however, in other glands. That a nodule is encapsulated does not make it a neoplasm.

Non-neoplastic proliferative conditions may "recur" after removal of the main mass and implantation of non-malignant tissue may be followed by its growth—as a graft—without there being any question of neoplasia. In these circumstances reappearance of tissue is only too likely to be assumed to be neoplastic and it is important that a clear distinction should be made. Various types of cellular proliferation merge into one another and all gradations may be found between hyperplasia and true neoplasia. The absence of any sharp dividing line between what, in their fully developed form, are quite different phenomena is a fundamental and important proposition. It is necessary, nevertheless, to distinguish between the fully developed types. In the literature it is clear that the distinction has not always been made and it has often been assumed that all or most proliferations of tissue which show any persistence are to be regarded as neoplasms. It is possible that the idea of the neoplastic nature of many examples of hyperplasia was engendered and supported by the rarity of indubitable examples of neoplastic conditions. The position is partially clarified by the observation of a well-defined example of true parathyroid malignancy.

REPORT OF CASE

Clinical history

D. C., a female, then aged 37 years, sustained a fall in Jan. 1943 which was not in itself serious but was followed by such discomfort in the knees as to make walking difficult. In Dec. 1943 she had another fall, followed by more severe pain and greater disability. In March 1944 she was found to have a "tumour" in the upper part of the right femur and spontaneous fracture occurred at this site. X-ray examination showed general rarefaction of the bone and a localised area of apparently complete disappearance of the shaft.

Biochemical investigations then showed the serum calcium to be 18.0 mg. per 100 c.c., the serum phosphorus 4.3 mg. per 100 c.c. and the alkaline phosphatase 22 units. Blood urea was 87 mg. per 100 c.c. Bence Jones protein was present in the urine. The total calcium excreted in the urine in 24 hours was 70.5 mg.

X-ray examination of all the bones now showed gross rarefaction (figs. 1 and 2) and there were shadows in the renal areas indicating metastatic calcification.

In August 1944 exploration of the neck was undertaken and a large nodule in the region of the lower left parathyroid gland was excised.

Pathological examination of biopsy specimen. The excised nodule was ovoid in form and measured $4 \times 3 \times 3$ cm. It had a well-defined fibrous capsule, was slightly lobulated and of soft consistency. On section it was composed of soft yellowish-brown tissue with some areas of more solid consistence and paler colour. There were some small areas of haemorrhage (fig. 3).

Microscopically, the tissue was composed of polyhedral cells arranged in masses and cords with some irregular alveoli. The cells varied considerably, the protoplasm of most being clear, but some had a granular oxyphil character. The nuclei were ovoid and vesicular (fig. 4). There was some irregularity in size and shape of both cells and nuclei, most obvious in the areas where the form

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FIG. 1.—X-ray photograph of skull showing rarefaction with miliary stippling.

of the cell masses or groups was most irregular. Here the cell groups were separated by strands of fibrous tissue of variable thickness. Vessels were numerous and in places there were blood-containing spaces lined by tumour cells and having occasional epithelial cells in their interior. These spaces were interpreted as sinusoidal rather than the result of operative manipulation. The tissue was readily recognisable as parathyroid and was no more irregular in form than many of the benign parathyroid "tumours" which we have examined.

Biochemical examinations were now repeated, with the following results :—

Date	Serum calcium	Serum phosphorus	Alkaline phosphatase
1 week after operation .	9.8 mg./100 c.c.	3.6 mg./100 c.e.	63 units
3 weeks after operation .	7.2 , , ,	2.3 , , ,	47 , , ,

Convalescence was slow but satisfactory and after a time she failed to attend for observation. She remained well until December 1946 when she began to lose weight. She did not seek treatment and her condition deteriorated progressively so that by February 1948 she had lost 3 stones in weight, now weighing only 5 st. 8½ lb. There had been some dry retching in the mornings. From July 1947 onwards there had been aching in the bones, particularly of the limbs.

This history was obtained and the condition discovered during a "follow-up". Biochemical investigation showed :—

Date	Serum calcium	Serum phosphorus	Alkaline phosphatase
26.2.48	19.3 mg./100 c.c.	2.3 mg./100 c.c.	78 units
19.5.48	19.7 , , ,	2.5 , , ,	76 , , ,

X-ray examination in February showed gross rarefaction of all bones. The area of "cyst" formation in the upper part of the right femur, through which fracture had occurred in 1944, had now become filled with bony though rarefied material. The skull showed a fine spotty rarefaction similar to that present in 1944. X-ray examination of the thorax revealed some large and several small nodules in the lung fields (fig. 5).

