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A histological comparison of adenomatous and hyperplastic parathyroid glands

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SUMMARY The histological findings in 18 cases of parathyroid hyperplasia associated with chronic renal failure and haemodialysis have been compared with a series of 35 cases of primary adenomatous hyperparathyroidism. Analysis of several features suggests that there are no definite criteria for distinguishing microscopically between individual enlarged glands in primary and secondary hyperparathyroidism, although nuclear pleomorphism is more common in primary adenoma and nodules are more common in secondary hyperplasia. These findings are discussed.

Hyperparathyroidism may be caused by a single enlarged autonomous parathyroid gland, an adenoma, or hyperplasia of two or more glands (Castleman and Mallory, 1935; 1937). Whereas an adenoma results in primary hyperparathyroidism hyperplasia may either be the cause of primary hyperparathyroidism or result from chronic parathyroid stimulation. This is usually due to chronic renal failure, often in association with long-term haemodialysis.

The extent of operative resection required varies with the cause of hyperparathyroidism. Cope *et al.* (1958) showed that a significant proportion of cases of primary hyperparathyroidism are due to hyperplasia. It is this group that causes the real problem for the surgeon. A means of identifying at operation whether a single enlarged gland is an adenoma or just one of several enlarged glands would enable the surgeon to judge the extent of resection needed. It is often stated that a microscopic distinction is not possible unless a rim of normal fatty parathyroid tissue surrounding an 'adenoma' can be found (Roth, 1962; Kay, 1976), and it appears that many surgeons believe that the distinction can usually be made on cryostat sections at the time of operation.

This paper reassesses the value of histological criteria in the distinction between adenoma and hyperplasia by comparing known cases of solitary parathyroid enlargement (adenoma) with known cases of secondary hyperplasia. Two cases of primary hyperplasia are also included.

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Material and methods

Thirty-five cases of solitary parathyroid adenoma are compared with 18 cases of hyperplasia, all secondary to renal failure, and two cases of primary hyperplasia. A brief summary of the clinical presentation and radiological findings in each group is given in Tables 1 to 3. Positive *x*-ray findings include subperiosteal erosions, bone cysts, pathological fractures, and generalised lytic or sclerotic lesions of the vertebrae and skull. Renal calculi and nephrocalcinosis are not included.

All the material was removed at operation; no postmortem material is included. Patients operated on for secondary hyperplasia had bone pain and/or radiological evidence of renal osteodystrophy and soft tissue and vascular calcification, together with one or more of the following: raised parathormone level, raised hydroxyproline excretion, mild hypercalcaemia, failure to suppress parathormone levels or hydroxyproline excretion after a calcium infusion

Table 1 *Hyperparathyroidism due to solitary adenoma*

Clinical presentation	*Total*	*Female*	*Male*	*Bone x-ray positive**
Renal stones	14	10	4	3
Bone pain	7	6	1	7
Bone pain + renal stones	2	2	0	1
Incidental finding	6	5	1	3
Gastrointestinal	4	2	2	1
Other renal cases	2	2	0	0
Total	35	27	8	15

*See text.

Table 2 *Hyperparathyroidism secondary to chronic renal failure*

Age	*Sex*	*Cause of renal failure*	*Haemo-dialysis (years)*	*Radiology*
36	M	'Obstructive uropathy'	4	+
40	M	Gout	9	+
17	F	Membranous glomerulo-nephritis	7	+
18	M	Pyelonephritis?	2	+
47	F	Pyelonephritis, hypertension	2	+
27	M	Alport's syndrome	6/12	+
43	F	Glomerulonephritis, hypertension	6	Not recorded
46	M	Glomerulonephritis?	13	+
36	M	Membranous glomerulo-nephritis	10*	Not recorded
37	F	Pyelonephritis	3	Not recorded
14	M	Vesico-ureteric reflux	1/12	+
8	F	Vesico-ureteric reflux	3	+
52	F	Glomerulonephritis?	6*	Nil
48	F	Glomerulonephritis, hypertension	12	+
48	F	Amyloidosis	8	+
45	M	Pyelonephritis	8	+
53	F	Analgesic abuse?	6/12†	+
29	F	Polycystic kidneys	18/12†	+

*Includes successful renal transplant.
†Peritoneal dialysis only.

