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Invited Review

Papillary carcinoma of thyroid: Classical and variants

John K.C. Chan
Institute of Pathology, Queen Elizabeth Hospital, Hong Kong

Summary. Papillary carcinoma, the commonest primary cancer of thyroid, exhibits a broad morphological spectrum. In this review, the clinicopathological features of papillary carcinoma, classical and its variants (follicular, solid, cribriform, variant with exuberant nodular fasciitis-like stroma, encapsulated, diffuse sclerosing, diffuse follicular, tall cell, columnar cell, oxyphil cell, «dedifferentiated», occult, latent and microcarcinoma) are summarized.

Key words: Papillary thyroid carcinoma, Papillary carcinoma, Thyroid neoplasm

Introduction

Papillary thyroid carcinoma (PTC) is the commonest primary cancer of the thyroid (Hirabayashi et al., 1961; Woolner et al., 1968; Beaugie et al., 1976; Rosai, 1989). It occurs in any age group, and accounts for 80% of all thyroid cancers in patients under the age of 40 years (Woolner, 1971). The mean age at presentation is 42-43 years (Meissner and Adler, 1958; McConahey et al., 1986), and women are more commonly affected than men. PTC is characterized by a propensity to local invasion and lymph node metastasis. Distant metastasis is uncommon (9-14%) and generally occurs late in the disease (Lindsay, 1969; Franssila, 1973; Carcangiu et al., 1985c). The tumour is indolent, and relapses can occur as late as 30 years after initial treatment (Tubiana et al., 1985). The prognosis is very good, and the cancer mortality is only 6.5% on long-term follow-up (McConahey et al., 1986).

The morphological spectrum of PTC is very broad, and many variants have been identified. Though some are merely morphological variants, they merit recognition because they draw attention to unusual patterns that PTC may assume and therefore aid in diagnosis. There are also variants (tall cell, diffuse sclerosing, dedifferentiated, columnar cell and diffuse follicular) that require special attention because of their more aggressive behaviour.

The clinicopathological features of classical and variant PTCs are detailed in this review. Since the variants emphasize different aspects (such as growth pattern, size or cytological features) of PTC, they are not mutually exclusive entities. For example, a PTC may be a microcarcinoma and at the same time of the encapsulated and oxyphilic variant.

Offprint requests to: Dr. John K.C. Chan, Institute of Pathology, Queen Elizabeth Hospital, Wylie Road, Kowloon, Hong Kong

Classical PTC

Definition

In the revised W.H.O. Classification, PTC is defined as a malignant epithelial tumour showing evidence of follicular cell differentiation, typically with papillary and follicular structures as well as characteristic nuclear changes (ground glass, large size, pale, irregular outline with deep grooves and pseudoinclusions) (Hedinger et al., 1988). This is significantly different from the previous one: «malignant epithelial tumour containing papillary structures» (Hedinger and Sobin, 1974), illustrating the increasing emphasis placed on the nuclear features in the diagnosis of PTC (Rosai et al., 1983; Carcangiu et al., 1985d). The term «mixed papillary-follicular carcinoma» (Meissner and Warren, 1969) should no longer be used; all such cases are now classified as PTC.

Patterns of growth

PTCs are typically invasive (Fig. 1), but can be circumscribed or encapsulated. Some tumours exhibit prominent unicystic or multicystic change; they may be mistaken for benign cysts (Fig. 2). Multifocal involvement of one or both lobes occurs in about 20% (Meissner

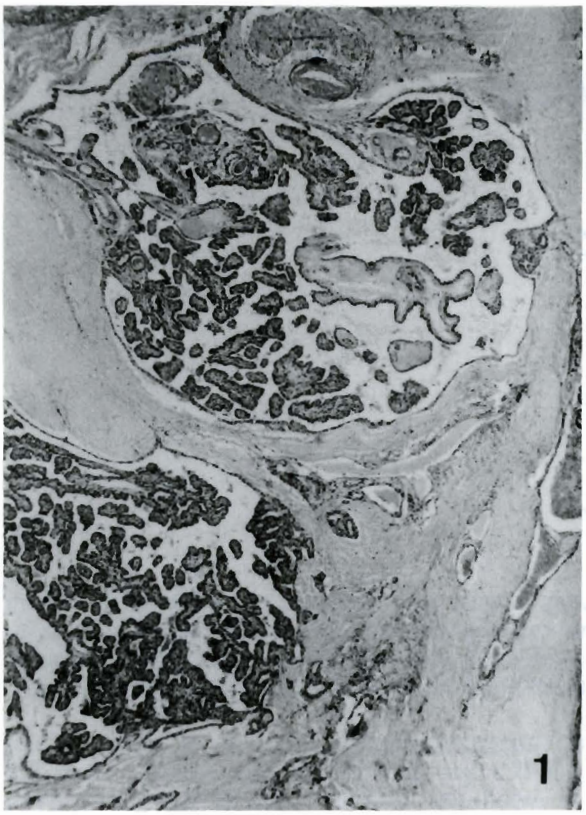

Fig. 1. Classical PTC with invasive borders, arborizing delicate papillae and stromal sclerosis. H&E. × 30

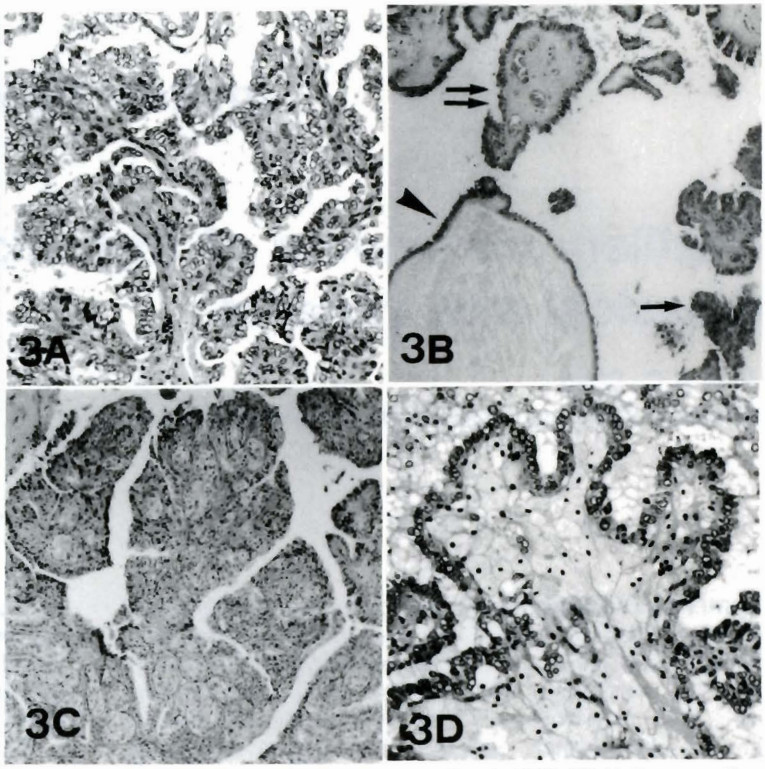

Fig. 3. Varied appearances of papillae in PTC. (A). Delicate papillae with fibrovascular core. × 100. (B) Papillae with fibrocellular stroma (single arrow), hyalinized stroma (double arrows) and oedematous stroma (arrowhead). × 50. (C) Macropapillae with small follicles in the core. × 50. (D) Papilla with accumulation of foamy macrophages in the core × 100. All H & E.

and Adler, 1958; Hawk and Hazard, 1976; Carcangiu et al., 1985c), but the percentage goes up to 87.5% if the whole gland is sectioned (Russell et al., 1963). This, however, should not be taken as an argument for radical thyroidectomy, since these minute tumour foci have limited growth potential. Most studies have shown that unless gross malignant tumour is left behind or in high risk-group patients, hemithyroidectomy yields the same good results as total thyroidectomy (Ito et al., 1980; Carcangiu et al., 1985c; Mazzaferri, 1987; Vickery et al., 1987; Hoie et al., 1988). Lymphatic permeation is a frequent finding.

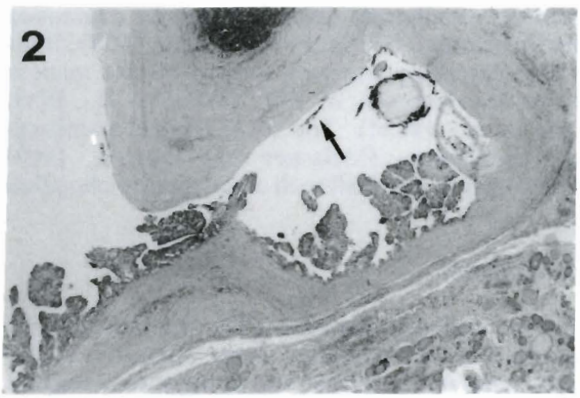

Fig. 2. Unicystic PTC lined partly by papillae and partly by attenuated epithelium (arrow). H&E. × 20

The papillae of PTC are varied in appearance. They are frequently arborizing and delicate, and possess fibrovascular stalk (Figs. 1, 3a). However, they can be broad, with fibrocellular, oedematous or hyalinized cores which may be infiltrated by foamy macrophages, or they can be formed by cellular tufting alone (Fig. 3). Exceptionally, adipose cells may form the cores (Vestfrid, 1986; Bruno et al., 1989; Gnepp et al., 1989). Papillae of PTC must be distinguished from the macropapillae seen in hyperplastic nodules, in which the cells are usually columnar with non-crowded, basal, dark and round nuclei. However, it should be noted that macropapillae can also occur in PTC (Fig. 3c). Small papillae are also common in thyrotoxicosis, but they are blunt projections bulging into the follicles and often lack defined cores (Rosai and Carcangiu, 1987). Some papillae can occur in follicular adenoma/carcinoma (particularly Hurthle cell type), or even medullary carcinoma, but the typical nuclear features of PTC are lacking (Rosai, 1989; Sambade et al., 1989).

