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REVIEW ARTICLE

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Carcinomas of the breast with endocrine differentiation: a review

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Abstract The occurrence of endocrine differentiation in some mammary carcinomas seems well-established, but pathologists continue to debate its significance. Contemporary thinking suggests that endocrine tumours of the breast do not constitute a single clinicopathological entity with a consistent histogenesis but rather that endocrine differentiation represents a pathway of neoplastic development available to a range of breast cancers. This pattern of differentiation occurs in tumours with vastly different morphological appearances, such as: ductal carcinoma in situ, mucinous carcinoma, a variant of lobular carcinoma, and low grade invasive ductal carcinoma. Although such tumours share some characteristics with intestinal endocrine neoplasms, the typical pattern of intestinal carcinoid virtually never occurs in mammary lesions. Conventional microscopy permits the diagnosis in most cases. Specialized techniques (histochemistry, immunohistochemistry, and electron microscopy) can serve as the basis for diagnosis in the absence of the appropriate morphological features. Although the system of nomenclature proposed by the World Health Organization for use with endocrine tumours in other organs can be used for endocrine tumours of the breast, only a minority of lesions will fit the established criteria. Most lesions are classifiable in the conventional categories of mammary carcinomas. No special prognostic significance is attached to these tumours at the present time.

Key words Breast carcinoma · Neuroendocrine Carcinoid

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Introduction

In 1963, Feyter and Hartmann [20] described two breast carcinomas that displayed a carcinoid growth pattern ("carcinoide Wuchsform"), and on this basis the authors suggested that the tumours might posses a degree of (neuro) endocrine differentiation. Their suggestion met with little reaction until 1977, when Cubilla and Woodruff [10] ignited a controversy by naming the tumours "carcinoids". Strident voices raised objections immediately, and the ensuing decade of bickering produced a disorderly literature that leaves most readers bewildered. Some points of contention probably arose because Cubilla and Woodruff did not provide sufficiently explicit guidance for the recognition of endocrine tumours. The authors advised that: "Histological suspicion of carcinoid of the breast should be confirmed by a positive argyrophil reaction and ultrastructural evidence of small, opaque, membrane-bound neurosecretory granules." The writers did not, however, describe or illustrate the full range of morphological patterns that raise "histological suspicion", nor did they discuss the limitations inherent in the performance and interpretation of either silver precipitation techniques or ultrastructural studies of dense core granules. Subsequent investigations have addressed these points, but sceptics continue to point out fundamental differences between mammary and intestinal carcinoid tumours. The latter arise from indigenous endocrine cells and form repetitive histological patterns that do not overlap with those of other types of carcinoma except in unusual examples. Endocrine tumours of the breast probably do not arise from pre-existing endocrine cells, since investigators have observed them only rarely and then only in small numbers [2, 3, 34, 44]. Furthermore, mammary endocrine tumours do not grow with unique histological characteristics; instead the neoplasms often resemble other types of breast cancer and virtually never duplicate the appearances of intestinal or pulmonary carcinoid tumours.

It seems fruitless to continue viewing endocrine tumours of the breast in the same way that one regards tra-

ditional carcinoid tumours. We propose that endocrine differentiation of breast tumours does not indicate an origin from pre-existing endocrine cells but rather one expression of the differentiation potential inherent in several conventional types of breast cancer. Endocrine features, much like nuclear atypia or mitotic figures, represent an aspect of some tumours that better serves to describe the neoplasms than to unite them as a single, diagnostic entity. These ideas seem to underlie the comments of Rosen and Oberman [43]: "neoplasms with argyrophilic granules do not constitute a specific histopathologic category of female mammary carcinoma. These are variants of mammary adenocarcinoma in which neuroendocrine traits constitute structural and/or biochemical metaplasia presumed to result from altered gene expression or 'genomic depression' as a consequence of neoplastic transformation".

Using this point of view, we reviewed the literature concerning endocrine tumours of the mammary gland and found that most disagreements revolve around four inter-related questions:

1. What histological findings suggest the presence of endocrine differentiation?
2. What specialized studies provide convincing evidence of endocrine differentiation?
3. Does the presence of endocrine features carry prognostic implications?
4. What diagnostic term seems most appropriate for tumours with endocrine traits?

By considering each question in turn we hope to achieve consensus and to create order amid a tangled body of information.

1. What histological findings suggest the presence of endocrine differentiation?

Endocrine differentiation arises in the setting of several types of breast cancer, so no single description can suit all examples of the phenomenon. Three characteristics, however, occur with sufficient frequency that their presence should bring to mind the possibility of endocrine differentiation. First, most endocrine tumours, with the exception of small cell undifferentiated carcinomas, look low-grade; second, the nuclei at the periphery of the cell aggregates show a tendency to form palisades; and third, the stroma in the vicinity of the tumour often consists of dense, sparsely cellular, collagen. In-situ endocrine carcinomas form a homogeneous group with consistent histological characteristics; but the invasive tumours vary greatly in appearance, and the specific morphological details depend on the nature of the underlying neoplasm. Papotti et al. [38] have catalogued seven patterns (Types A–G) of invasive endocrine carcinomas; four varieties (Types G, B, F, and A) encompass the range of morphologies displayed by most endocrine tumours.