Table 3 *Hyperparathyroidism due to primary hyperplasia*

Age	*Sex*	*Clinical presentation*	*Radiology*
43	M	Incidental finding (subarachnoid haemorrhage)	Nil
35	F	Weakness: proximal myopathy. Osteomalacia and deformity	+

test, and, more recently, insensitivity to 1-25 dihydroxycholecalciferol. Primary hyperplasia was diagnosed when three or more enlarged glands were found in the absence of renal impairment or malabsorption. Any case in which there was any doubt as to the final pathological diagnosis was deliberately excluded, as were cases in which the clinical and biochemical findings did not clearly differentiate primary from secondary hyperparathyroidism.

In each case of adenoma the entire enlarged gland was removed. In five of these cases a normal gland was also biopsied or removed, but it is not the normal practice of our surgeons to biopsy normal glands, although all glands are identified *in situ* if possible. At least three glands and often part of the fourth were removed in cases of hyperplasia.

I have reviewed all the cryostat sections and subsequent paraffin sections, all stained with haematoxylin and eosin. Serial sections were not cut. No attempt has been made to analyse the macroscopic findings as the series includes some cases going back as long as 10 years and there is no uniformity in the methods of description.

The parathyroid glands removed at operation were assessed for the presence or absence of the following: 1 A rim of normal fat-infiltrated parathyroid tissue adjacent to the enlarged gland. 2 Foci of fat cells, visible with a low-power scanning lens, within the enlarged gland. 3 Mitotic figures. 4 Nuclear pleomorphism, that is, marked variation in nuclear size apparent while scanning the section at medium power (Fig. 1). 5 Distinct nodules of different cell type or pattern, compressing surrounding parathyroid tissue. 6 Calcification within the gland or its capsule.

In addition, the predominant cell type and pattern were assessed. These two indices proved most difficult to assess objectively, and each has been rationalised into groups; the cell type into chief cells only, oxyphil cells only, and mixed cell types; the pattern into solid and mixed groups. The solid pattern includes only sheets of uniform cells, while the mixed pattern includes glandular, trabecular, and cystic areas together with solid nests and sheets.

The hyperplasia cases have been scored as positive for a particular feature if one or more glands showed that feature. Only where the findings are definitely present have they been scored as positive.

The Chi-square test (χ^2) was used to calculate the significance of these observations while Fisher's exact test was used when the numbers were very small, as in the case of mitotic figures. The level of probability taken as significant was 5% ($P < 0.05$).

Results

Table 4 shows the results. The number of cases in each group positive for each feature is shown, along with the results of statistical analysis of the cases of adenoma and secondary hyperplasia. The primary hyperplasia cases are also shown in Table 4.

The table shows that the only significant positive finding in adenomas is the presence of nuclear pleomorphism, while in secondary hyperplasia the only significant positive features are nodules and calcification. No other feature, including the rim of compressed normal parathyroid tissue, reaches significance.

Discussion

This is the first recorded detailed analysis comparing specific histological features of hyperparathyroidism due to adenoma with that due to hyperplasia.

The presence of a rim of normal parathyroid tissue adjacent to an enlarged gland has often been used as a criterion for the diagnosis of an adenoma. Black

Table 4 *Results of histological assessment*

Diagnosis	*Total*	*Rim*	*Fat*	*Mitoses*	*Nuclear Pleomorphism*	*Nodules*
Adenoma	35	12	20	1	17	5
Secondary hyperplasia	18	2	13	3	3	11
χ^2 for adenomas		NS	NS	NS	$P < 0.05$	—
χ^2 for hyperplasia		NS	NS	NS	—	$P < 0.005$
Primary hyperplasia	2	0	1	0	2	1

Diagnosis	*Chief cells only*	*Mixed cell types*	*Oxyphil cells only*	*Solid pattern*	*Mixed pattern*	*Calcification*
Adenoma	14	19	2	9	26	2
Secondary hyperplasia	5	13	0	5	13	5
χ^2 for adenomas	NS	NS	—	NS	NS	—
χ^2 for hyperplasia	NS	NS	—	NS	NS	$P < 0.05$
Primary hyperplasia	2	0	0	0	2	0

NS=not significant at 5% level ($P < 0.05$)

and Utley (1968) have warned against accepting this and have seen a rim in some cases of hyperplasia. The findings in this series support their view (Fig. 4; Table 4). Clearly, hyperplasia does not involve all glands in a uniform manner, and rapidly growing nodules may push normal looking tissue to one side.