In PTC, follicles are almost always present (Fig. 4a). Most follicles are small, but some may be large and lined by attenuated cells. Lesions composed predominantly of large cystic follicles can mimic colloid or adenomatous goitre (Fig. 4b). Intrafollicular haemorrhage is common in large follicles. In the colloid, multinucleated giant cells or foamy histiocytes may be found.

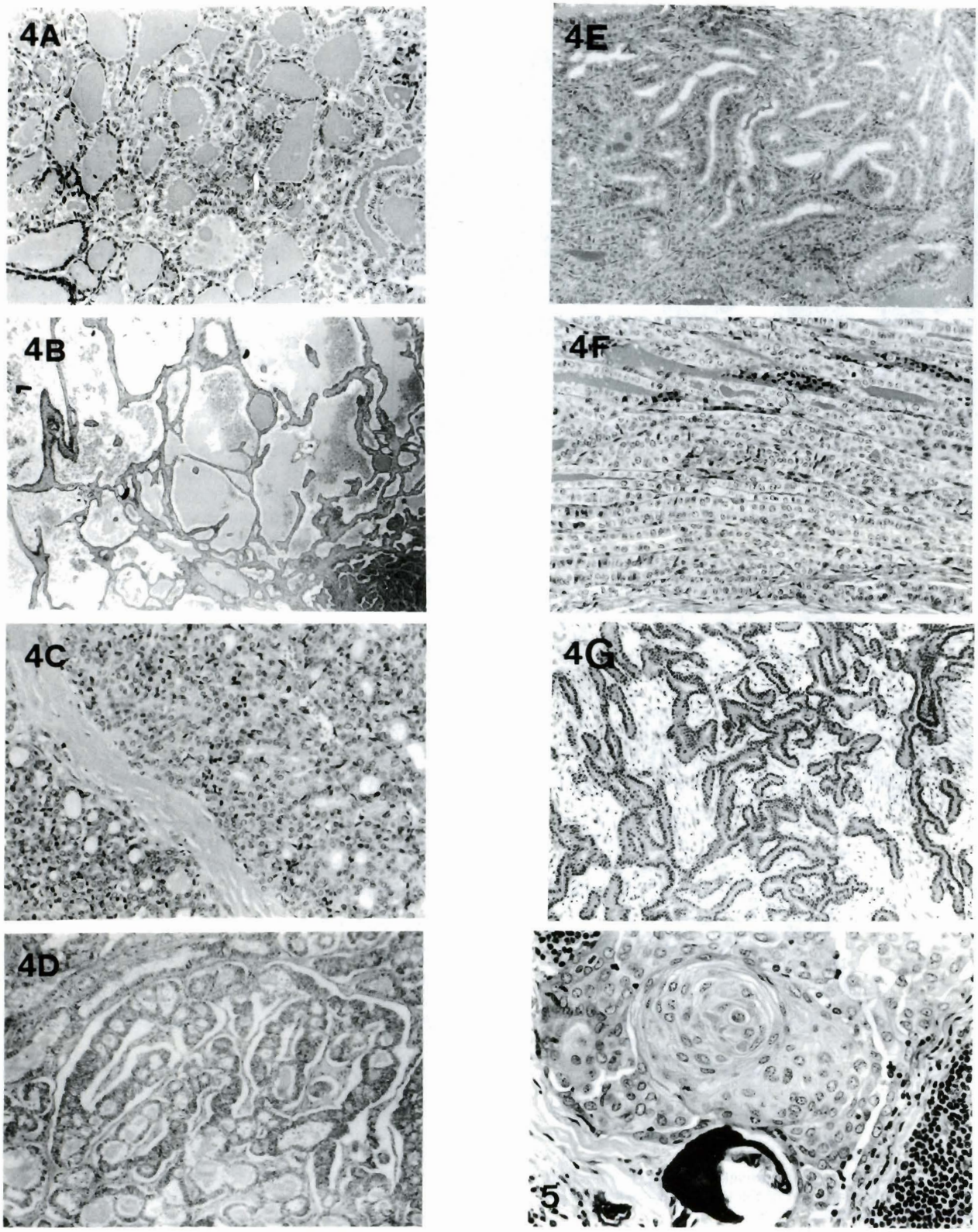

Fig. 4. Varied architectural patterns of PTC. (A) Follicles, with some being elongated. × 100. (B) Honeycomb appearance formed by large cystic follicles. Note intrafollicular haemorrhage. × 20. (C) Microglandular pattern. × 100. (D) «Garland» pattern formed by linear anastomosing glandular structures or perhaps coiling of tubular structures. × 50. (E) Complex tubulopapillary pattern. × 75. (F) Narrow tubular and trabecular pattern. × 100. (G) Anastomosing narrow tubules separated by cellular stroma. × 100. All H&E.

Fig. 5. Psammoma body (lower field) and squamous metaplasia. H&E. × 200

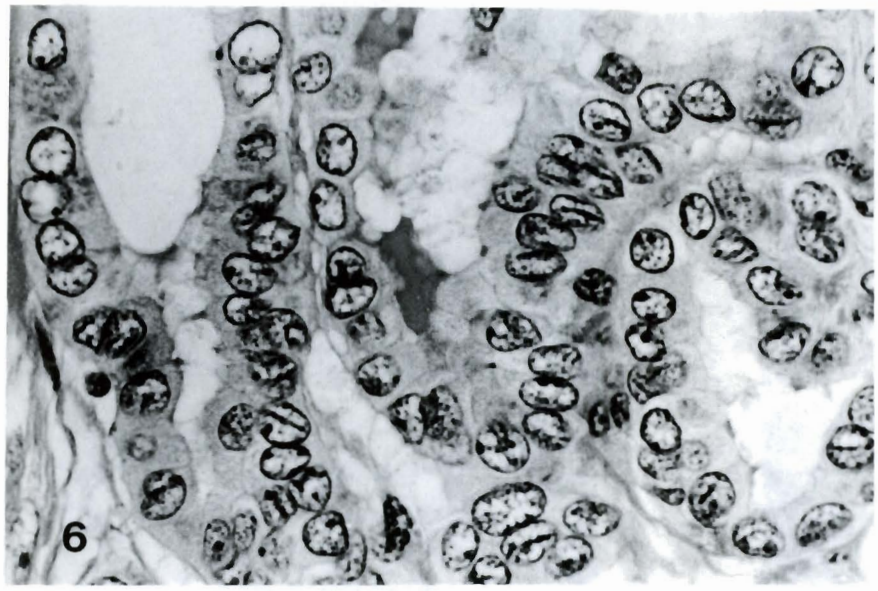

Fig. 6. Typical nuclear features of PTC. Nuclei in the left upper coner are ground-glass. Others are grooved but not ground-glass. Note the small distinct nucleoli, often apposed to the nuclear membrane. The cytoplasm is lightly eosinophilic. H&E. × 750

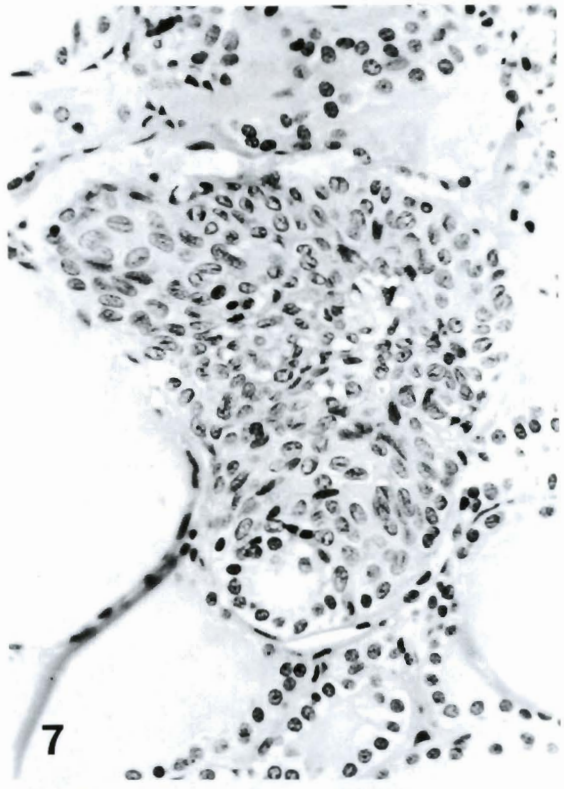

Fig. 7. Solid cell nest of Yamaoka. Tiny epithelial island resembling Walthard rest of the female genital tract. Note nuclear grooves. H & E. × 300

Sometimes, a microglandular or «garland» pattern is formed by anastomosing glandular structures (Figs. 4c, d). A tubulopapillary pattern formed by a complex blend of papillae, tubules and follicles is common (Fig. 4e). Growth may take the form of closely packed narrow tubules merging with long trabeculae, or anastomosing tubules separated by cellular stroma (Fig. 4f, 4g) (Chan and Rosai, 1990). A solid pattern is also by no means rare (Please see section on «solid variant»).

Stroma

There is often a dense sclerotic stroma which may be calcified or ossified (Fig. 1). Sometimes the stroma is more cellular (desmoplastic), particularly in the invasive fronts. Variable numbers of lymphocytes, plasma cells and macrophages (which may be foamy or haemosiderin-laden) are present in the stroma.

