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Review

Histological type and typing of breast carcinomas and the WHO classification changes over time

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Summary
The World Health Organization's new classification of breast tumors has just been published. This review aims to examine the morphological categorization of breast carcinomas which is still principally based on histological features and follows the traditions of histological typing. It gives a subjective and critical view on the WHO classifications and their changes over time, and describes the changes related to some of the most common or challenging breast carcinomas: in situ carcinomas, invasive breast carcinomas of no special type, lobular, cribriform, tubular, mucinous, papillary, metaplastic carcinomas and carcinomas with medullary pattern and those with apocrine differentiation are discussed in more details. Although the 5th edition of the classification is not perfect, it has advantages which are mentioned along with problematic issues of classifications.

Key words: breast carcinoma, histological type, WHO classification

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Introduction

A philosophical background to histological types of breast carcinoma

Breast cancers can be and are classified according to many of their aspects, with histological presentation being the basis of the World Health Organization (WHO) classifications of breast tumors for a long time in successive editions of "the blue book" [1-5], further referred to as editions in this review.

Mankind has always been interested in making order in the world around itself and undertook this with more or less success. The interest in classifying things, making a difference between the good and the bad, the dangerous and the harmless is probably as old as our species. Practically anything can be classified and everything can be classified along innumerable characteristics, features, aspects… etc. A good classification is orderly. Order means that everything has a proper place, and can be (virtually) put there as drugs in a pharmacy, where the pharmacist generally knows which drawer or shelf to search for to find a given product. Making order in biological entities is more difficult. As Bill Bryson mentions in his short history of nearly everything, there is great deal of disorder in the taxonomy of the animal and plant kingdoms, and compares this to a battleground rather than a science or an art [6]. Our perception and cataloguing of tumors is hopefully closer to the latter similes, but is certainly

not perfect. In theory, optimal order in tumor classifications means that anything one encounters, can be (recognizing the human right for mistakes – *errare humanum est* – , rightly or wrongly) put into a category to which it fits; every lesion has its place and can be put into only one place in one classification (and other places in other classifications).

The appearance of the 5th edition of the WHO blue book on breast tumors [5] made the author think about the past and the present of breast cancer classification, and initiated this review.

A tumor is a lump, traditionally a palpable lump, in the original meaning of the word, a lump of any type. Although all graduates from medical disciplines know that "*tumor*" is, for example, a cardinal symptom of inflammation, in the contemporary meaning, tumors are often meant to represent neoplastic proliferations only. However, lumps in the breast (like in other organs) can be the results of inflammation (e.g. granulomatous mastitis or posttraumatic fat necrosis), hyperplastic proliferation (like in sclerosing adenosis) or simply fluid accumulation (in gross cysts), not only neoplastic proliferations. On the other hand, with the advent of breast cancer screening, neoplastic proliferations can be present without lump formation. Owing to this complexity of clinical and pathological presentation, the classification of breast tumors has always faced challenges that had been solved according to the actual global knowledge available on the diseases and adherence to traditions, but also according to the knowledge and preferences of those who made the classification. As such, the 5th edition does not differ from earlier ones, it includes benign and malignant neoplasms and non-neoplastic disorders (e.g. usual ductal hyperplasia) which may be tumor forming, but not all breast lesions that may be tumor forming, even not all subsets of neoplastic lesions considered as given entities (at one time or the other) by some authors.

As every representative of the Homo sapiens species is a unique unprecedented and unrepeatable entity, it is probable that despite many similarities, all breast cancers have minor or major differences. People involved in making classifications can be divided into the two broad categories of lumpers and splitters (a classification itself), those who want as few categories as possible and those who think that minor differences and similarities in the main group (e.g. breast carcinomas) warrant the formation of a new (sub)group. Breast cancers themselves may be classified along many aspects (size, nodal status, differentiation, prognosis, method of detection, biomarker expression, genetic alterations… to mention only a few of the dozens of dozens of possible classifications). The gold standard of diagnosing breast cancers is by histology, and as the histological appearance of cancers may be similar or different, histological typing has been a goal since the first WHO classification appearing in 1968 [1], and despite the insights into the molecular and genetic backgrounds, histology remains the basis of the classification today [5].