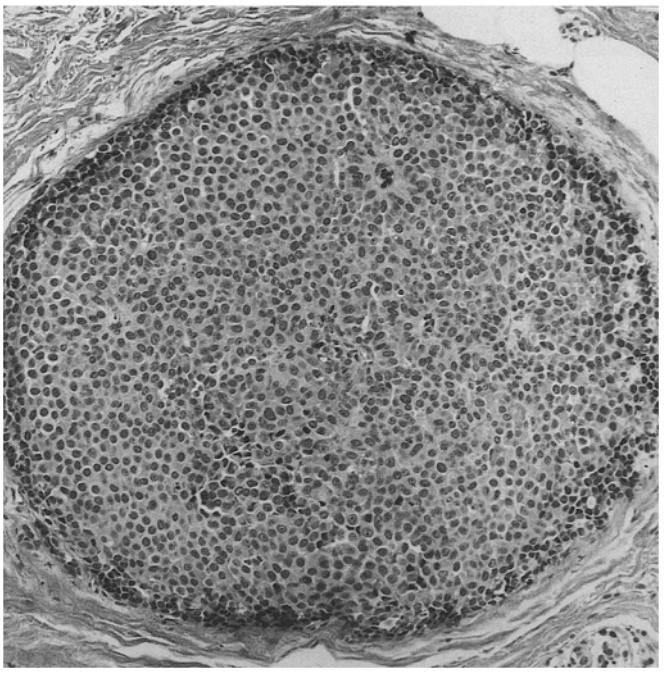

Fig. 1 Intraductal carcinoma with neuroendocrine differentiation. A solid proliferation of medium size mildly atypical cells fills the duct

Ductal carcinoma in-situ

The existence of intraductal endocrine carcinoma, growing either in a pure form or as the dominant component of an invasive breast cancer, was first recorded by Azzopardi in 1982 [1]. His observations and descriptions were later expanded by his colleagues [9] and by us [26]. These writers consistently recorded the following morphological characteristics: polypoid growth pattern, cellular homogeneity, low-grade cytological atypia, cytoplasmic abundance and eosinophilia, and a hyaline appearance of the stroma. The tumours usually grow as solid and papillary masses that fill and expand large ducts, thereby creating smoothly contoured nodules of tumour cells (Fig. 1). Slender collagen bundles and delicate capillaries course through the nests and support a population of monotonous epithelial cells. Most are cuboidal or columnar, but they can become elongate or even spindle shaped. The nuclei look uniform, round or oval, and contain punctate chromatin and nucleoli of modest size (Fig. 2). The nuclei abutting the stroma often align themselves in a parallel array to produce a palisade. Most cells have abundant cytoplasm that often demonstrates a fine, eosinophilic granularity. If the cells produce mucin, the cytoplasm looks amphophilic; and if abundant, the mucin can accumulate so as to displace and indent the nucleus, creating a signet ring cell. The cells can form a few pseudorosettes and, rarely, true rosettes, but the formation of spaces does not stand out as a prominent feature. Mitotic figures are frequently present. The stroma within and surrounding the nodules often displays extensive hyalinization and simulates amyloid.