Psammoma bodies occur in about half of the cases. They are laminated calcified structures of varying sizes, being found in the stalks of papillae, stroma or among tumour cells (Fig. 5) (Rosai, 1989). They are believed to be formed by the following mechanisms: (1) thickening of basal lamina of vessels in papillae followed by thrombosis, calcification and tumour cell necrosis, and (2) intralymphatic tumour thrombi becoming necrotic and calcified (Johannessen and Sobrinho-Simoes, 1980). They show positive staining by mucin stains (Chan and Tse, 1988). Psammoma bodies are practically diagnostic of PTC with rare exceptions (Vickery et al., 1985). Whenever they are found as an isolated finding (aptly described as «tombstones» of PTC), careful search must be made for the presence of PTC somewhere in the thyroid, by step sections and more extensive sampling. Calcified colloid, which is fairly common in Hurthle cell neoplasms and hyalinizing trabecular adenoma, should not be mistaken for true psammoma bodies.

Nuclear features

The nuclei are characteristically large, crowded, ground-glass and grooved (Fig. 6). These features may be prominent throughout the tumour, focal or inconspicuous. The nuclei are usually oval with small distinct nucleoli.

Ground-glass change refers to the peculiar clearing of the chromatin, and is found in over 80% of PTC (Hapke and Dehner, 1979; Carcangiu et al., 1985d; Chan and Saw, 1986). It is believed to be an artifact of formalin fixation because it is not evident in frozen section or cytological preparation (Hapke and Dehner, 1979), but Kraemer (1987) has identified this feature in 37.5% of frozen sections of PTC. The nuclei appear empty and the scanty marginated chromatin is dusty (Fig. 6). However, this feature is not pathognomonic because benign lesions (such as hyperplastic nodule, adenoma, Graves' disease or Hashimoto's thyroiditis) may exhibit such nuclei as a focal phenomenon (Rosai and Carcangiu, 1987).

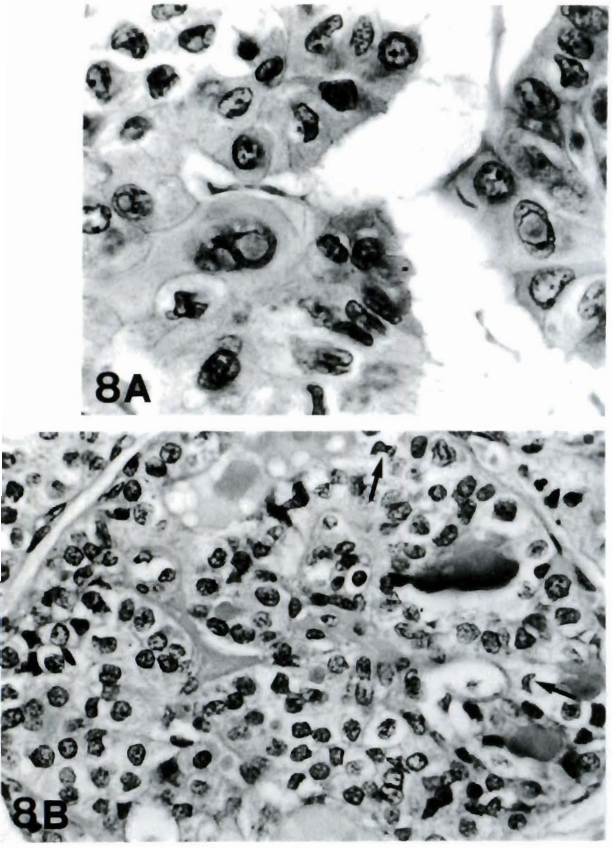

Fig. 8. (A) Three nuclear pseudoinclusions are shown. × 500. (B) In PTC, many nuclei may not fit the typical description. Collapsed nuclei can often be found (arrows). × 300. All H & E

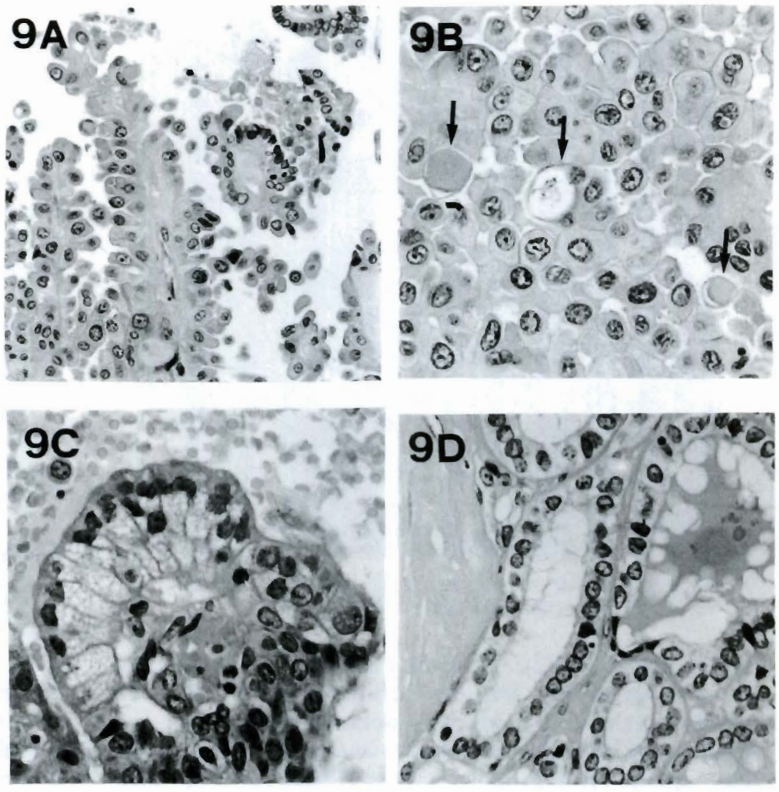

Fig. 9. Varied appearances of the cytoplasm. (A) Hob-nail cells, with formation of some cellular tufts. The cytoplasm is oxyphilic. × 150. (B) Oxyphilic cells with vacuoles showing staining properties of mucin (arrows). Some nuclei in this tumour have coarse chromatin. × 300. (C) Oxyphilic cells with clearing of the cytoplasm at the base of the cells. × 300. (D) Clear cell change. × 300. All H & E.

Irregularities in the nuclear membrane and deep grooves are frequently observed. The groove represents a deep cleft along the longitudinal axis of the nucleus (Fig. 6) (Chan and Saw, 1986). In general, grooved nuclei are not ground-glass, but are pale or even chromatin-rich. The proportion of nuclei exhibiting ground-glass change and grooves varies considerably from case to case. Care must be exercised not to over-interpret the significance of nuclear irregularities in suboptimally fixed tissue, in which the nuclei in almost any lesion can appear wrinkled. Since grooved nuclei can be appreciated in cytologic preparations, they are helpful in the intraoperative and fine needle aspiration diagnosis of PTC, particularly if they are readily found (Deligeorgi-Politi, 1987; Shurbaji et al., 1988; Gould et al., 1989; Rupp and Ehya, 1989). Grooved nuclei are not pathognomonic of PTC, because they can occur focally in hyperplastic nodule, follicular adenoma, hyalinizing trabecular adenoma, follicular carcinoma and poorly differentiated carcinoma (Chan and Saw, 1986; Carney et al., 1987). Neither can nuclear grooving be employed to distinguish PTC from papillary adenocarcinoma of other sites since grooving is common in many adenocarcinomas. Another lesion in the thyroid that exhibits nuclear grooving consistently is the solid cell nest, but its nuclear feature has received little attention in the literature (Fig. 7). Solid cell nests are small epithelial islands which probably represent remnants of the ultimobranchial body, and are frequent incidental findings in the thyroid (Yamaoka, 1973; Harach, 1988). They can be distinguished from latent PTC by the consistently small size, smooth contour of the nests, solid growth pattern, lack of sclerosis, lack of true follicular or papillary structures (though solid cell nests may occasionally wrap around pre-existing follicles) and absence of nuclear clearing. Solid cell nests are cytokeratin-positive but thyroglobulin-negative, and many calcitonin-positive cells are frequently found in the vicinity or within the islands (Harach, 1988; Chan and Tse, 1989).

Nuclear pseudoinclusions are found in about 50% of PTCs, though a high figure of 100% has been reported (Chan and Saw, 1986; Oyama, 1989). They are more easily found in tumours showing greater nuclear pleomorphism. Since they are formed by invaginations of the cytoplasm into the nucleus, they are delineated by a sharp nuclear membrane and should stain like the cytoplasm (though usually lighter) (Fig. 8a). Again pseudoinclusions are not entirely pathognomononic of PTC (Glant et al., 1984).