Histological types of breast cancers are prognostically relevant [7], and histological type has been included as a category I prognostic factor of breast cancers by the College of American Pathologists Consensus Statement in 1999 [8]. Even if some types have no substantial prognostic impact, their recognition may make sense for example to allow one to recognize a tumor as being primary in the breast. For example, mucinous cystadenocarcinomas are extremely rare in the breast as primary, and are relatively more common in the ovaries or the pancreas, therefore not knowing that they may be primary in the breast would immediately label them as metastatic at this site. A carcinoma of the same type and morphology may have dissimilar prognosis depending on the site: e.g. adenoid cystic carcinoma of the breast has a better prognosis than adenoid cystic carcinoma of the salivary glands [5]. Histological types may be associated with radiological findings (e.g. mucinous, encapsulated papillary, "medullary", some grade 3 invasive ("ductal") carcinomas may mimic benign lesions by being circumscribed; lobular carcinomas still have a propensity to remain occult… etc.), with different metastatic patterns (that of lobular carcinomas differing from the rest), but mainly with different morphologies along which they have been classified. This review aims to give an overview of the five editions of the WHO blue books on breast tumors, specifically on breast carcinomas, especially their types/classes making the frame of their classification.

The classifications

As wisely mentioned in the preface of the first edition, the classifications reflect the then current state of knowledge, with modifications almost certain to be needed. Indeed, minor and major changes have occurred through the editions. Table I gives basic ideas and statistics about the five editions of the WHO blue books on breast tumors, whereas Table II summarizes the types of malignant epithelial tumors listed in the classifications. The speed of the broadening of medical knowledge is reflected by the time elapsed between the editions (13, 22, 9 and 7 years) and the changes in the titles of the volumes starting by histological typing [1,2], continuing as pathology and ge-

netics [3] and ending with classification [4,5]. Each edition demonstrates an increase in pages, with an increase in page size occurring at the 3rd edition.

The classifications have not followed the same basic approach. Starting with a six-tiered categorization of benign non-neoplastic proliferations, benign tumors, malignant epithelial tumors, malignant mesenchymal tumors (sarcomas), mixed malignant tumors (carcinosarcomas) and unclassified entities [1], the following editions have attempted a histogenetic first delineation with biological behavior coming only second [2-5], either with benign lesions and in situ carcinomas preceding carcinomas [2,5] or starting with invasive epithelial malignancies [3,4]. At one moment (some) papillary tumors started to appear under separate cover [3], clinical presentations of breast carcinoma made their way to the classification [3], and other minor differences occurred; therefore the organization of the classifications is different.

After this brief general summary of the consecutive editions, some histological types are put into their historical perspectives. In the following subtitles, I have chosen to base the discussion on the 1st edition and label many of the discussed entities as they first appeared in the classification and as they appear now. Some additional categories missing from the 1st edition are also discussed, but this is not a comprehensive coverage of all tumors listed.

1. Intraduct and intralobular non-infiltrating carcinoma (including Paget's disease of the breast) [1] - In situ carcinomas [5]

In situ carcinoma refers to an early carcinoma, which by definition does not invade and therefore has no metastatic potential. It is currently defined by the presence of a natural barrier, the myoepithelial cell layer around the neoplastic proliferation. The entity implies that normal breast structures (ducts and acini) are partially or completely filled with the tumor cells, and do not extend further. This is why this entity was initially named intraductal, i.e. *intraduct non-infiltrating carcinoma* [1]. The 2nd edition was the one introducing the separate entities of *ductal carcinoma in situ* (DCIS) (of solid, comedo, papillary and cribriform patterns) and lobular carcinoma in situ (LCIS). The papillary DCIS cases illustrated in the text [2] would all be micropapillary according to current nomenclature. The 3rd edition departed from the architectural classification (although it states that the architecture should be reported), and distinguished between low-grade, intermediate grade and high grade DCIS and unusual variants (spindle cell, apocrine, neuroendocrine, signet-ring cell, clear cell, squamous) with uncertainty in grading; this approach was maintained in the following editions [3-5]. (The 3rd edition also offered an alternative nomenclature for non-invasive ductal neoplasms encompassing flat epithelial atypia, atypical ductal hyperplasia, and different grades of DCIS in the form of *ductal intraepithelial neoplasia* – DIN). Some forms of DCIS recognised by others, (e.g. *DCIS with mucin formation* [9], *cystic hypersecretory DCIS* [10]) are not part of the WHO classifications.

As mentioned above, LCIS was introduced in the 2nd edition, already mentioning *lobular neoplasia* as an alternative name which later became the title of the chapter in the 3rd and 4th editions [3,4]. The 3rd edition also mentions the three-tiered graded *lobular intraepithelial neoplasia* (LIN) terminology [3], whereas the 4th edition, at least in its illustrations returns to the traditional atypical lobular hyperplasia (ALH), LCIS subdividing terminology and also introduces *pleomorphic LCIS* as a subset [4]. This is further expanded by the addition of *florid LCIS* in the 5th edition [5] to the "Non-invasive lobular neoplasia" main chapter divided to ALH and LCIS subheadings. In 2017, the American Joint Committee on Cancer (AJCC) departed from the tradition of including LCIS in the pTis staging category in its Cancer staging manual [11]. This was not followed by the 8th edition of the Union for International Cancer Control (UICC) TNM classification published in the same year [12,13], contrarily to what is written about this in the 5th edition [5]. Thus, followers of the UICC classification still continue to stage LCIS as pTis(LCIS), which may be supported by the findings that screen-detected, biopsy sampled florid and pleomorphic LCIS are too often associated with upstaging to invasive lobular carcinomas on excision [14].