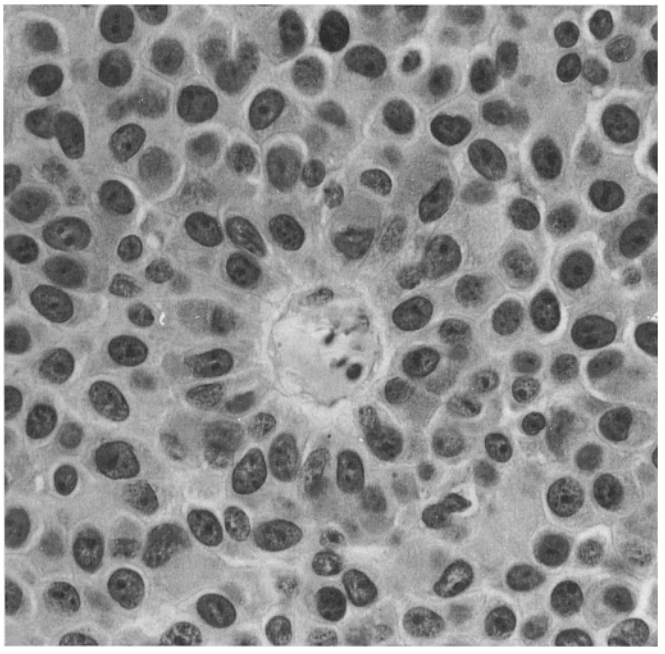

Fig. 2 A perivascular pseudorosette in DCIS with neuroendocrine differentiation

Two clinically important diagnostic difficulties arise as the consequence of these characteristics. First, one might have difficulty appreciating the tumour's malignant nature. Cases with many spindle cells and minimal cytological atypia bear a striking resemblance to examples of ductal-type epithelial hyperplasia (epitheliosis), and those growing within large ducts and containing prominent stroma look very much like papillomas. Features that help to exclude these benign lesions from consideration include: peripheral palisading of the nuclei, formation of pseudorosettes, accumulation of intracellular mucin, and the demonstration of endocrine features by silver precipitation or immunohistochemical methods. Second, the evaluation of invasion almost always poses a problem. The presence of a desmoplastic stromal reaction serves as the most reliable evidence of invasion, but if the tumour produces mucin, its presence in the stroma probably also provides the same evidence, at least by current criteria. In the absence of stromal changes, one can evaluate by low magnification the appearance of the tumour. Large, irregular nests of cells, surpassing the size or shape expected for mammary ducts or acini, should suggest the presence of invasion: but these findings alone may not suffice to make a confident diagnosis.

Small cell undifferentiated carcinoma (Type G)

Small cell undifferentiated carcinoma represents both the most distinctive and the least common type of breast carcinoma showing endocrine differentiation. Pathologists have reported seven examples of this tumour [24, 39, 51, 53]. The tumours resemble either small cell undifferentiated carcinomas of the lung or Merkel cell carcinomas of the skin. Like their counterparts in other organs, the breast tumours grow as sheets, clusters, or trabecula and sometimes from aggregates that resemble the alveolar clumps seen in some lobular carcinomas. The cells appear small, contain only a scant amount of cytoplasm and a hyperchromatic nucleus that lacks a nucleolus (Fig. 3). Mitotic figures average about one per high power field. The presence of necrosis, vascular invasion, and the Azzopardi phenomenon completes the resemblance to pulmonary small cell carcinomas. Papotti and co-workers [39] observed intraductal growth of malignant cells in the four cases in their group, leaving little doubt that these tumours arose in the breast. Special studies revealed dense core granules in four cases, chromogranin A in two, and Grimelius positive cells in two. Special investigations seem superfluous, though, since the histological and cytological features are distinctive.

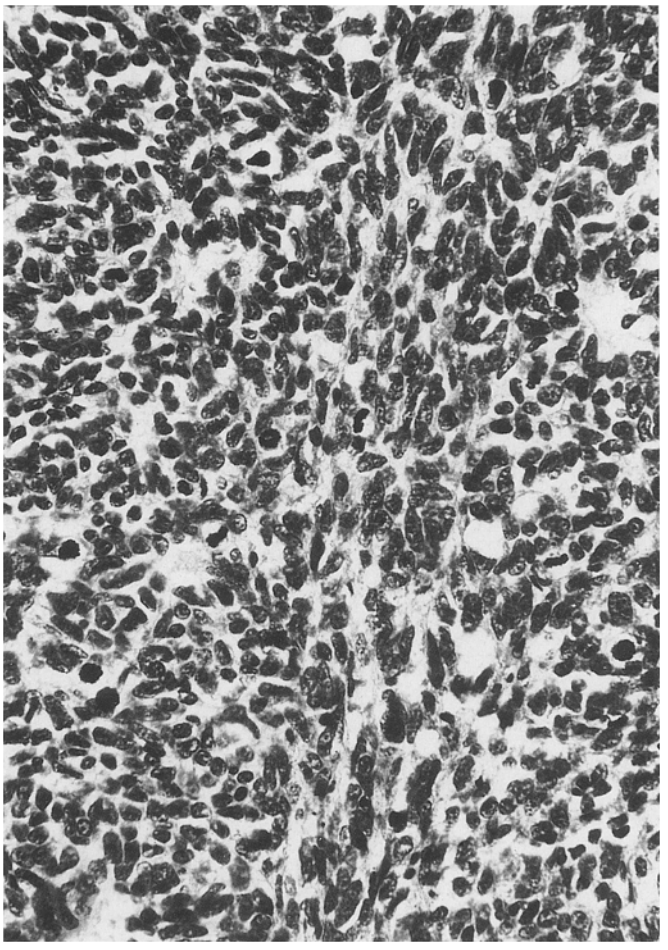

Fig. 3 Small cell carcinoma of the breast. These tumours resemble small cell carcinoma of the lung of Merkel cell carcinoma of the skin