There was a clear overlap between the histology of adenomatous and hyperplastic glands, and every feature assessed could be found in some cases from each group. Black and Utley (1968) came to a similar conclusion and added that the gross features of colour, size, and shape had little bearing on the diagnosis. Although the gross features have not been analysed the impression is that they are of no value.

It seems that only nuclear pleomorphism (Fig. 1) is a pointer to the diagnosis of an adenoma and that only the presence of nodules (Fig. 2) is useful in pointing to hyperplasia. It is of interest that both cases of primary hyperplasia studied show nuclear pleomorphism, and one shows nodule formation. Others have commented on nodules but not on nuclear pleomorphism in primary hyperplasia (Black and Haff, 1970). Ectopic calcification is so common in secondary hyperparathyroidism that the finding of calcification in hyperplastic glands was to be expected. Nevertheless it may be present in adenomas.

The finding of mitotic figures in three hyperplastic glands and one adenoma was not expected (Fig. 3). Mitotic figures have been used as a criterion for

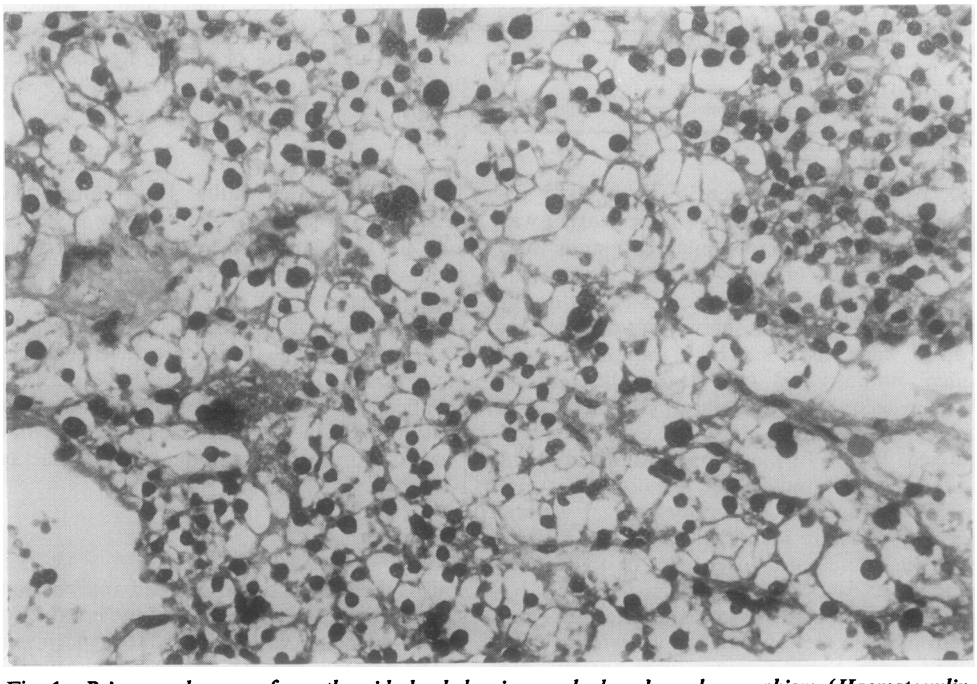

Fig. 1 *Primary adenoma of parathyroid gland showing marked nuclear pleomorphism. (Haematoxylin and eosin × 400)*