At this time clinical examination showed general wasting, but apart from bowing of the right femur at the site of the old fracture no significant abnormality was found. There was no bowing of other bones and no evidence of any abnormality in the neck.

Her condition deteriorated rapidly after this and she appeared to shrink in size, particularly as regards the chest. This was clearly shown in subsequent X-ray photographs (fig. 6). A course of deep X-ray therapy had no appreciable effect on the progress of the condition. She died on 31st October 1948.

Post-mortem examination

This was carried out on 1.11.48. The body was emaciated, weighing 65 lb. There was deformity of the thoracic cage, which was collapsed, conforming with but greater in degree than the condition shown on previous X-ray examination, and the chest wall could be moulded

like a soft elastic tissue. There was a malunited fracture of the upper part of the shaft of the right femur (*vide supra*) and recent fractures of the right humerus (supracondylar) and left femur (mid-shaft). The mandible was shrunken and soft. The bones of the limbs were not bent.

In the skin of the neck there was an old healed operation scar of "collar" type. The thyroid gland was normal. Posterior to each upper pole, loosely attached to but not embedded in the gland, was a small ovoid nodule of yellow tissue. That on the right side measured $5 \times 3 \times 2$ mm., that on the left $3 \times 2 \times 2$ mm. Similar nodules measuring $4 \times 3 \times 2$ mm. were present just posterior to the lower poles, that on the left side being well encapsulated and apparently normal. No other tissue resembling parathyroid tissue was found in the neck or mediastinum. The lymph nodes were not enlarged.

The pleural sacs contained no fluid and no adhesions were present. The lungs were small, being partially collapsed. There was no consolidation. Two subpleural rounded nodules about 2 cm. in diameter were visible in the right upper lobe and another, slightly larger, in the apical region of the lower lobe. A nodule just over 2 cm. in diameter was palpable in the left upper lobe and two smaller nodules, 6 mm. in diameter, in the lower lobe. The lungs were fixed by instilling 10 per cent. formalin solution into the trachea and were cut some days later. The presence of nodules of growth was confirmed. They were composed of firm pale homogeneous tissue (fig. 7). No other abnormalities were found. The tracheo-bronchial lymph nodes were not enlarged.

The heart and pericardium were normal and the vascular system generally showed no abnormality.

The kidneys were normal in size and weight but the surface was grooved irregularly. The capsules were adherent, especially in the grooves. The cortex was slightly reduced in width and the pyramids showed linear streaking with yellow calcareous material. One papilla in the lower part of the right kidney was eroded and the corresponding calix contained an ovoid concretion. The suprarenal and pituitary glands showed no significant abnormality. All other viscera were normal.

The bones were all decalcified to such a degree that they could be cut easily with a knife. The process was diffuse and no area of cyst formation was found. In addition to deformities of the ribs there was partial collapse of the thoracic vertebræ and some encroachment of the acetabular region upon the cavity of the pelvis on the right side. The shafts of the long bones contained pink friable tissue.

Histological examination

The nodules in the lungs were composed of masses of polyhedral cells showing some acinar arrangement (figs. 8-10). Thin-walled