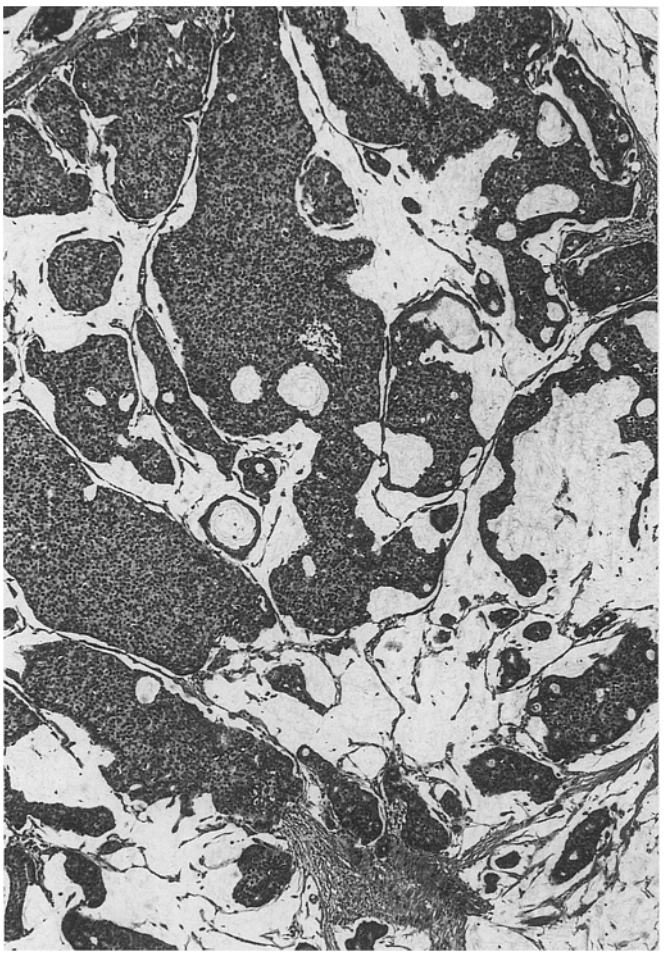

Fig. 4 Mucinous carcinoma of the neuroendocrine type. Large nests and islands of cells separated from the stroma by mucin

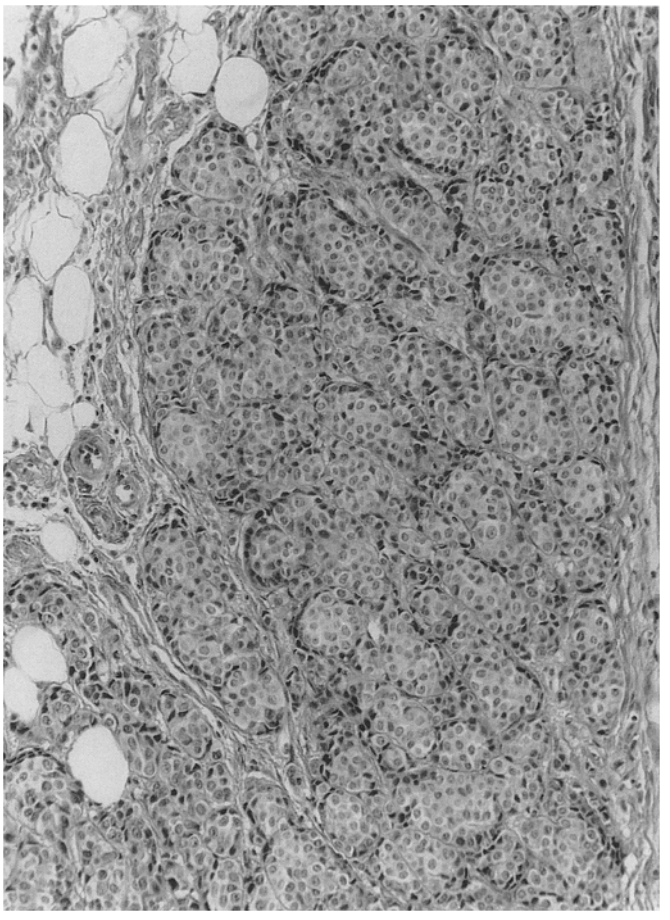

Fig. 5 Alveolar type of lobular carcinoma. Round nest of cells confer a distinctive appearance to this variant of infiltrating lobular carcinoma

Cellular mucinous carcinoma (Type B)