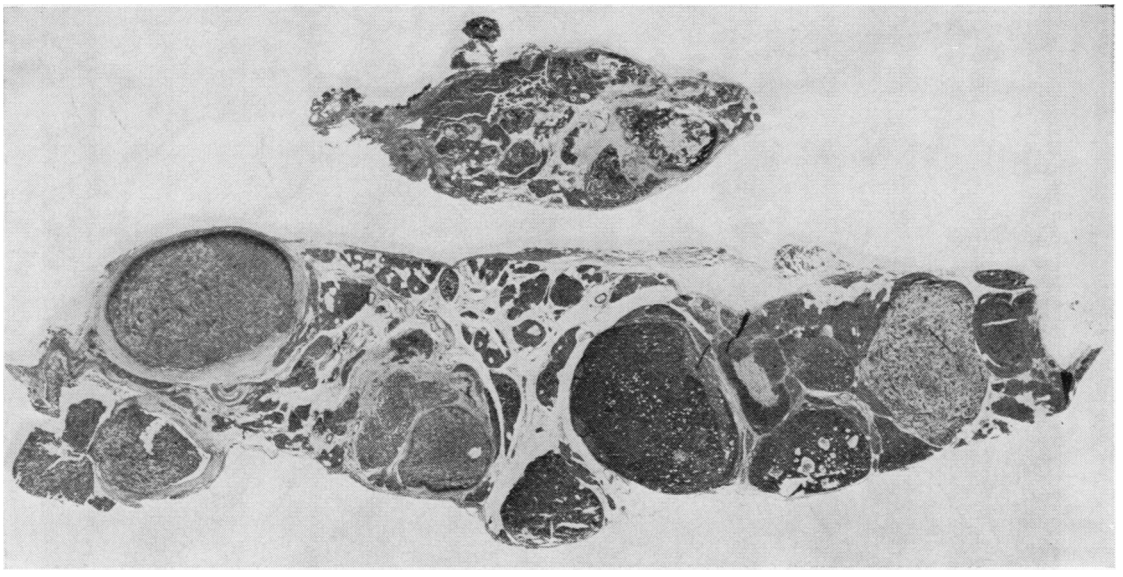

Fig. 2 *Secondary hyperplasia of parathyroid gland showing pronounced nodule formation. (H and E × 7·5)*

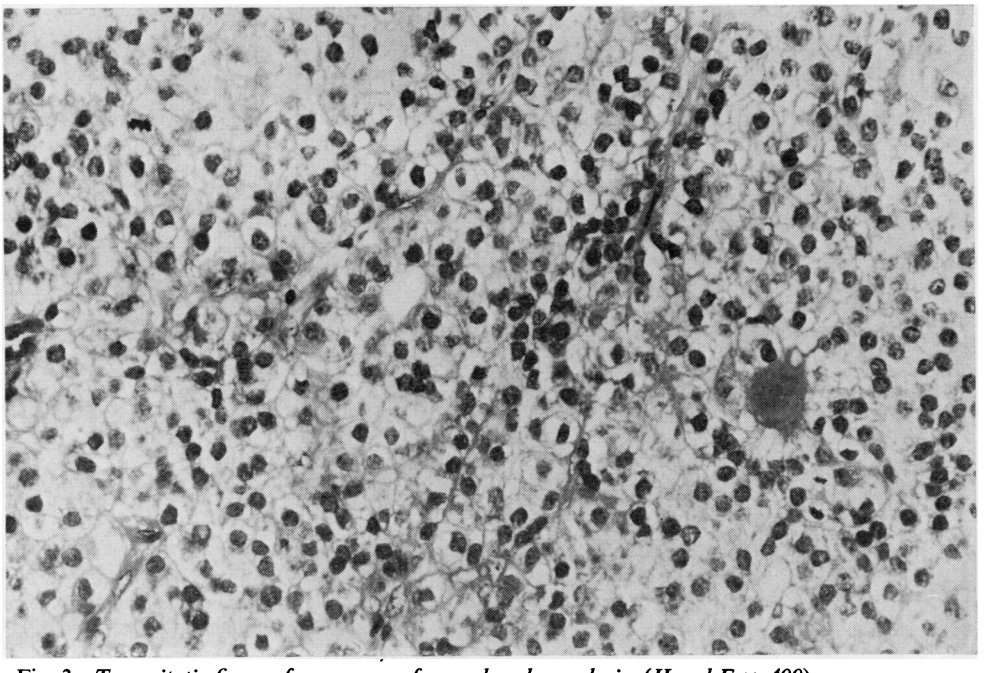

Fig. 3 *Two mitotic figures from a case of secondary hyperplasia. (H and E × 400)*

diagnosing carcinoma (Schantz and Castleman, 1973). However, they were present in very small numbers, and there were no other features such as adherence to surrounding structures, capsular invasion, vascular invasion, or metastases to suggest carcinoma.