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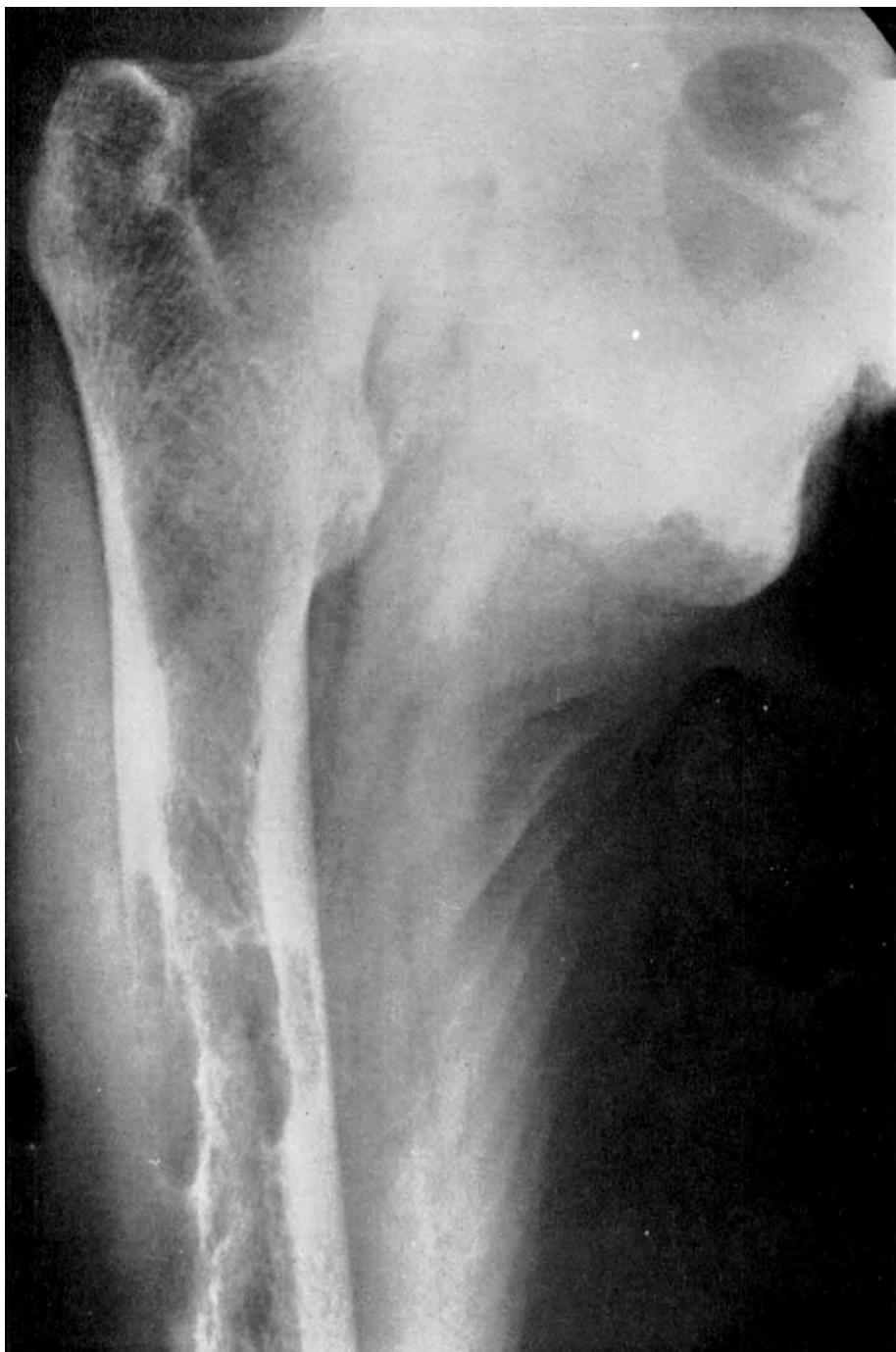


FIG. 2.—X-ray photograph of right femur in March 1944, showing the rarefaction and localised “fibrocystic” changes which led to further investigation and treatment. After a period of improvement similar changes reappeared. The degree of rarefaction can be gauged by comparing the density of the bone cortex with that of the muscle shadows.

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FIG. 3.—Photograph of the primary tumour from the left lower parathyroid region. $\times 1\cdot5$.