Fisher et al. [21] and Capella et al. [5] first reported the presence of argyrophilia in a large proportion of mucinous breast cancers, and the latter authors appreciated a correlation between certain histological characteristics and argyrophilia. Capella et al. [5] separated mucinous carcinomas into two types (type A and type B) and recognized a third transitional group displaying a mixture of characteristics. The type A tumours contain a higher percentage of mucin and a smaller number of cells, and the cells form cords or rings but not clumps (smoothly contoured aggregates). The nuclei appear slightly pleomorphic, and the cytoplasm looks dense and lacks granularity. The writers could detect intracellular mucin only with the aid of mucin stains. None of these tumours displayed argyrophilia, and the single case studied ultrastructurally lacked dense core granules. Type B tumours, in contrast, contain less mucin, and the cells form insular, cribriform, or solid patterns (Fig. 4). The nuclei appear uniform and the cytoplasm eosinophilic and finely granular. About one-third of the tumours contained abundant intracellular mucin that occasionally formed signet ring cells. Seventy percent of the cases demonstrated positive silver staining, and all of the five cases examined with the electron microscope contained dense core granules. Coady and co-workers [8] and Fetisoff et al. [19] described similar findings, and our own observations mirror these reports. Coady et al. [8] also discovered that tumours in the first group lack S-100 protein, whereas the type B tumours usually stain for the molecule and always contain carcinoembryonic antigen (CEA). We support these writers in their proposal that the type B pattern usually represents mucinous carcinoma with endocrine differentiation.

Lobular carcinoma, alveolar type (Type F)

Infiltrating lobular carcinomas of the conventional type do not display histological characteristics suggesting endocrine differentiation; but one subtype, the "alveolar" variant, might bring this possibility to mind. Fechner [16] first identified this variant, which he designated

"confluent". Of the six cases he described, three grew solely as confluent nests in a hyalinized, collagenous stroma. Cubilla and Woodruff [10] wondered if some of these cases might display endocrine qualities. Martinez and Azzopardi [27] analysed variants of infiltrating lobular carcinoma and appreciated two types of alveolar pattern: "an alveolar pattern is used to describe a more-or-less globular aggregate of 20 or more cells, as seen in two planes, the cells being similar to those seen in other parts of the tumour. The term 'loose alveolar' refers to this pattern when the cells, as is often the case, are loosely arranged as if lacking significant cohesion. A cohesive alveolar pattern is self-explanatory" (Fig. 5). Most subsequent writers [12, 35, 48] have not maintained this distinction. In fact, the photographs in each of the latter three publications illustrate tumours with the cohesive alveolar pattern. Shousha et al. [48] and du Toit et al. [14] found that most examples of this tumour contained high levels of oestrogen receptors, and Nesland et al. [35] discovered that eleven of thirteen cases of lobular carcinoma of the alveolar type showed endocrine differentiation. These findings hint at the possibility that this tumour represents a distinct variety of carcinoma with endocrine qualities.

Low-grade insular ductal carcinoma (Type A)

Of the types of mammary endocrine tumours, this one probably occurs most frequently and simulates intestinal carcinoids most closely (Fig. 6). It is used to illustrate endocrine features by authors such as Azzopardi et al. ([1], Figs. 1–5), Page et al. ([36], Figs. 15.9 and 15.10), and Tavassoli ([50], Fig. 9.23). The neoplasms grow as well-defined, compact nodules composed of blunt, irregular nests or sheets of cells (Fig. 6). The aggregates fit together closely, leaving scant intervening collagenous or hyalin stroma that often contains capillaries. The tumour cells appear monotonous and cohesive; most are polygonal, but others grow as long, slender, spindle cells. The cytoplasm usually displays fine granularity and eosinophilia. The nuclei are round or oval and vary only slightly, and the nucleoli appear inconspicuous. Around the perimeter of the cell nests, the nuclei align themselves to create a palisade. One can usually find a few mitotic figures, but they look normal. Necrosis occurs in only a minority of cases.

Although the five preceding categories encompass the majority of mammary endocrine tumours, other patterns do occur. Some neoplasms seem to span two categories; in fact, Papotti et al. [38] recognized a specific group of tumours (Type C) that combine features of both the mucinous and insular types. Other unusual endocrine tumours demonstrate features that overlap with conventional, non-endocrine breast cancers. This bridging of categories need not invalidate either the classification schema or the concept of endocrine differentiation, for no system of classification successfully encompasses every variety of neoplasm. The occasional ambiguous case should remind the observer that these categories serve only as framework to help pathologists organize a wide array of histological features and solve diagnostic difficulties.