However, a significant proportion of nuclei in PTC may not show the typical features (Tscholl-Ducommun

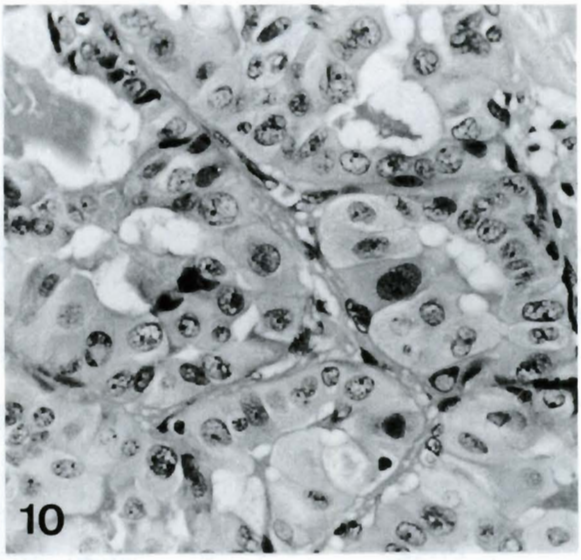

Fig. 10. So-called marked cellular atypia. Note variation in nuclear size and chromatin pattern. H&E. × 300

and Hedinger, 1982). Often they are merely pale or even chromatin-rich (Fig. 8b); the chromatin may be coarse in neoplasms showing moderate nuclear atypia. A peculiar feature that has not been emphasized is that many nuclei may appear collapsed or crescent-shaped (Fig. 8b). These nuclear features per se are not diagnostic; cytological features in other areas and the overall architectural pattern have to be assessed to reach a diagnosis.

Nuclear bubbling is a not uncommon artifact mimicking the nuclear features of PTC. The nuclear bubbles are single or multiple, and structureless. They apparently result from improper processing or fixation of the tissue. They differ from ground-glass nuclei in that they appear as «globules» within the nuclei devoid of a chromatin rim. They differ from pseudoinclusions in the lack of delimitation by nuclear membrane, lack of content, and that they often involve many cells in one area of or throughout the slide; pseudoinclusions are never as plentiful.

Mitotic figures are usually sparse to absent, but they may be easy to find in some invasive recurrences and highly invasive tumours of old patients (Hazard, 1968; Vickery et al., 1985; Sobrinho-Simoes et al., 1989).

Cytoplasmic features

The cells in PTC are mostly cuboidal to polygonal, but may be columnar, flattened, dome-shaped or hob-nailed (Fig. 9). The cell borders may or may not be distinct, and the cytoplasm is amphophilic to eosinophilic. Some cells may accumulate sufficient mitochondria so as to appear oxyphilic, while some may appear clear (Fig. 9); neither change is of no prognostic importance (Hazard, 1968). The mechanisms resulting in cytoplasmic clearing in PTC include accumulation of glycogen, accumulation of lipid,

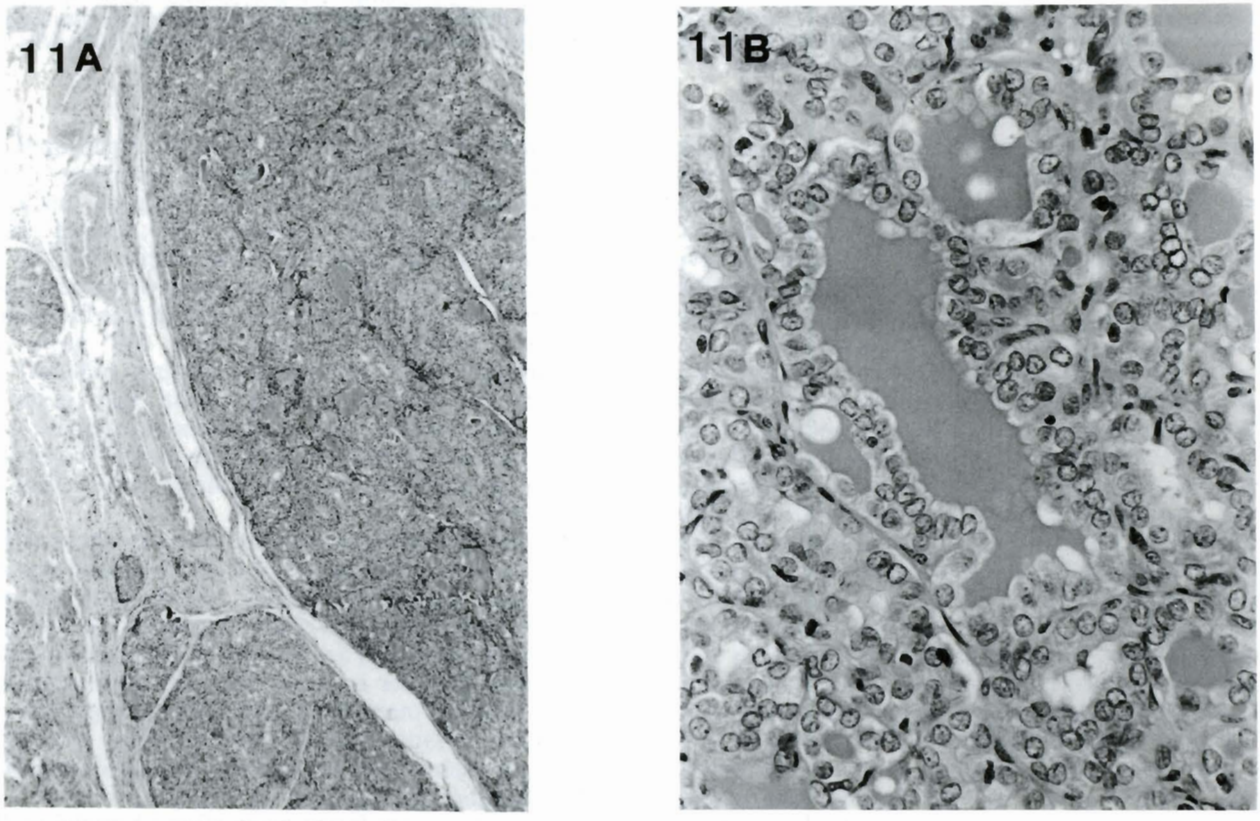

Fig. 11. Follicular variant. (A) Typical multinodular growth pattern with sclerosis. × 30. (B) Many follicles are elongated with tiny papillary tufts pushing into the lumina. Note dark-staining colloid. × 300. All H & E.

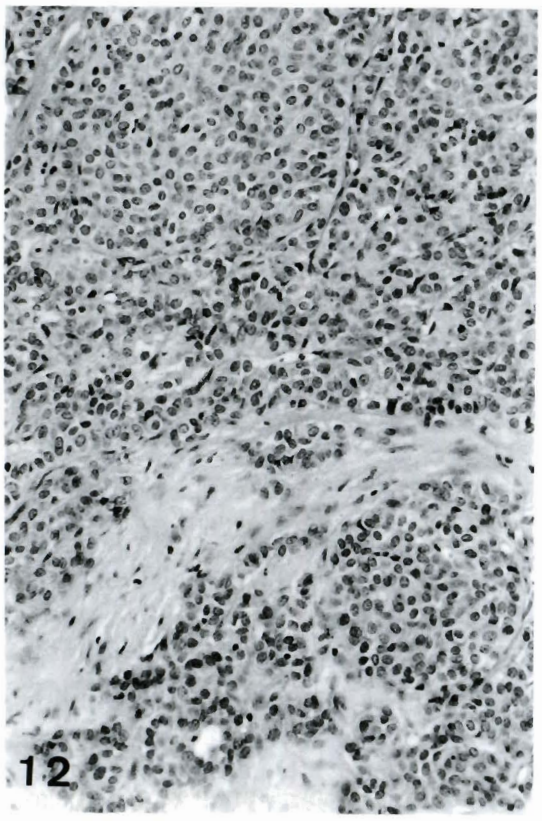

Fig. 12. Solid variant. Solid sheets of tumour traversed by delicate septa. Typical papillae are present elsewhere. H & E. × 150

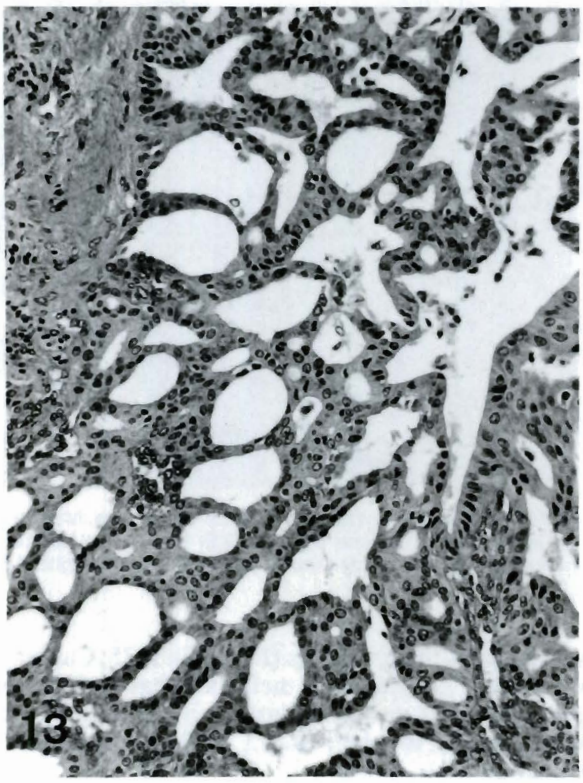

Fig. 13. Cribriform variant. Note resemblance to cribriform intraduct carcinoma of breast. H&E. × 150

mitochondrial dilatation with rarefaction, and membrane-bound vesicles containing granular precipitate (Variakojis et al., 1975; Dickersin et al., 1980; Carcangiu et al., 1985a; Schroder and Bocker, 1985).

Cytoplasmic globules or luminal content with staining properties of mucin may occur in PTC (Fig. 9b), therefore mucin-positivity does not exclude the possibility that a carcinoma is of thyroid primary (Mlynek et al., 1985; Chan and Tse, 1988).

Squamous differentiation is found in 45% of PTCs (Fig. 5). The nuclei in the squamous foci are regular and usually chromatin-rich. Staining for thyroglobulin is often but not invariably negative. It should not be misinterpreted as squamous cell carcinoma (which if present markedly worsens the prognosis).