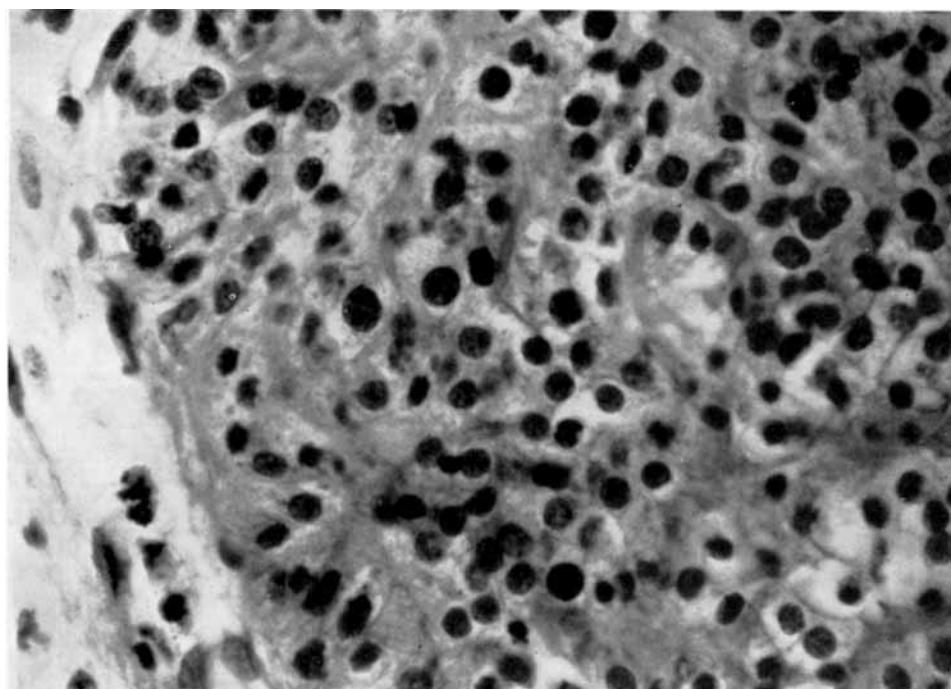


FIG. 4.—Histological structure of the tumour. Note variation in nuclear size. $\times 480$.

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FIG. 6.—X-ray photograph of chest in July 1948, showing intense rarefaction of the bones of the thoracic cage and shoulder girdle, with deformity of ribs. There is little change in the lung nodules.

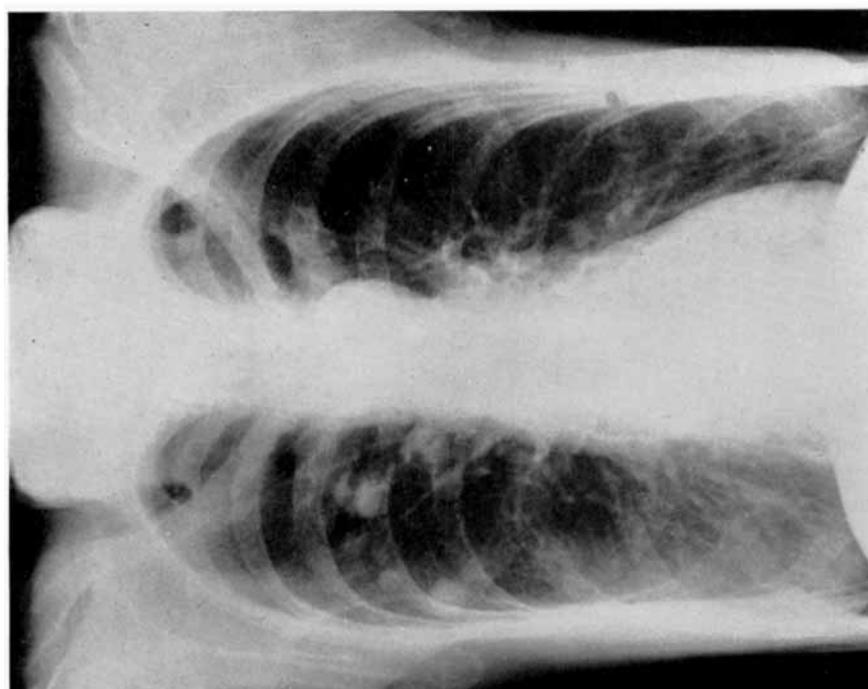


FIG. 5.—X-ray photograph of chest in March 1948, showing general rarefaction of bones and several well-defined rounded shadows in the upper half of the right lung.

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FIG. 7.—Cross section of lungs, showing spherical secondary deposits sharply delimited from the parenchyma.