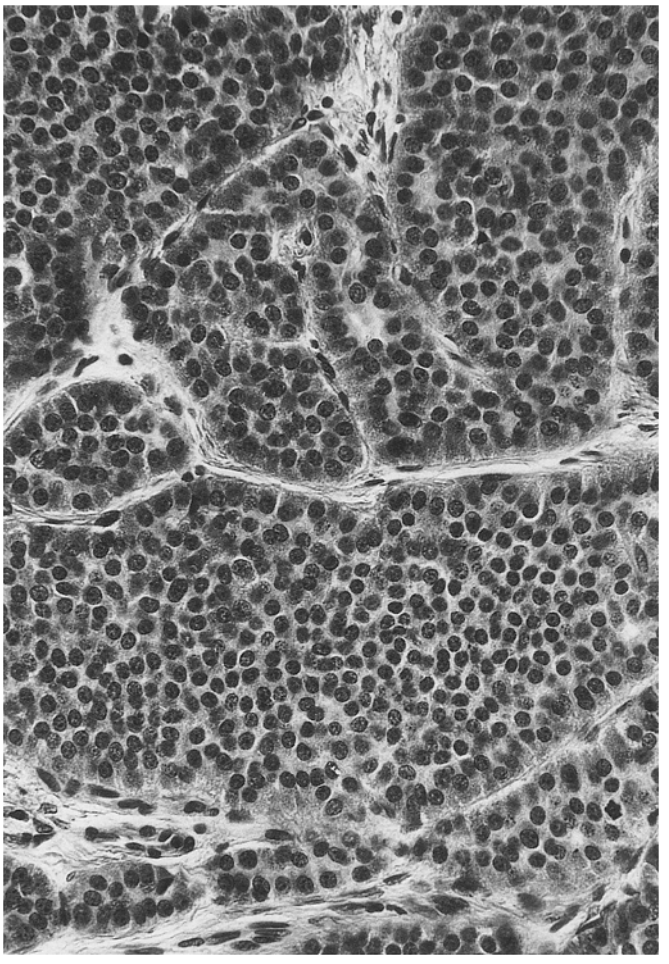

Fig. 6 Insular type of invasive ductal carcinoma. Large islands of tumour cells with sharp interlocking contours separated by scant stroma. These mammary tumours closely resemble conventional carcinoids

2. What specialized studies provide convincing evidence of neuroendocrine differentiation?

In 1977, when Cubilla and Woodruff [10] published their study, pathologists had only two specialized studies at their disposal: silver precipitation staining, and electron microscopy. The interpretation of both seemed uncomplicated; positive results indicated the presence of endocrine molecules. Subsequent experience, however, has revealed that molecules not usually considered endocrine can also give rise to positive results with both methods of study. For instance, some silver precipitation techniques, such as the Sevier-Munger [4, 7] and possibly the Churukian-Schenk [28] methods, lead to a positive reaction in the apical cytoplasm of cells in the lactating

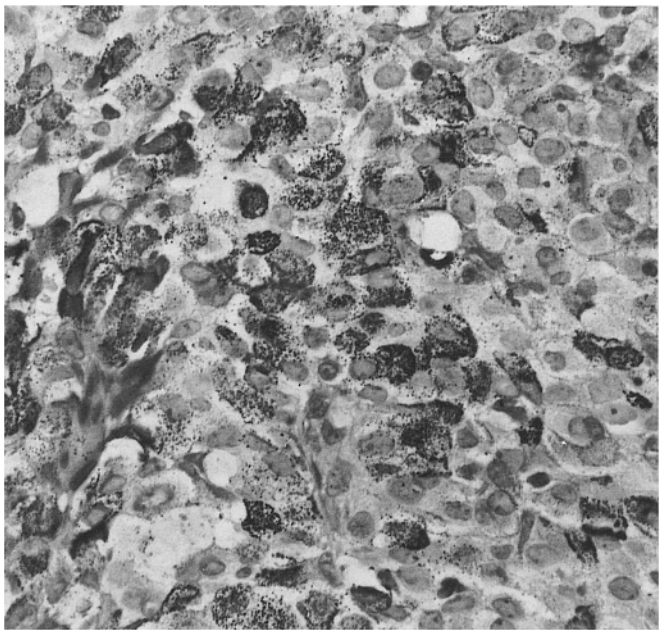

Fig. 7 Positive Grimelius stain in a carcinoma of the breast with neuroendocrine differentiation. There is intense granular cytoplasmic staining

breast. The phosphate groups in casein molecules probably precipitate the silver. The Grimelius method, on the other hand, apparently does not permit this reaction to take place; and so most investigators regard it as the silver precipitation technique of choice for the evaluation of endocrine differentiation (Fig. 7). Ultrastructural studies face similar difficulties. Dense-core granules occur in normal breast epithelial cells during resting periods [15, 18], pregnancy, and lactation [17, 18]. Most occupy the subluminal apical cytoplasm and fail to show either uranaffin or argyrophil reactivity. Observers do not regard granules like these as endocrine in nature, but rather as indicative of protein secretion [6, 23]. Genuine endocrine granules permeate the cytoplasm, sometimes clustering at the cell's vascular pole; they give a positive result with both uranaffin and argyrophil techniques [5, 23, 36, 49]; and they do not contain lactalbumin [6].