Clinicopathological correlation

Besides the variants to be discussed below, a number of features are correlated with prognosis, the most important being age, size of tumour and extent of local disease (Hawk and Hazard, 1976). Some but not all studies have found the male sex to be associated with a worse prognosis (Fraeunhoffer et al., 1979; Tscholl-Ducommun and Hedinger, 1982; Tennvall et al., 1986; Mazzaferri, 1987).

PTCs, occurring in old people are more aggresive; mortality is rare below the age of 40 years (Woolner et al., 1968; Ito et al., 1980; Tubiona et al., McConahey et al., 1986; Tennvall et al., 1986; Mazzaferri, 1987).

The impact of tumour size on prognosis has been clearly demonstrated by long follow-up studies from the Mayo Clinic (McConahey et al., 1986). The risk of death increases progressively with the size of the primary tumour. Tumours measuring less than 1-1.5 cm are associated with an excellent prognosis (Ito et al., 1980; Schroder et al., 1984b). All tumours must therefore be measured.

An important poor prognostic factor is tumour invasion into the surrounding tissue (extrathyroid extension) (McConahey et al., 1986; Vickery et al., 1987).

There is no evidence that the proportion of follicles in PTC influences the prognosis (Lindsay, 1969; Carcangiu et al., 1985c). Encapsulated tumours have an excellent prognosis (Schroder et al., 1984a). Tennvall et al. (1985, 1986), in a multivariate analysis, reported marked cellular atypia (MCA) to be associated with a worsened prognosis in PTC. MCA, defined by multilayered cells with marked variation in cellular and nuclear size and shape, and uneven distribution of chromatin, is a focal finding in 4% of PTCs (Fig. 10). Unfortunately, it is uncertain from their study whether it is a prognostic factor independent of age, therefore more studies are required to confirm the significance of MCA in PTC. A high density of S-100 protein-positive histiocytes (Schroder et al., 1988) and slight or absent Leu-M1-positivity have been suggested to be favorable prognostic factors (Schroder et al., 1987). Invasion of sizable blood

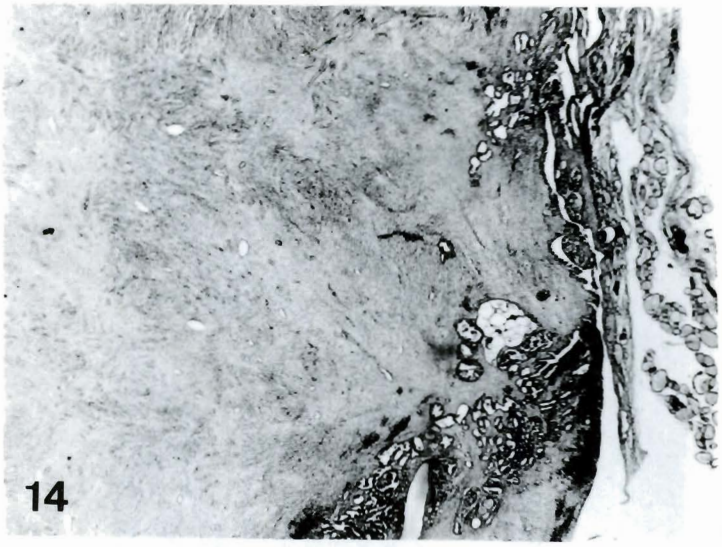

Fig. 14. PTC with exuberant nodular fasciitis-like stroma. Most of the tumour is formed by cellular stroma, with only some islands of carcinoma beneath the rim of normal thyroid tissue on the right. H & E. × 12

vessels worsens the prognosis (Franssila 1975; Carcangiu et al., 1985c). Lymph node metastasis has no influence on prognosis, but distant metastasis is associated with a poor prognosis (Woolner et al., 1968; Franssila, 1975; McConahey et al., 1986).

Follicular variant

PTCs composed entirely of follicles are designated as the follicular variant (Chen and Rosai, 1977). The follicles are round, cystically dilated, elongated or tubular with occasional abortive papillae projecting into the lumina. The colloid is typically dark-staining and scalloped (Rosai et al., 1983). The diagnosis of PTC is rendered based on the typical nuclear features. Though some PTCs of follicular variant are encapsulated (sometimes referred to as «Lindsay's tumour») making distinction from follicular carcinoma or adenoma difficult, most grow in a multinodular, invasive pattern with areas of sclerosis (Figs. 4A, 11). Psammoma bodies may be found. The immunophenotypic profile (cytokeratin AE1/AE+, LN2+, HLA-DR+, Helix promatia+) is similar to that of classical PTC and differs from that of follicular carcinoma (Wick et al., 1989).

The clinical features and behaviour of the follicular variant do not differ from those of classical PTC, and there is a similar tendency for lymph node metastasis (Chen and Rosai, 1977; Carcangiu et al., 1985d). In the metastatic deposit, papillary structures may occur.

Solid variant

PTCs with more than 50% solid areas are called the solid variant, and behave no differently from classical PTC (Meissner and Adler, 1958; Woolner, 1971; Carcangiu et al., 1985c). The tumour cells form small to large islands which may be traversed by delicate fibrous septa

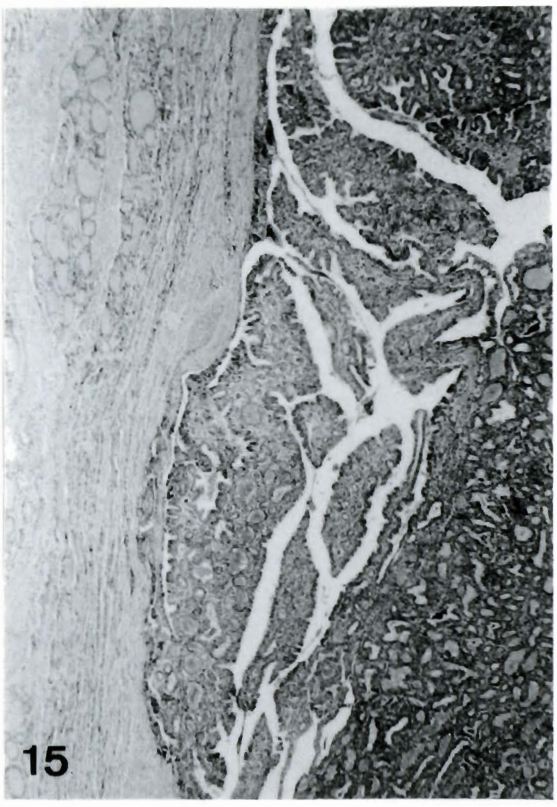

Fig. 15. Encapsulated variant with well formed fibrous capsule. H & E. × 30

(Fig. 12). This variant must not be confused with the more aggressive poorly differentiated (insular) carcinoma, anaplastic carcinoma, squamous cell carcinoma or medullary carcinoma. Essentially the nuclei are typical of those of PTC; comparison with those in the papillary/follicular areas will give the answer in most situations. The cells are smaller and nuclei more hyperchromatic in poorly differentiated carcinoma, and nuclear pleomorphism should be obvious in anaplastic/squamous cell carcinoma. There are usually delicate fibrovascular septa and nuclei with stippled chromatin in medullary carcinoma; staining for thyroglobulin and calcitonin can be helpful in difficult cases.

Cribriform variant

PTC may exceptionally take up a growth pattern simulating cribriform (intraductal or invasive) carcinoma of the breast. Discrete cribriform structures are scattered in a sclerotic background (Fig. 13), and the nuclear features are those of typical PTC. In a personally studied case, a 16-year-old female remains disease-free at 4½ years (Chan and Loo, 1990). This is a probably merely a morphological variant with no prognostic significance.

PTC with exuberant nodular fasciitis-like stroma

Exceptionally, PTC is associated with a nodular fasciitis-like stroma which is so abundant that the neoplastic nature of the lesion may be obscured (Fig. 14).