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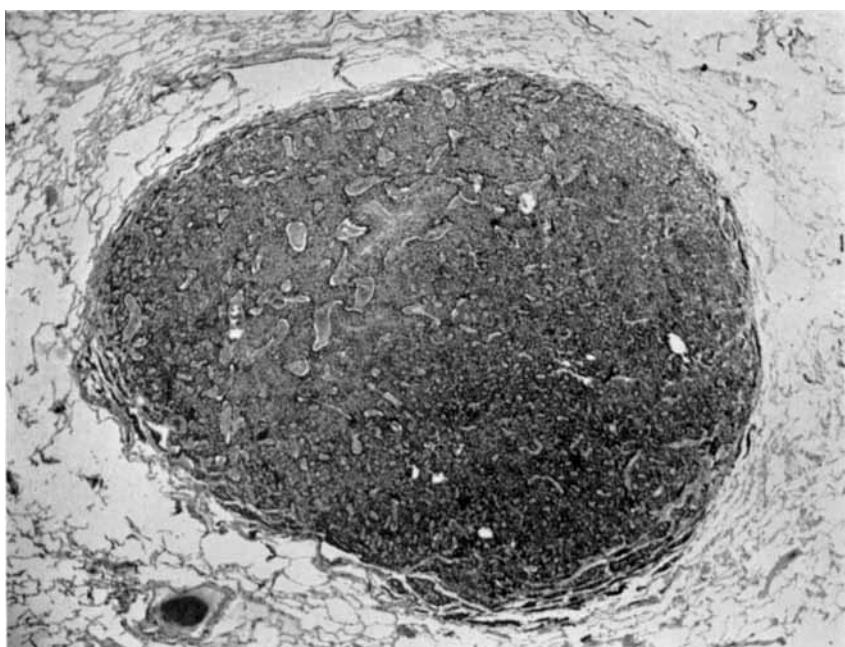


FIG. 8.—Low-power photomicrograph of a small secondary nodule in the lung. $\times 18$.

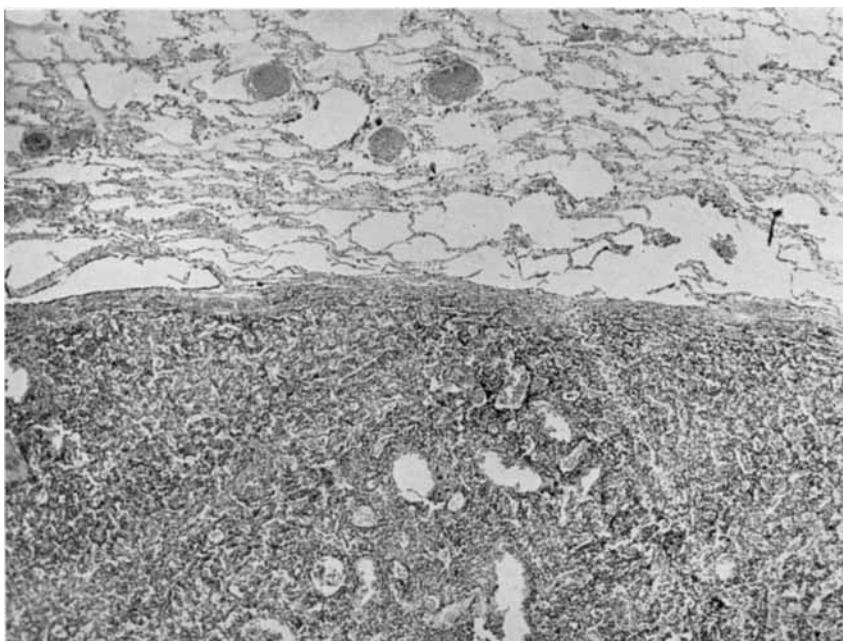


FIG. 9.—Photomicrograph of margin of larger nodule, showing the general structure of the tumour tissue and its sharp demarcation from lung tissue. $\times 30$.