Contemporary investigators have turned to immunohistochemical techniques to search for evidence of endocrine differentiation in other ways. Like the experience with silver precipitation methods and electron microscopy, though, early immunohistochemical studies generated some misleading information. One problem arose because of contamination of an antiserum directed against alpha-lactalbumin. The reagent reacted with strongly argyrophilic breast carcinomas [7] suggesting that lactalbumin secretion, rather than endocrine differentiation, explains the presence of argyrophilic dense-core granules. Absorption of the contaminant abolished the staining [4, 25], and it therefore seems unlikely that production of lactalbumin accounts for the argyrophilia of breast cancers. Other confusions arose because of incomplete understanding of the specificity of proposed "neuroendocrine markers". For example, in 1985 Monaghan and Roberts [29] chose neuron specific enolase (NSE) as an indicator of endocrine differentiation because of "its known specificity for amine precursor uptake and deamination (APUD) cells". Their study, as well as others [32, 33], demonstrated the enzyme in at least 25% of unselected breast cancers, and other investigations showed its wide distribution in neural and non-neural tissue [22, 52]. In the light of these results, one probably should not accept the presence of neuron specific enolase as a specific marker of endocrine differentiation. In fact, Tavassoli [50] states "in my experience, however, NSE does not appear to be a specific marker for anything."

According to current thinking, the presence of two structural molecules, synaptophysin and chromogranin, does provide secure evidence of endocrine differentiation. Synaptophysin localizes to the membranes surrounding small, clear vesicles that probably represent pre-synaptic vesicles [30]. The chromogranins form a family of proteins that includes at least three members: types A, B, and C [41]. Endocrine breast cancers can synthesize either type A or type B; tumours producing only the latter tend to occur in postmenopausal women and pursue an indolent clinical course [2, 46]. Both types of chromogranin contribute to the matrix of dense core granules [2, 6, 37, 46] and probably give rise to the granules' argyrophilia [2, 3, 6, 37, 41]. In fact, Capella et al. [6] imply that dense core granules gave positive reactions with both the Grimelius technique and immunohistochemical staining for chromogranin in all three of the cases they studied thoroughly. These findings strike us as conclusive, and we see little reason for continuing debate concerning this topic. Each specialized study (Grimelius staining, electron microscopy, and chromogranin immunohistochemistry) requires care in its application and interpretation; but we believe that when used properly the techniques provide reliable evidence for the presence of peptide-containing granules, which most observers accept as a manifestation of endocrine differentiation.

As a final point, we caution that one cannot use the results of specialized studies to make the diagnosis of endocrine differentiation in the absence of the appropriate histological findings. Although Cubilla and Woodruff [10] never even hinted that one might do so, a few investigators have tried. Six publications describe the results of Grimelius staining of unselected breast tumours [1, 19, 32, 37, 46, 51], and they report frequencies from 3% to 21%. In two series [32, 46], most of the Grimelius-positive tumours displayed other evidence of endocrine differentiation; but in the other four groups, positive tumours included conventional ductal and lobular carcinomas as well as specialized carcinomas. Nesland et al. [31] performed electron microscopy on a group of 450 unselected carcinomas and found dense core granules in 22 cases. One tumour had the characteristics of an endocrine tumour, but the remaining 21 examples represented conventional carcinomas. We believe this evidence points to a clear conclusion: the recognition of endocrine differentiation begins with an evaluation of the histologi-

cal characteristics, and one should turn to specialized studies only to evaluate histologically suspect cases.

3. Does the presence of endocrine features carry prognostic implications?

Of the five types of breast tumours commonly displaying endocrine differentiation, the literature contains prognostic information concerning only one: small cell undifferentiated carcinoma. The seven case reports each recount the patient's history, and five of the seven patients died in 15 months or fewer. Despite the small number of the cases, the similarity between the clinical courses of these mammary tumours and their pulmonary counterparts indicates that this type of breast tumour carries an especially dire prognosis.

One can find little to say about the prognosis of the four remaining major types of endocrine tumours. Cross et al. [9] and Azzopardi et al. [1] described sixteen cases of exclusively or predominantly intraductal endocrine carcinoma, but the authors offered no follow-up information. A similar situation pertains to the reports of mucinous endocrine tumours by Capella et al. [5] and Coady et al. [8], but two other studies include limited survival information. Rasmussen et al. [40] failed to demonstrate a difference in the natural history of endocrine mucinous carcinomas compared with conventional mucinous tumours, but Cubilla et al. [11] claimed to show a less favourable prognosis for the endocrine variants. Both groups used a broad definition of mucinous carcinoma, and the design of both studies raises questions; as a result we regard their conclusions as provisional. Only one publication documents endocrine features in alveolar variants of lobular carcinomas [35], but once again the clinical information proves difficult to interpret. Other groups have studied the natural history of the alveolar type of lobular carcinoma without documenting its endocrine nature. Based on limited information, Nesland et al. [35] and Shousha et al. [48] believe that these tumours carry a more favourable prognosis than conventional infiltrating lobular carcinomas. The survival data of DiConstanzo et al. [12] support this belief, but the findings reported by Dixon et al. [13] do not. Finally, Scopsi et al. [46] compared the outcome of a group of tumours that we believe represent low grade insular ductal carcinomas with the behaviour of a collection of conventional non-argyrophilic carcinomas. Although the former tumours spread to lymph nodes less frequently, the authors could not detect a difference in the survival of the two groups.