The UICC TNM classification also includes an in situ carcinoma category for *Paget's disease* without associated DCIS or invasive carcinoma, pTis(Paget) [12]. Paget's disease of the breast was part of the 1st edition of the WHO classification and was partly interpreted as it is now: infiltration of the epidermis by an "underlying intraduct or invasive carcinoma" [1]. The difference is probably that nowadays the underlying carcinoma is more commonly a high grade DCIS involving the lactiferous ducts than in earlier times, but an invasive carcinoma is quite often associated with this former [5]. The pTis(Paget) category without these underlying tumors is rare, only 7/114 belonged to this category in a series from the European Institute of Oncology [15], the percentage reported being 0-13% [5].

2. Infiltrating carcinoma [1] - Invasive breast carcinoma of no special type (IBC-NST) [5]

Tumors not fitting into any of the special histological variants [1], any of the other categories [2], failing to exhibit sufficient characteristics to achieve classifica-

tion as a specific histological type [3,4], which cannot be classified morphologically as any of the special histological types [5] were grouped under an "umbrella" or "waste-basket" category (Tab. II). This concept has therefore been present from the 1st edition, but the most proper name for the category needed some time to gain acceptance [4,5]. Starting as "*infiltrating carcinoma*", this was preferentially called "*invasive ductal carcinoma* (*IDC*)" only from the 2nd edition (basically remaining as such in the 3rd edition, too), with a number of synonyms like carcinoma of no special type (the currently preferred term occurring as early as 1981), infiltrating duct carcinoma not otherwise specified (NOS), infiltrating duct carcinoma with productive fibrosis, scirrhous carcinoma, infiltrating carcinoma, carcinoma simplex [2], and no specific type (ductal NST) [3]. Approaching the logical aspects, we deal with an antagonistic dichotomous categorization: there are special types of breast cancer and the rest is of no special type (NST) and not "ductal". Ductal, originally, was thought to reflect the hypothesized ductal origin of these tumors in contrast to the believed lobular origins of lobular carcinomas – none of which are considered true now; but as we love traditions, lobular carcinoma has kept its name, and this is not bad, because everyone knows what this term means. To better understand the special type versus non-special type dichotomization, we could think about the analogy of colours: the antagonistic category to white is not black, but non-white. (It is just a bit ironic that the precursor lesion is "ductal" carcinoma in situ.)

Obviously, due to the nature of the definition, this group is very heterogeneous in gross and microscopic aspects, and the new histological types of breast cancer showing up in consecutive new editions of the blue book were all segregated from this one (Tabs. I and II). The editors and authors of the 5th edition have decided to cut on the number of recognized types and to replace some of these (notably *oncocytic, lipid-rich, glycogen-rich, clear cell* and *sebaceous carcinoma*, "*medullary carcinoma*" and *NSTs with neuroendocrine differentiation*) but not others (like *carcinomas with apocrine differentiation*, *mucinous, tubular*… etc. *carcinomas*) as special *morphological patterns of IBC-NST*. *Pleomorphic carcinoma*, *carcinoma with osteoclast-like giant cells* or *choriocarcinomatous* or *melanocytic features* had been subsets of the NST category since the 3rd edition. It is difficult to resist to the somewhat humourous basic tripartite grouping of breast carcinomas the new edition offers: special types – no special types with special morphological patterns – and no special types with no (without) special patterns (i.e. the rest).

If a component is minor, the tumor must to be categorized according to the predominant pattern, however extensive mixtures require multiple diagnoses; this was the first mention of multiple recognised morphologies within a breast carcinoma [2]. Mixed morphologies have been recognized for many years, and traditionally they meant and were defined as the occurrence of IBC-NST admixed with another special type, which was present in insufficient quantity (up to 90%) to qualify as a pure special type carcinoma. The lower limit of special types to qualify as *mixed special type* (mixed lobular, mixed tubular, mixed mucinous, mixed micropapillary were the commonest) was 50% [3,4]. This left carcinomas with less than 50% recognizable special type morphology to be classified as NST or IDC NOS, and sometimes resulted in surprises when the disease metastasized or recurred as a special type carcinoma, suggesting another primary tumor. The problem has been dealt with most wisely: the 5th edition recommends the use of *mixed IBC-NST and special type* whenever the latter is present in 10-90% with the estimated proportion to be given. For special types being present in <10%, the approach is to classify the carcinoma as IBC-NST with the option of mentioning the minor special type in the description [5]. On the other hand, even the new edition does not seem to cover the coexistence of two special types whether collision tumors or derivates of the same parent cells. Tubular and lobular carcinomas are known to be associated with lobular neoplasia more commonly than a random event [16,17], and therefore may be found in association with each other, too.