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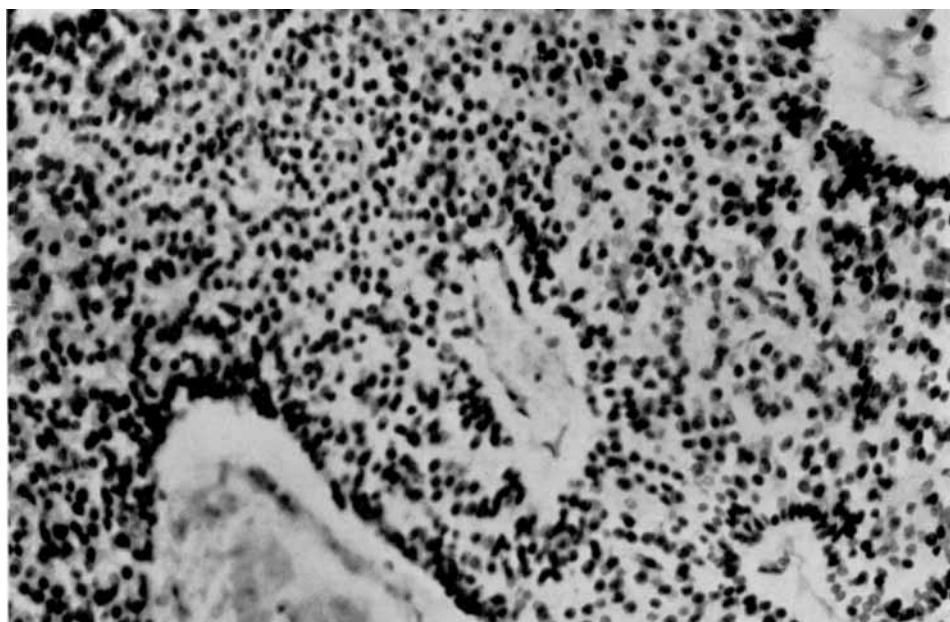


FIG. 10.—Higher-power photomicrograph of a lung nodule showing polyhedral-cell structure. $\times 180$.

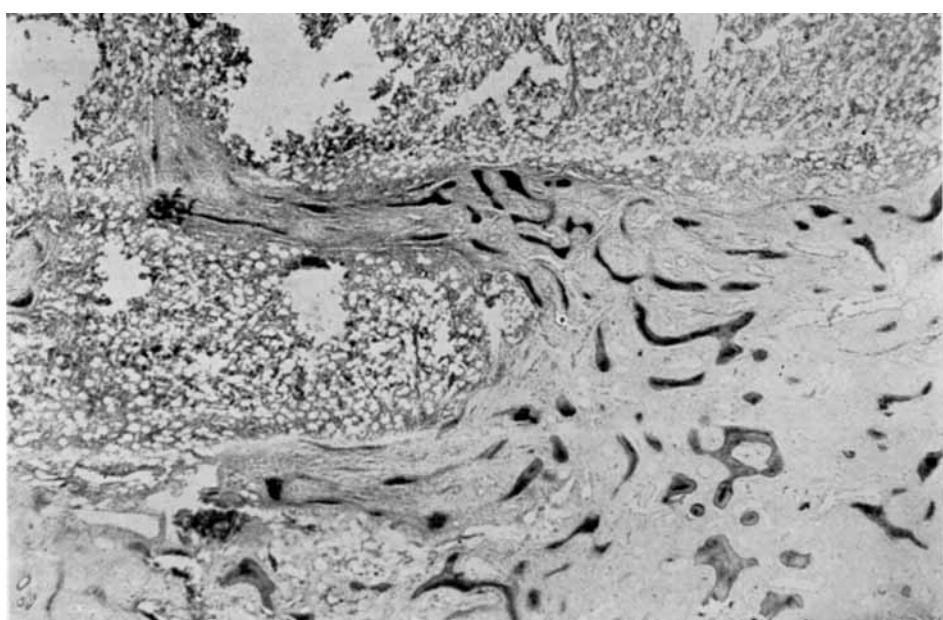


FIG. 11.—Photomicrograph of a section from the right femur showing gross de-calcification of the bony trabeculae so that a vascular osteoid tissue constitutes most of the cortex. The bone marrow is hyperplastic. $\times 18$.

vessels of sinusoidal type were present amongst them. The cells varied somewhat in size and some had clear, others granular oxyphil protoplasm. Some nuclear variation was present also but was within the limits of variation observed in parathyroid "adenomata."

The two lower and the upper right parathyroid glands were well encapsulated and, apart from their rather large size, presented a normal appearance. The upper left nodule showed many foreign-body giant cells in relationship to a small piece of silk.

Tissue obtained from the bones could be cut by the microtome without decalcification. The trabeculae were small and in only a few places were there indications of calcium salts (fig. 11). Between these there was a loose fibro-cellular tissue.

DISCUSSION

Several features of this case are of special interest. The serum-calcium level—over 19 mg./100 c.c.—was extremely high and, on the assumption that the calcium was in the usual proportion of ionised and non-ionised forms, closely approached the upper limit of the recorded range for human beings. Repeated observations were made and the level remained high during the last few months of life. The serum phosphorus was low, even though renal function, as indicated by a raised blood-urea level, was poor. The serum alkaline phosphatase level, as would be expected from the gross bone disturbance, was greatly raised.