4. What diagnostic term seems most appropriate for tumours with endocrine traits?

The nomenclature of "neuroendocrine" tumours has provoked about as much controversy as the existence of mammary "carcinoids." Early workers observed that many complex epithelia contain cells showing characteristics of both neural and endocrine cells and created the term "neuroendocrine" to describe them. It proved only a short step to propose the diagnosis of "neuroendocrine tumour" for neoplasms deriving from these cells or demonstrating their characteristics. Although conceptually elegant, this proposal generated controversy since the diagnosis of "neuroendocrine tumour" could apply equally well to a bronchial carcinoid and a small cell undifferentiated carcinoma. It seems illogical to subsume under a single diagnosis neoplasms with as disparate clinical, pathological, and biological characteristics as these two. So, as the World Health Organization began publication of the second edition of its Histological Classification of Tumours, the editor-in-chief [47] outlined the group's philosophy of nomenclature by writing: "The WHO programme recognized the need to separate terms that describe entities from those that describe concepts. The latter are necessary to communicate ideas, e.g. to seek histogenetic relationships among the tumours. The former are needed to communicate specific diagnoses; they are based on cellular descriptions rather than cellular origins; and they are specific rather than generic". He went on to give an example: "So, the various WHO classification groups have opted for familiar diagnostic terms such as carcinoid and small cell carcinoma rather than APUDoma, neurolophoma, neuroendocrinoma, and Kultchitsky cell carcinoma". The editorial board of the Armed Forces Institute of Pathology, supervising the preparation of the third series of its Atlas of Tumour Pathology, has adopted the same stance for the same reasons.

Both groups recognize four categories for tumours of "neuroendocrine" nature: small cell undifferentiated carcinoma, atypical carcinoid tumour, carcinoid tumour, and paraganglioma. Applying this convention to tumours of the breast, we believe that one can rightly use the diagnosis of small cell undifferentiated carcinoma for those rare cases. Papotti et al. [38] described a single tumour that suggested the appearance of "atypical carcinoid as seen in the lung," so this diagnosis seems to have a place as well. We have not seen a mammary endocrine tumour that duplicates the appearance of either an intestinal or a pulmonary carcinoid tumour, and Rosai [42] reports having seen only one instance. We could find no reports of a primary paraganglioma of the breast. Thus, this classification schema encompasses the rarest of mammary endocrine tumours but excludes all the common examples. One must therefore classify the usual cases according to conventional diagnostic criteria and indicate the presence of endocrine differentiation as a refining comment. For example, one would use the terms, "intraductal carcinoma with endocrine features," "mucinous carcinoma with endocrine features," and "lobular carcinoma with endocrine features" for the cases we have illustrated. The low grade insular ductal carcinoma poses a problem of nomenclature since the WHO classification does not recognize it as a distinct entity. Perhaps the name, "low grade infiltrating ductal carcinoma with endocrine features" would suffice.

Two final points bear brief mention. First, endocrine breast carcinomas usually contain oestrogen receptors, sometimes at very high levels. We could not find a systematic study of this observation, but several of the cancers with extremely high receptor concentrations described by Wong et al. [54] displayed endocrine characteristics. Second, a surprisingly high number of carcinomas of the male breast show evidence of endocrine differentiation. About 5% of breast tumours in women have endocrine qualities [1], but this number grows to 20% in males [45]. Endocrine tumours arising in men display more histological uniformity than those occurring in women. Most of the tumours of men have the pattern of low-grade insular ductal carcinomas.

In conclusion, the phenomenon of endocrine differentiation of breast cancers appears firmly established. It does not imply that the neoplasms arise from pre-existing endocrine cells and cannot unite the tumours into a single coherent group; instead, endocrine differentiation probably reflects neoplastic activation of certain pathways of maturation. Endocrine characteristics occur in all examples of one rare type of breast cancer (small cell undifferentiated carcinoma) and frequently in some more common varieties (cellular mucinous carcinoma, the alveolar variant of infiltrating lobular carcinoma, and low-grade in-situ and infiltrating ductal carcinoma). We believe that pathologists should classify these tumours using conventional histological criteria and classification schemes and modify the diagnosis to indicate the presence of endocrine features as appropriate. Although the recognition of endocrine differentiation can help the pathologist resolve diagnostic confusions, investigators have not published information defining the clinical relevance of the phenomenon. We hope that this more systematic approach to diagnosis and nomenclature will allow for such investigations.

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