Table I. Summary and basic statistics about the WHO Breast blue book editions*.

Edition	1st	2nd	3rd	4th	5th
Year	1968	1981	2003	2012	2019
Authors	14	13	132**	92	153
Countries	12	11	23**	24	21
Pages	37	75	112	240	355
Diseases/entities listed*	29	36	94	113	108
Types of carcinoma recognized*	10	18	40	59	44

*The number of entities and carcinomas listed is subject to subjectivity, as subtypes are sometimes mentioned separately; **The book includes gynaecological cancers, too.

Table II. Entities tabulated in consecutive editions of the blue book on breast tumors*.

1st edition (1968)
Intraduct and intralobular non-infiltrating carcinoma
Infiltrating carcinoma
Special histological variants of carcinoma:
• Medullary carcinoma
• Papillary carcinoma
• Cribriform carcinoma
• Mucous carcinoma
• Lobular carcinoma
• Squamous carcinoma
• Paget's disease of the breast
• Carcinoma arising in cellular intracanalicular fibroadenoma (i.e. cystosarcoma phylloides)
2nd edition (1981)
Noninvasive
• Intraductal carcinoma
• Lobular carcinoma in situ
Invasive
• Invasive ductal carcinoma
• Invasive carcinoma with predominant intraductal component
• Invasive lobular carcinoma
• Mucinous carcinoma
• Medullary carcinoma
• Papillary carcinoma
• Tubular carcinoma
• Adenoid cystic carcinoma
• Secretory carcinoma (juvenile carcinoma)
• Apocrine carcinoma
• Carcinoma with metaplasia (squamous, spindle-cell, cartilaginous and osseous, mixed type)
• Others (lipid-secreting carcinoma, small cell carcinoma, signet-ring cell carcinoma)
Paget's disease of the nipple
3rd edition (2003)
Precursor lesions
• Lobular neoplasia
• Intraductal proliferative lesions
• Microinvasive carcinoma
• Intraductal papillary neoplasms
Invasive breast carcinoma
• Invasive ductal carcinoma, NOS
- Pleomorphic carcinoma
- Carcinoma with osteoclastic giant cells
- Carcinoma with choriocarcinomatous features
- Carcinoma with melanocytic features
• Invasive lobular carcinoma
• Tubular carcinoma
• Invasive cribriform carcinoma
• Medullary carcinoma
• Mucin producing carcinomas (mucinous/colloid carcinoma including cellular and hypocellular subsets, mucinous cystadenocarcinoma, columnar cell mucinous carcinoma, signet-ring cell carcinoma)
• Neuroendocrine tumors
• Invasive papillary carcinoma
• Invasive micropapillary carcinoma
• Apocrine carcinoma
• Metaplastic carcinoma
• Lipid-rich carcinoma
• Secretory carcinoma

Table II. *(continued)*

• Oncocytic carcinoma
• Adenoid cystic carcinoma
• Acinic cell carcinoma
• Glycogen-rich clear cell carcinoma
• Sebaceous carcinoma
• Inflammatory carcinoma
• Bilateral breast carcinoma
4th edition (2013)
• Precursor lesions
- Ductal carcinoma in situ
- Lobular neoplasia (Lobular carcinoma in situ – classic and pleomorphic; atypical lobular hyperplasia)
• Microinvasive carcinoma
• Invasive breast carcinoma
- Invasive carcinoma of no special type (NST)
- Pleomorphic carcinoma
- Carcinoma with osteoclast-like stromal giant cells
- Carcinoma with melanotic features
- Invasive lobular carcinoma
- Classic lobular carcinoma
- Solid lobular carcinoma
- Alveolar lobular carcinoma
- Pleomorphic lobular carcinoma
- Tubulolobular carcinoma
- Mixed lobular carcinoma
- Tubular carcinoma
- Cribriform carcinoma
- Mucinous carcinoma
- Carcinoma with medullary features
- Medullary carcinoma
- Atypical medullary carcinoma
- Invasive carcinoma NST with medullary features
- Carcinoma with apocrine differentiation
- Carcinoma with signet-ring cell differentiation
- Invasive micropapillary carcinoma
- Metaplastic carcinoma NST
- Low-grade adenosquamous carcinoma
- Fibromatosis-like metaplastic carcinoma
- Squamous cell carcinoma
- Spindle cell carcinoma
- Metaplastic carcinoma with mesenchymal differentiation (chondroid, osseous, other type)
- Mixed metaplastic carcinoma
- Myoepithelial carcinoma
- Carcinoma with neuroendocrine features
- Neuroendocrine tumor, well differentiated
- Neuroedocrine carcinoma, poorly differentiated (small cell carcinoma)
- Carcinoma with neuroendocrine differentiation
- Secretory carcinoma
- Invasive papillary carcinoma
- Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Polymorphous carcinoma
- Oncocytic carcinoma
- Lipid-rich carcinoma
- Gycogen-rich clear cell carcinoma
- Sebaceous carcinoma