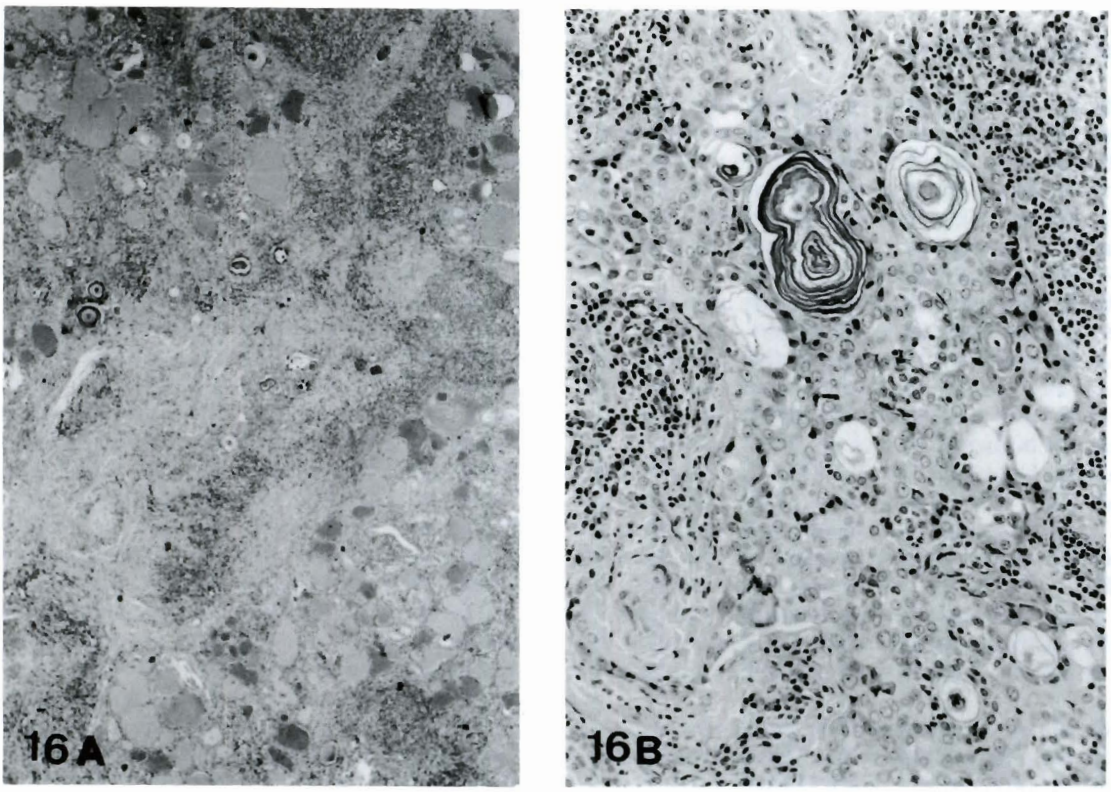

Fig. 16. Diffuse sclerosing variant. (A) Low power view showing diffuse sclerosis and heavy lymphocytic infiltration. Psammoma bodies are evident. × 30. (B) The tumour islands are often squamoid with many psammoma bodies. × 150. All H & E.

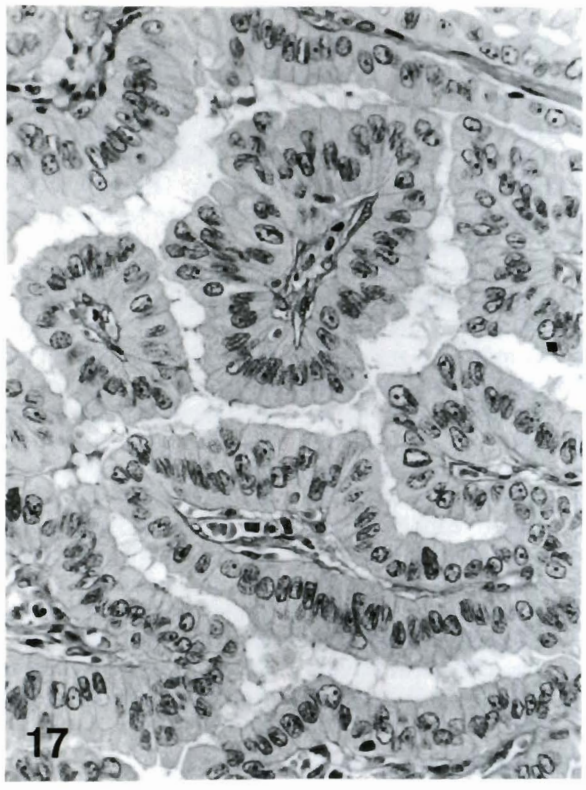

Fig. 17. Tall cell variant. Tall columnar cells with oxyphilic cytoplasm. The nuclei show characteristic grooving. H & E. × 300

The stroma is formed by short fascicles of spindle cells separated by variable amounts of myxoid matrix, collagen, extravasated red cells, lymphocytes and mast cells. An unusual feature is that the interaction between the stroma and PTC results in patterns reminiscent of fibroadenoma, phyllodes tumour or fibrocystic disease of the breast (Chan and Rosai, 1990). Again, this is probably merely a morphological variant.

Encapsulated variant

The encapsulated variant, which accounts for 4-14% of PTC, is enveloped by a fibrous capsule which may or may not be penetrated by tumour (Fig. 15) (Hazard, 1968; Franssila, 1973; Schroder et al., 1984a; Carcangiu et al., 1985c). The architectural feature is otherwise indistiguishable from conventional PTC, though those examples composed entirely of follicles may be difficult to distinguish from follicular adenoma or carcinoma. Intraglandular lymphatic spread may occur.

Lymph node metastasis occurs in 20-38% of cases, lower than that of classical PTC (Hazard, 1968; Schroder et al., 1984a; Carcangiu et al., 1985d). However, metastasis can develop even in the absence of capsular invasion. The prognosis is excellent; long-term follow-up shows no recurrence or development of further metastasis (Vickery, 1983; Schroder et al., 1984a; Evans, 1987). This might represent an early or slowly growing form of PTC.

Diffuse sclerosing variant

The diffuse sclerosing variant was first characterized by Vickery et al. in 1985, though illustrations of this entity can be traced back to 1952; a case which was misdiagnosed as thyroiditis with squamous metaplasia (Bullock et al., 1952; Chan, 1990). The 2 cases of PTC coexisting with «thyroiditis» reported by Crile and Fisher (1953) were probably also examples of this variant.

The diffuse sclerosing variant typically affects young adults and children (but occasionally old subjects), who have unilateral or bilateral swelling of the thyroid gland. The picture can mimic thyroiditis, particularly since some patients have raised anti-thyroglobulin and anti-microsomal antibodies (Chan et al., 1987; Soares et al., 1989). It accounts for 2-3% of all PTCs (Carcangiu et al., 1987; Chan et al., 1987; Soares et al., 1989). The studies from Italy and Portugal have shown this variant to be associated with a more aggressive course compared with classical PTC (Table 1). However, it is difficult to reconcile these findings with the favorable outcome of the probable examples of this variant as reported in the Japanese literature (Fujimoto et al., 1972; Kodama et al., 1986).

The excized thyroid shows diffuse replacement of one or both lobes by firm white tissue that is often gritty. Salient histological features include diffuse involvement, sclerosis, heavy lymphoplasmacytic infiltration and abundant psammoma bodies (Fig. 16). The residual thyroid follicles are normal or atrophic, and do not show the oxyphil changes as seen in Hashimoto's thryoiditis. The abundance of psammoma bodies provides the clue that one is not dealing with a simple case of thyroiditis. On careful examination, there are multiple small islands of tumour which may be difficult to recognize as being of papillary type because of extensive squamoid, squamous or mucoepidermoid metaplasia (Chan et al., 1987; Soares et al., 1989). The more typical papillae or follicles can be difficult to find. There is extensive lymphovascular permeation. S-100 protein-positive histiocytes are abundant (Chan et al., 1987; Gómez-Morales et al., 1989; Soares et al., 1989). We postulate that lymphovascular permeation early in the formation of tumour results in the diffuse growth pattern and a lack of dominant tumour mass (Chan et al., 1987). The metastatic deposits in lymph nodes are however not distinctive, and are the same as those of classical PTC.

Diffuse follicular variant

Sobrinho-Simoes et al. (1987) recently reported a diffuse follicular variant of PTC, but the article has not been published in full. This aggressive variant accounts for 2% of PTCs, and occurs in young patients (mean age 21.2 years). It is characterized by diffuse involvement of the whole thyroid without formation of discrete nodule, exclusive or predominant follicular growth pattern, and discrete or no fibrosis. Extrathyroid extension occurs in 12.5%, local recurrence in 0%, lymph node metastasis in 87.5% and distant metastasis (mainly pulmonary) in 100%. However, there is very good response to radioactive iodine treatment. Six of the 8 patients are alive 10-21 years after diagnosis, but three still have biochemical signs of persistent disease and one lung metastasis.

Tall cell variant

The tall cell variant was reported to be associated with a worse prognosis (Hawk and Hazard, 1976). This finding was confirmed by a recent study by Johnson et al. (1988), who found a higher incidence of extrathyroidal disease (42%), recurrence (58.3%), distant metastasis (16.7%) and mortality (25%) for the tall cell variant compared with conventional PTCs matched for age (corresponding figures being 0%, 8.3%, 0% and 0%). This variant can affect any age group, the mean age being 49.4 years. The cases reported as Hurthle cell- or mitochondrion-rich PTC by Sobrinho-Simoes et al. (1985, 1989) correspond closely to the tall cell variant.

The diagnostic criterion is presence of more than 30% tall cells, which are defined as cells with the height measuring at least twice the width (Fig. 17) (Johnson et al., 1988). The nuclei are the same as those of classical PTC and are often polarized to the lower half of the cells. The cytoplasm, which is plentiful, is oxyphilic to eosinophilic. These tumours are usually highly papilliferous (Hawk and Hazard, 1976).

Columnar cell carcinoma

Evans (1986) first coined the term «columnar cell carcinoma» for a distinctive thyroid carcinoma characterized by tall columnar cells and aggressive behaviour. Though some authors view this as a variant of PTC (LiVolsi, 1989; Rosai, 1989), I believe it represents a distinct entity because the nuclear features of PTC are lacking. However, further studies are required to clarify its relationship with PTC.

Four cases have been reported to date (Evans, 1986; Sobrinho-Simoes et al., 1988; Hui et al., 1990). They occur in patients aged 34 to 60 years. The tumour in 3 cases metastasized widely and caused death 20 months, 25 months and 5 years after diagnosis.

Histologically, there is a mixed papillary, complex gladular, microglandular and solid pattern, but the case reported by Sobrinho-Simoes et al. (1988) is purely papillary. The papillae and glands are lined by tall columnar cells with markedly pseudostratified oval to elongated chromatin-rich nuclei lacking ground-glass features (Fig. 18). The cells in the solid areas are often polygonal and smaller. Columnar cell carcinoma must be distinguished from the less lethal tall cell PTC. The former differs in having even taller cells, less abundant cytoplasm, non-oxyphilic cytoplasm, and more pseudostratified nuclei that are chromatin-rich.