Normally the clinical and biochemical features will clearly differentiate between primary and secondary hyperparathyroidism. However, there are two instances where differentiation is not clear cut. Firstly there is the patient with long-standing hyperparathyroidism and impaired renal function in whom

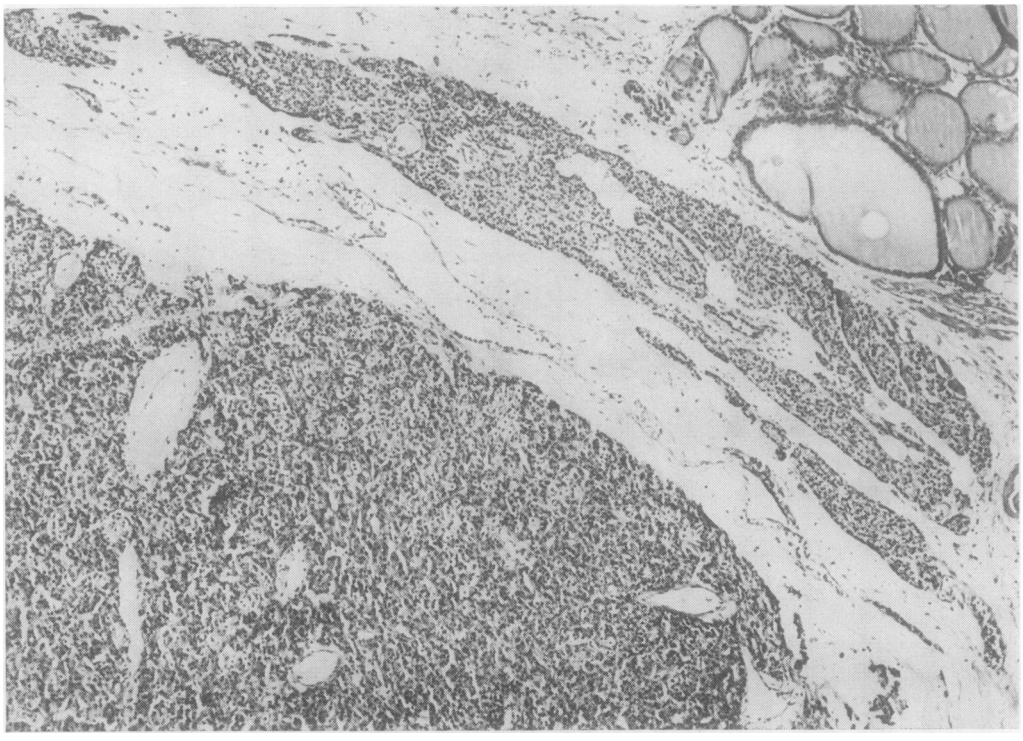

Fig. 4 *An apparent rim of normal tissue adjacent to an enlarged gland in secondary hyperplasia.* (*H and E* × *90*)

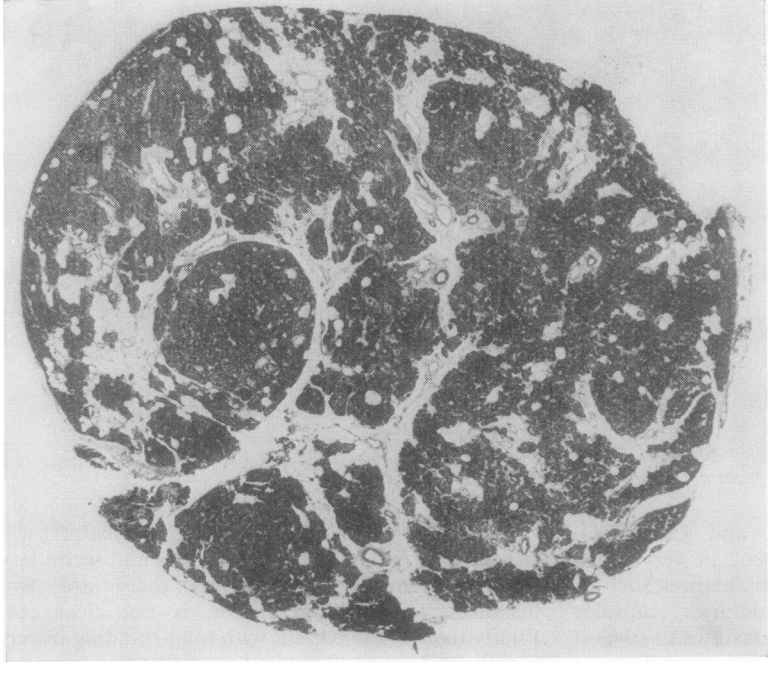

Fig. 5 *Same case as in Fig. 4, showing one of the other enlarged glands.* (*H and E* × *32*)