There was much less change in the kidneys than might have been expected from the degree of disturbance of the serum calcium level. Much more calcification and calculus formation has been found in some cases where there was much less skeletal change and a lower level of serum calcium.

Decalcification of the bones was such that almost all calcium had been resorbed. In view of the extreme deformity of the ribs and spine it is astonishing that there was no bending of the limb bones. The patient was bed-ridden towards the end of her life but had been ambulatory at a time when, from radiological examination, it was apparent that resorption of gross degree had occurred. Microscopic examination showed that there was still a trabecular, though decalcified, matrix. It is clear that in the tubular structures this relatively soft tissue was able to maintain the form of the bones. Since bending of bones has been regarded as a characteristic of osteitis fibrosa it would seem that the bending occurs either because, in many cases, the process is slower and any mechanical stresses are exerted for a longer period than in this case or, as seems more likely, because there is some additional factor, possibly nutritional or hormonal, causing a change in the connective tissue matrix in addition to the calcium resorption. This has been discussed by Albright and Reifenstein (1948).

The secondary tumours in the lungs showed a remarkably "normal" appearance. This accorded well with their great functional activity as evidenced by the profound general metabolic changes to which they had given rise.

An enlarged parathyroid gland was found at each of the four usual sites. None of these showed any evidence of neoplastic development and their capsules were well defined. Even the small nodule found in the region from which the original tumour had been removed appeared to be in every way an ordinary, though slightly enlarged, parathyroid gland. Indeed it was only the development of metastatic tumours which established the true nature of the original growth. Like some tumours of other tissues, e.g. thyroid, it clearly demonstrates that perfection of structure is not always incompatible with malignancy.

The cases described in the literature (table) fall into three groups:—
 1. Truly malignant tumours. If we accept the criteria of progressive invasion of tissue or clearly defined metastasis there have been only three examples of indubitable parathyroid malignancy (to which might be added a fourth, Gutman's case, mentioned by Albright and Reifenstein). 2. Conditions regarded as malignant neoplasms in which the criteria of malignancy have not been sufficiently rigid. 3. Tumours in which the evidence of the parathyroid nature of the growths is insufficient.

TABLE

Published cases of true and alleged parathyroid malignancy

Nature of condition	Number of cases	Authors
Tumour with visceral metastasis . . .	1	Meyer <i>et al.</i> (1939); Meyer and Ragins (1943)
Tumour with lymph node metastasis . .	2	Gentile <i>et al.</i> (1941) Black (1948)
Tumour with "carcinomatous" recurrence (statement incomplete)	1	Gutman (quoted by Albright and Reifenstein, 1948)
"Tumour" with "recurrence" after removal	2	Quick and Hunsberger (1931) Sainton and Millot (1933)
"Tumour" with "recurrence" after implantation	1	Burk (1947)
"Tumour" with histological diagnosis only	Several	Petersma (1937) Alexander <i>et al.</i> (1944)
Tumours in which nature of tissue not proven	Numerous	Guy (lit. 1929) Hall and Chaffin (1940)

In the present instance, despite the well differentiated character of the tissue, there had been the passage of tumour cells into the blood vessels, embolism of the lung capillaries and growth of the tumour cells in their new site—a combination of features which surely

constitutes malignancy. It is deduced from this case that, so far as parathyroid "tumours" are concerned, an opinion regarding malignancy cannot be reached from present-day histological criteria alone. Consideration must be given also to the general behaviour of the growths. Only the occurrence of blood- or lymph-borne metastasis can be regarded as conclusive.

SUMMARY

A case of hyperparathyroidism associated with a malignant tumour of the left lower parathyroid gland in a woman of 41 is described. After removal of this tumour the patient's bone condition recovered and biochemical studies showed a return to normal of the serum calcium, phosphorus and phosphatase levels. Recurrence of symptoms associated with the appearance of metastatic nodules in the lungs was soon followed by death. Post-mortem examination showed that there was no local recurrence but that the lung deposits were composed of histologically typical parathyroid tissue.

So far as has been determined from a review of the literature, this is only the second recorded case of visceral metastasis of a proved parathyroid growth.

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