Table II. *(continued)*

- …
Epithelial-myoepithelial tumors
- …
- Adenomyoepithelioma with carcinoma
- Adenoid cystic carcinoma
Papillary lesions
- …
- Intraductal papilloma with atypical hyperplasia
- Intraductal papilloma with ductal carcinoma in situ
- Intraductal papilloma with lobular carcinoma in situ
- Intraductal papillary carcinoma
- Encapsulated papillary carcinoma
- Encapsulated papillary carcinoma with invasion
- Solid papillary carcinoma (in situ)
- Solid papillary carcinoma (invasive)
Tumors of the nipple
- …
- Paget's disease of the nipple
Tumors of the male breast
- …
- In situ carcinoma
- Invasive carcinoma
Clinical patterns
- Inflammatory carcinoma
- Bilateral breast carcinoma
5th edition (2019)
Non-invasive lobular neoplasia
- …
- Lobular carcinoma in situ (classic, florid, pleomorphic)
Ductal carcinoma in situ (DCIS)
- DCIS of low nuclear grade
- DCIS of intermediate nuclear grade
- DCIS of high nuclear grade
- Invasive breast carcinoma
- Invasive breast carcinoma of no special type (including medullary pattern, invasive carcinoma with neuroendocrine differentiation, carcinoma with osteoclast-like stromal giant cells, pleomorphic pattern, choriocarcinomatous pattern, melanocytic pattern, oncocytic pattern, lipid-rich pattern, glycogen-rich clear cell pattern, sebaceous pattern)
- (Microinvasive carcinoma)
- Invasive lobular carcinoma
- Tubular carcinoma
- Cribriform carcinoma
- Mucinous carcinoma
- Mucinous cystadenocarcinoma
- Invasive micropapillary carcinoma
- Carcinoma with apocrine differentiation
- Metaplastic carcinoma (low-grade adenosquamous carcinoma, [high-grade adenosquamous carcinoma], fibromatosis-like metaplastic carcinoma, spindle cell carcinoma, squamous cell carcinoma, metaplastic carcinoma with heterologous mesenchymal [e.g. chondroid, osseous, rhabdomyoid, neuroglial) differentiation, mixed metaplastic carcinomas)
- Acinic cell carcinoma
- Adenoid cystic carcinoma
- Secretory carcinoma
- Mucoepidermoid carcinoma
- Polymorphous adenocarcinoma
- Tall cell carcinoma with reversed polarity

Table II. *(continued)*

Neuroendocrine neoplasms
- Neuroendocrine tumor (Grade 1, Grade 2)
- Neuroendocrine carcinoma
Papillary neoplasms
- …
- Papillary ductal carcinoma in situ
- Encapsulated papillary carcinoma
- Solid papillary carcinoma (in situ and invasive)
- Invasive papillary carcinoma
Epithelial-myoepithelial neoplasms
- …
- Malignant adenomyoepithelioma
- Epithelial-myoepithelial carcinoma
Tumors of the male breast
- …
- In situ carcinoma
- Invasive carcinoma

*The tabulated types of carcinoma appearing at the beginning of the relevant texts are sometimes complemented with variants/subtypes mentioned in the main body of the related chapters, and the 5th edition of the book has chapter starting tables in partial contradiction with the main body of the text, and therefore the chapter headings and content are better reflected in this table.

Although this is not listed in the blue book, by analogy, it feels appropriate to call such tumors as *mixed tubular and lobular* with the proportion of each given.