Oxyphil (Hurthle, Pink) cell variant

Some PTCs are composed predominantly of oxyphilic cells with eosinophilic granular cytoplasm due to accu-

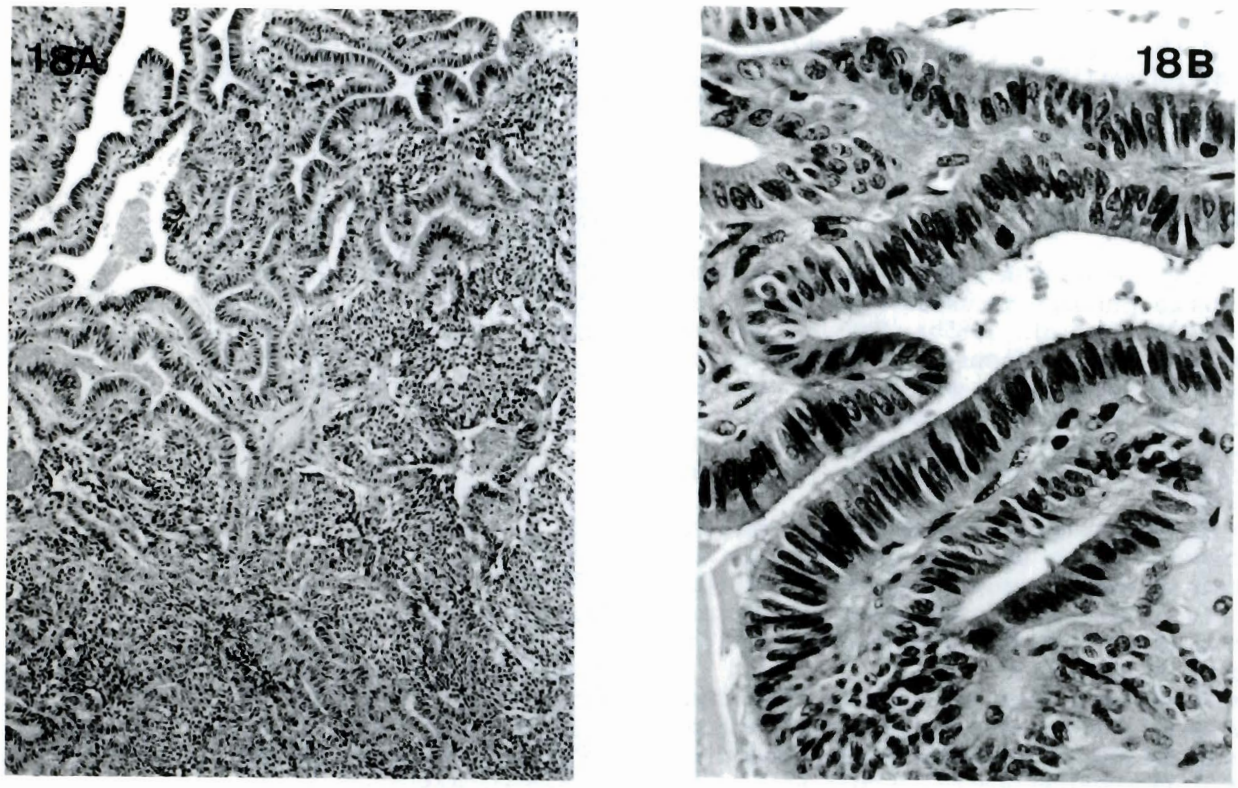

Fig. 18. Columnar cell carcinoma. (A) Complex papillotubular and solid pattern. The cells in the solid areas are smaller. × 75. (B) Papillae lined by tall columnar cells with pseudostratified hyperchromatic nuclei. × 300. All H&E.

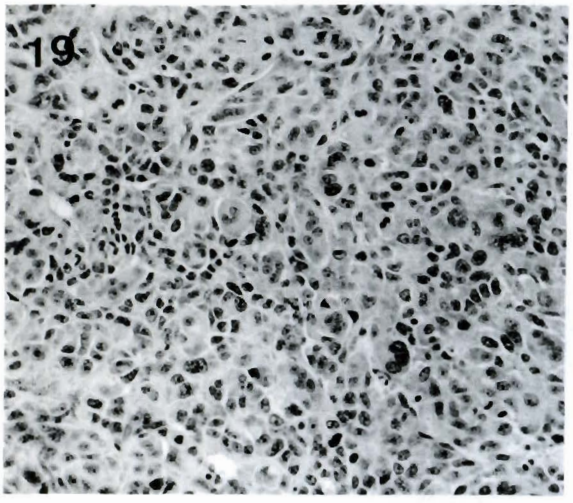

Fig. 19. Undifferentiated component in «dedifferentiated» PTC. Nuclear anaplasia is evident. H&E. × 150

mulation of mitochondria (Fig. 9a,b) (Hazard, 1968). Oxyphilic cells can undergo partial or total cytoplasmic clearing as a result of ballooning of the mitochondria (Fig. 9c) (Dickersin et al., 1980). The nuclei are no different from those of classical PTC, but they appear less crowded because of the abundance of cytoplasm.

The study from the Armed Forces Institute of Pathology (31 cases), in which the tumours are defined as those containing more than 50% oxyphilic cells, concludes that the behaviour is comparable to conven-

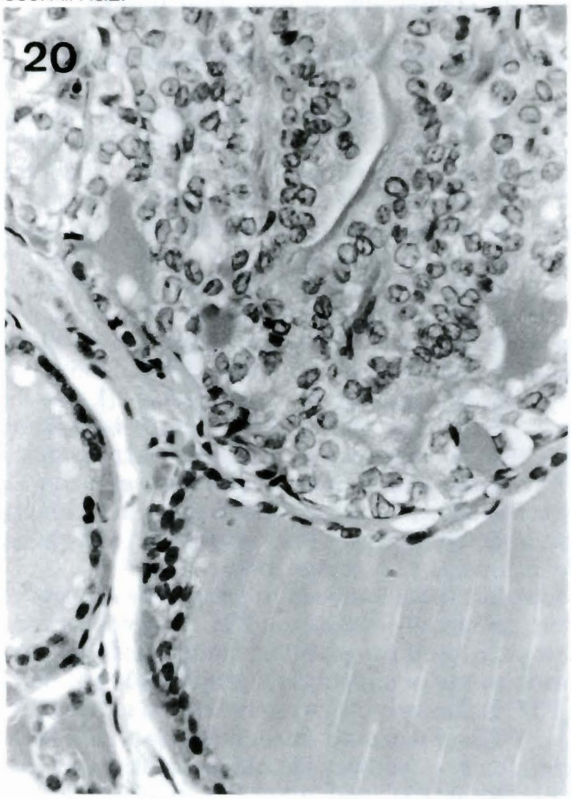

Fig. 20. Latent PTC. Note sharp transition of the neoplastic follicles (left) with the normal follicles (right). The nuclei in the neoplastic component are pale and overlapping with some collapsed forms. H&E. × 300

tional PTC (Beckner and Oertel, 1987). Tscholl-Ducommun and Hedinger (1982) have reported similar findings. It is therefore important not to equate this oxyphil/pink cell variant with the more agressive tall cell variant (LiVolsi, 1989).

«Dedifferentiated» PTC

PTC may coexist with undifferentiated or poorly differentiated (insular) carcinoma (Carcangiu et al., 1984; Carcangiu et al., 1985b). Probably the well differentiated PTC transforms into the poorly differentiated component, similar to what has been well documented in lymphomas, liposarcomas and chondrosarcomas. Once a «dedifferentiated» component is present, the prognosis is greatly worsened (Lindsay, 1969; Spires et al., 1988).

The undifferentiated component is characterized by a high degree of nuclear atypia and pleomorphism, and sometimes sarcomatoid growth pattern (Fig. 19) (Carcangiu et al., 1985b). Poorly differentiated carcinoma is characterized by islands of relatively small dark cells with interspersed microfollicles.

It is of interest that not only is the undifferentiated portion found to be aneuploid, but the well differentiated PTC component is also aneuploid (Galera-Davidson et al., 1987). Since conventional PTC is rarely aneuploid, it is likely that aneuploid PTCs are more unstable and prone to be complicated by high grade tumour.

Occult PTC, latent PTC and microcarcinoma

There is much confusion in the literature on occult PTC. The term has often been used inappropriately to refer to PTC smaller than 1 or 1.5 cm. The revised W.H.O. classification has rectified this by recommending the term «papillary microcarcinoma» for tumours smaller than 1 cm (Hedinger et al., 1988). The significance of small size lies in the excellent prognosis (Ito et al., 1980; McConahey et al., 1986). However, lymph node metastasis can occur no matter how small the tumour is (Sampson et al., 1971; Chen, 1989). Very rarely, distant metastasis can develop (Laskin and James, 1983; Strate et al., 1984). Kasai and Sakamoto (1987) further suggest that papillary microcarcinomas can be subgrouped as minute (0-5 mm) and tiny (5-10 mm) carcinomas, because of differences in incidence of lymph node metastasis (13% versus 59%) and extrathyroidal extension (3% versus 10%).

However, there is a need to retain a descriptive term for the incidentally discovered PTC. Employing the terminology as used for prostatic cancer, patients having metastatic tumour and subsequently found to be harbouring PTC in the thyroid can be considered to have «occult PTC». PTCs discovered incidentally in thyroidectomy specimens or at autopsy should be considered «latent PTCs». Occult PTC and latent PTC may or may not be microcarcinoma.