nephrocalcinosis and calculi have damaged the kidneys to such an extept that an element of secondary hyperparathyroidism may be present. Operative findings will clearly differentiate most of these cases, as will calcium suppression tests. The second problem is that of 'tertiary' hyperparathyroidism after a hypocalcaemic stimulus, such as chronic renal failure, in which apparent autonomous parathormone secretion develops, leading to hypercalcaemia and marked vascular and soft tissue calcification, as well as lytic bone lesions. There are reports of large autonomous 'adenomas' co-existing with three hyperplastic glands (Golden *et al.*, 1965; Kramer, 1970). A similar case is illustrated in Figs 4 and 5, in which an enlarged gland, 1·5 cm in diameter, showed an apparent rim of normal parathyroid in the presence of other enlarged glands. However, as explained above, a rim is a poor criterion to use, and it is doubtful whether a clear-cut distinction between secondary and tertiary hyperparathyroidism can be made. Indeed all patients with renal failure coming to parathyroidectomy can be said to have autonomous parathormone secretion in that their calcium metabolism is clearly out of control. In this case there was also much nuclear pleomorphism in the gland, a rim making the suggestion of adenoma more tempting (Fig. 6). Others have commented on the hazards of diagnosing 'tertiary' adenoma (Smith, 1970; *American Journal of Medicine*, 1972).

It is clear that the final diagnosis rests on a proper evaluation of the parathyroid glands at surgery. All four parathyroid glands must be identified, or one enlarged gland (adenoma) removed and at least one normal gland removed or biopsied to establish the diagnosis of adenoma (Cope *et al.*, 1958; Roth *et al.*, 1975; Taylor, 1976). Differentiation of a small hyperplastic gland from a normal gland is sometimes difficult. Roth and Gallagher (1976) have found that normal glands contain intracytoplasmic fat. Imprints of glands have also been used to make rapid differentiation at operation (Silverberg, 1975).

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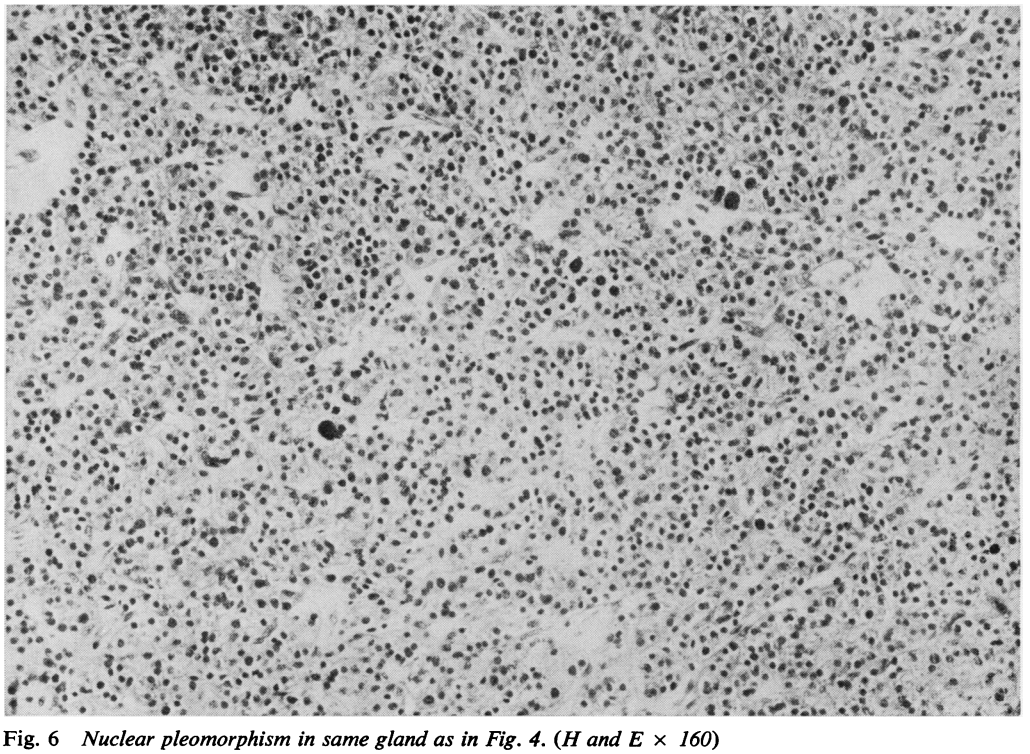

Fig. 6 *Nuclear pleomorphism in same gland as in Fig. 4. (H and E × 160)*

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