Of the patterns listed under IBC-NST, *carcinomas with neuroendocrine differentiation* are the least well delineated, and their separation from *neuroendocrine neoplasias* (NEN; forming a separate category with *neuroendocrine tumors* (NETs) of Nottingham grade 1 or 2 and *neuroendocrine carcinomas* (NEC) of either small cell or large cell type) is less than obvious. It is clear that neither type B mucinous carcinoma nor solid papillary carcinoma with neuroendocrine differentiation belong to any of these categories. The ubiquitous small cell carcinomas are rather distinctive in terms of light microscopic appearance, but no diagnostic boundary has been provided in the related chapter to draw the line between small cell NEC and large cell NEC [5], and the notion that more than two-thirds express neuroendocrine markers (chromogranin and synaptophysin) is just disturbing as a feature of NECs; how are the less than one-third negative ones classified as NEC then? The rather rare NENs are separated from the *IBC-NST with neuroendocrine differentiation* (which seem to be relatively common) by the presence and extent of histologic features characteristic of neuroendocrine differentiation. "Distinct and uniform enough" neuroendocrine features and neuroendocrine marker expression make a tumor NET or NEC; in the absence of these latter or lack of any special histologic type defining features, neuroendocrine differentiation will remain a pattern of IBC-NST. The segragation is further confused by the notion that 10-90% neuroendocrine differentiation allows for *mixed NEN*s [5]. Finally, the fact that breast NENs are described as tumors lacking the organoid features of other typical NENs, like carcinoid tumors of the lung or NETs of the gastrointestinal tract [5], do not make the recognition of "distinct and uniform neuroendocrine features" easier and the distinction between *IDC-NST with neuroendocrine differentiation* and NENs obvious.

3. Lobular carcinoma [1] - Invasive lobular carcinoma (ILC) [5]

This is a special histological type featured in the initial classification. Interestingly, the example shown in the low power figure in the 1st edition does not show the features associated with classical ILC. It is more a nest forming tumor than one with discohesive cells infiltrating in a "lobular pattern", i.e. single cells, Indian filing, concentric periductal and/or perilobular arrangement. This is because the type was considered an indefinite entity at the time, and was interpreted as a tumor mainly being intralobular but with superimposed invasion of mammary stroma [1]. In the 2nd edition (and through to the last one), ILC is defined as the classical form, on morphological grounds. The definition has a reference to the cellular analogy with LCIS, a lesion described in 1942 by Foote and Stewart [18], but illustrated even earlier as a precancerous lesion by Evans [19]. The "*tubulo-lobular*" and *solid variants* are also mentioned [2], with the inclusion of further variants, the *alveolar*, the *pleomorphic* and the *mixed* ones in the 3rd edition [3]. All these variants remained

through further editions [4,5]. The terminology has slightly and changed disturbingly little without notice with "patterns" replacing "variants"; it is not known whether this is a conceptual change like with IBC-NST or just a stylistic alteration, although the latter is favoured. In the last edition, all main headings are presented in a structured way, and the ILC chapter states "None" under the subheading "Subtype(s)", what does not preclude a reference to "histological subtypes" further ahead in the text when alluding to the receptor status or the prognosis of different variants/patterns.

The description of *extracellular mucin production* as a further possible morphologic feature of ILC also occurs for the first time in the 5th edition, although not in the ILC chapter, but the general "Introduction to tumors of the breast" and the chapter on mucinous carcinoma [5]. Interestingly, a *trabecular variant*, which was also alluded to by Martinez and Azzopardi in the same article as the alveolar [20] never made it to the WHO classification, although it is sometimes mentioned in current papers [21]. It could add a morphologic variant to the diagnostic spectrum and would enable non-classical, non-alveolar, non-solid, non-pleomorphic cases to be subclassified among the ILCs with IBC-NST-like low-power appearance.

The 3rd edition was the first to mention the loss of E-cadherin function behind the typical discohesive morphology of ILCs [3]. This is further elaborated in the later editions, where the loss of other members of the E-cadherin complex are also mentioned and a better molecular/genetic characterization of ILCs is given [4,5]. To note, at no point has E-cadherin loss been a defining criterion of lobular carcinomas in the blue books, although it was made clear that this is one of the most consistent molecular alteration in this histological type. (In contrast, the Armed Forces Institute of Pathology fascicles, in their 4th series mention E-cadherin loss in the definition of ILCs [22].) It is acknowledged that about 15% of ILCs (and lobular neoplasias) may have aberrant E-cadherin staining, which may be cytoplasmic, weak/focal membranous, and rarely marked membranous, but this should not deter the diagnosis of a lobular carcinoma whether invasive or in situ, if the morphology is in keeping with the diagnosis [5,23,24] (Fig. 1). On the other hand, non-lobular carcinomas may lack E-cadherin expression.