Varying prevalence rates of latent PTC have been reported in different countries (Table 2), the highest

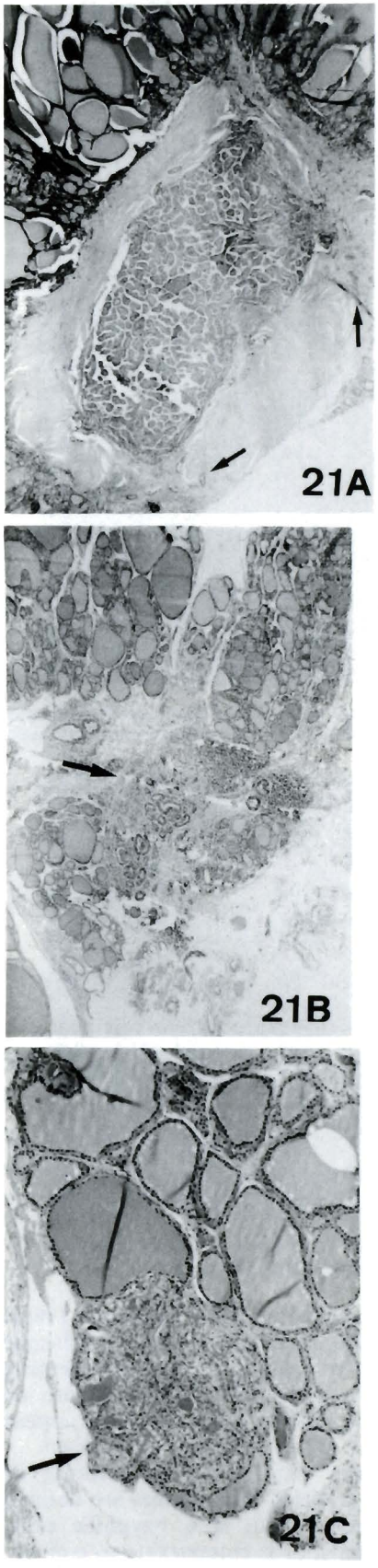

Fig. 21. Latent PTC. (A) This tumour is papillary and sclerotic. The invasive elements are indicated by arrows. × 20. (B) Tumour formed predominantly by follicles. Sclerosis is present. × 20 (C) Circumscribed type without sclerosis. Same tumour as shown in Fig. 20. × 50. All H & E.

Table 1. Diffuse sclerosing variant versus conventional PTC

	ITALY SERIES (Carcangiu et al., 1987)		PORTUGAL SERIES (Soares et al., 1989)	
	DSV	PTC	DSV	PTC
Number of cases	8	233	10	259
Mean age at diagnosis	30.2 years	41.3 years	34.7 years	42.3 years
Delay in diagnosis	3 years	1 year	NA	NA
Extrathyroid invasion	NA	NA	30%	18.1%
Lymph node involvement	100%	54.3%	100%	38.6%
Distant metastasis	37.5%	14.1%	50%	14.3%
Disease-free survival	25%	77.6%	NA	NA
Mortality rate	NA	NA	10.0%	8.6%

DSV = Diffuse sclerosing variant; PTC = Conventional papillary carcinoma; NA = not available

Table 2. Reported prevalence rates of latent thyroid carcinoma in autopsy series

COUNTRY	AUTHORS	PREVALENCE
Finland, Helsinki	Harach et al., 1985	35.6%
Japan, Hiroshima-Nagasaki	Funkunaga and Yatani, 1975; Sampson, 1977	17.9-28.4%
Hawaii (Japanese)	Funkunaga and Lockett, 1971	24.2%
USA, Michigan	Ludwig and Nishiyama, 1976	13.0%
Argentina, La Plata	Ottino et al., 1989	11.0%
Poland, Gliwice	Funkunaga and Yatani, 1975	9.1%
Sweden, Malmo	Bondeson and Ljungberg, 1981	8.6%
Portugal, Oporto	Sobrinho-Simoes et al., 1979	6.5%
West Germany, Hannover	Lang et al., 1988	6.2%
Canada, Ontario	Fukunaga and Yatani, 1975	6.0%
USA, Minnesota	Sampson, 1977	5.7%
Colombia, Cali-Medellin	Fukunaga and Yatani, 1975	5.6%
Hungary	Balazs and Krasnai, 1974 (quoted by Sampson, 1977)	4.5%
Chile, Santiago	Arellano and Ibarra, 1984	3.6%
Switzerland, Basel	Heitz et al. (quoted by Sampson, 1977)	1.2%

rates having been reported in Finland and Japan. Some of the differences are at least attributable to different diagnostic criteria and techniques of examination. Latent PTC can occur in children or even newborns (Franssila and Harach, 1986; Mills and Allen, 1988). It appears that most latent PTCs appear after puberty, and the prevalance does not increase with age thereafter (Sampson, 1977; Franssila and Harach, 1986; Komorowski and Hanson, 1988). Therefore it appears that the vast majority of these small latent tumours remain dormant and do not grow to clinically apparent disease (Vickery et al., 1985; Lang et al., 1988). The lack of female predominance in latent PTC and the dissociation between the prevalence rates of latent and clinical thyroid carcinoma in various countries provide further support the latent PTCs are biologically different from the clinically manifest PTCs (Sampson, 1977). No further treatment is required if it represents an incidental finding in a lobectomy or thyroidectomy specimen.

The latent PTCs vary in size and morphology, most

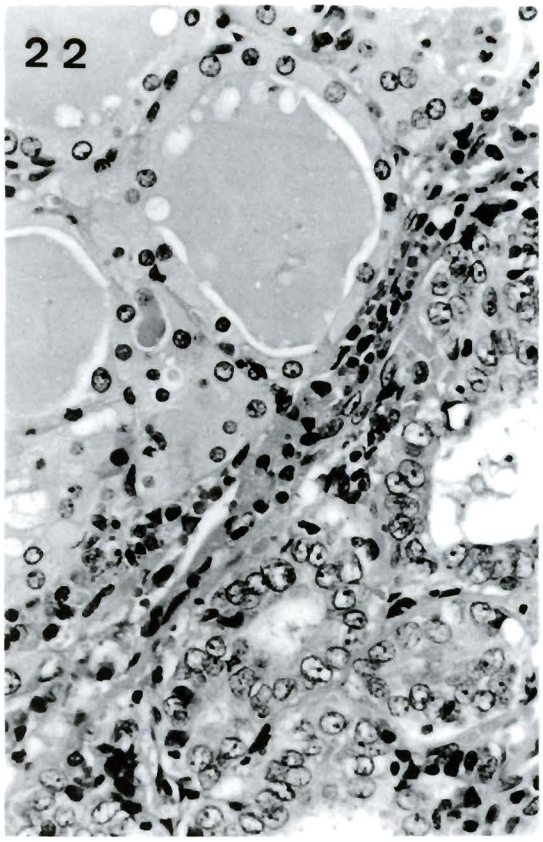

Fig. 22. Abrupt difference in nuclear morphology between the PTC (right lower corner) and the non-neoplastic component involved by Hashimoto's thyroiditis (left upper corner). In the Hashimoto's component, some nuclei show clearing but there is no overlapping. In the PTC, the nuclei are larger, pale to clear and overlapping, with occasional grooves. H & E. × 300

being tiny. Most are predominantly follicular in pattern, and they are recognized by the typical nuclear morphology and their sharp transition with the surroundings (Fig. 20). One type is invasive and often associated with considerable sclerosis, hence the popular term «occult sclerosing PTC» (Fig. 21a,b). The other type is circumscribed, with aggregates of neoplastic follicles apparently in harmony with the surrounding follicles; there is minimal or no sclerosis (Fig. 21c). Rare ones are encapsulated (Schroder et al., 1984b). The invasive type is more frequently associated with lymph node metastasis than the circumscribed type (Lang et al., 1988).

Conclusion: Making a diagnosis of PTC

The diagnosis of PTC rests on a constellation of features, not all of which may be present in any one tumour (Hedinger et al., 1989). There is no single feature which is pathognomonic, though there is a tendency to place more emphasis on the nuclear details. Obviously, in a frankly invasive thyroid tumour with numerous papillae, sclerosis and psammoma bodies, one would have no hesitation in calling it PTC even though the nuclei are not the most typical (subject of course to confirmation by thyroglobulin staining in atypical cases). However, in a circumscribed or encapsulated and purely follicular lesion with some ground-glass nuclei, in which the differential diagnosis is between follicular adenoma and follicular variant of PTC, one has to apply more stringent criteria, that is, typical nuclear features have to be present for a firm diagnosis of PTC. More extensive sampling and examining deeper cuts may help in looking for psammoma bodies and rare papillae that may be present. The distinction may indeed be very difficult. However, if there is any uncertainty, it is preferable to state the element of doubt in the diagnosis or simply call it a follicular adenoma. Even if the tumour is a PTC, the patient will require no further treatment since encapsulated PTC is associated with an excellent prognosis (Vickery, 1983; Carcangiu et al., 1985c).

Another characteristic feature of PTC is the abrupt change between the neoplastic component and the surrounding normal or reactive follicles. If one sees a group of follicles with clear nuclei suspicious of PTC, gradual merging with the surrounding argues strongly against a diagnosis of PTC. If the suspicious follicles are discrete and differ sharply in nuclear morphology from the surrounding follicles (which usually possess dark round nuclei), a diagnosis of PTC is favoured (Fig. 22).

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