The *tubulolobular variant* of ILC (*tubulolobular carcinoma*, TLC) was described by Fisher et al. in 1977. They found the prognosis of this type of carcinoma intermediate between the prognosis of classic ILC and tubular carcinoma, and felt that it was a philosophical question whether to classify it as a variant of tubular or lobular carcinoma. They chose the second because they felt that the infiltration pattern was of greater importance than the structures seen in the tumor; they also noted that the light microscopic appearance of tumor cells more closely resembled that of classic lobular carcinoma cells despite ultrastructural features more suggestive of ductal NST carcinoma [25]. The statement that about one-third of TLCs are associated with lobular neoplasia is repeated in the last three editions of the blue book [3-5], but lobular neoplasia is not infrequently associated with tubular carcinomas or low grade NST carcinomas either [17]. In the 3rd edition, it was also stated that E-cadherin studies should clarify the classification of TLCs as lobular or tubular. Such studies were performed before the publication of the 4th edition, and they demonstrated strong membranous staining for E-cadherin (and the catenins if tested) in all [17,26,27] or the majority [28] of the overall 76 TLCs cases tested. Although these results and the three-dimensional reconstruction of TLCs [29] favor a wrong classification of TLC as lobular carcinoma variant, TLC has remained a variant/pattern of ILC in the latest edition, too [5]. The value of these statements should not be compromised by the phenomenon (which is also not described in the blue book) that E-cadherin negative "pseudocribriform" and/or tubule-like structures (tubules) may rarely occur in ILC and their presence should not alter the diagnosis of ILC [24,30] (Fig. 2).

About 5% of breast carcinomas have both invasive NST carcinoma and ILC features (Fig. 3), a phenomenon approached with the category of mixed carcinomas in the 3rd and 4th editions of the blue book, but referred to as *ductulolobular carcinomas* in the ILC chapter of 5th edition. Of note, the IBC-NST chapter lists *mixed IBC-NST and ILC* as an example of mixed carcinoma.

Considering that some ILCs are not of the classic type, and IBC-NST-like morphologies exist (solid, trabecular, alveolar patterns and tubule-like structure formation may occur), that E-cadherin is not lost in all cases of ILC but may be lost in some other forms of IBC, and that IBC-NST may have a morphology simulating the infiltration pattern of lobular carcinomas (as depicted in Figures 2.90 and 9.03 of the 5th edition), the diagnosis of ILC is not always easy. Adherence to the morphological definition, the use of E-cadherin and/or the catenins (most commonly beta-catenin and p120 catenin) in doubtful cases may be a pragmatic approach. Although it is widely accepted that membranous E-cadherin and alpha-, beta-, gamma- or p120-catenin staining should not alter the diagnosis of ILC in a morphologically typical case, it is advisable to base the diagnosis on immunostaining in doubtful cases: making it lobular when the staining is lost to altered/aberrant and making it non-lobular when it is nicely membranous.

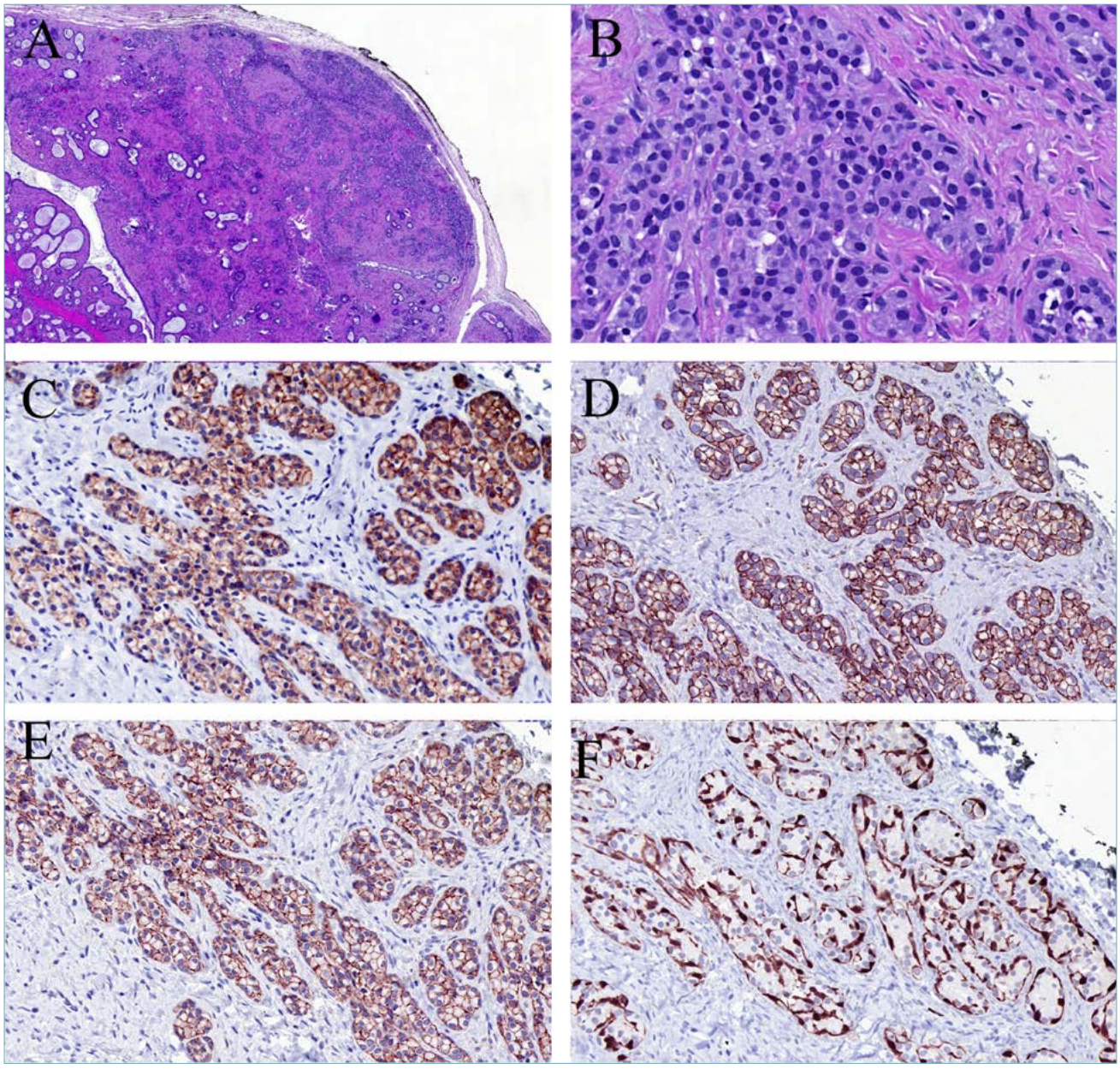

Figure 1. LN with aberrant membranous E-cadherin complex protein expression. Fibroadenoma with lobular neoplasia, which can be seen between the 12 and the 3 o'clock position (A: HE x5); with a higher magnification, the discohesive cellular composition fulfils the diagnostic criteria of lobular neoplasia (B: HE x70), but the membranous staining with E-cadherin (C, x40), β-catenin (D, x40) and p120 (E, x40) are aberrant. S100 highlights the myoepithelial cells (F, x40).

4. Cribriform carcinoma [1] - Invasive cribriform carcinoma (and tubular carcinoma) [5]

Although *tubular carcinoma* is a relatively common but special type of breast carcinoma, it was not represented in the 1st edition. On the other hand, *cribriform carcinoma* was there, but it also included tumors labelled as adenoid cystic carcinoma and cylindroma, as no experience was available with these rarer types. It is to note that the cribriform carcinomas illustrated in the book all represent *non-high grade cribriform DCIS* with or without necrosis. Cribriform carcinoma has been defined as a type of invasive breast cancer in the 3rd edition. The definition of this type included the >90% purity rule, but with a "facilitation" to make

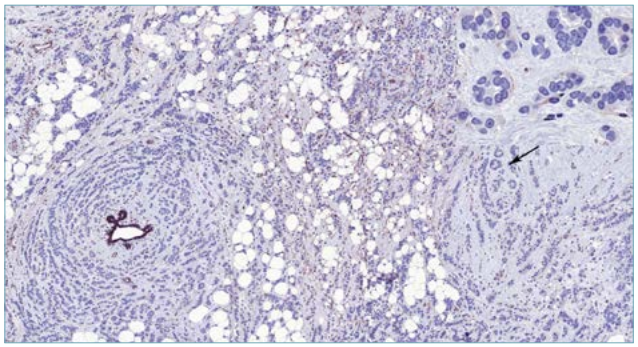

Figure 2. Tubules in ILC. This is an ILC with some trabecular pattern (alveolar elsewhere) which demonstrates some tubules (arrow and inset; β-catenin, x5 and x20 - inset). All tumor cells are β-catenin negative (and were also E-cadherin negative and – high molecular weight cytokeratin/34βE12 positive – not shown.) Whether these tubules are genuine ILC components or minor non-ILC component lacking the function of the E-cadherin-complex is subject to interpretation, but the former is favoured.

this diagnosis even if >90% of the tumor was of mixed tubular and cribriform patterns with the latter predominating [3,4], but this facilitation was abandoned in the 5th edition, requiring >90% cribriformity for the diagnosis [5]. The original description of invasive cribriform carcinoma also included a reverse rule, calling tumors with mixed tubular and cribriform patterns with the former predominating as tubular carcinomas [31]. This rule is also part of the Royal College of Pathologists current recommendations on reporting of breast cancer [10], but the blue book editions never included this mention, and required (and still do) >90% tubular carcinoma morphology for a pure tubular carcinoma [3-5].

It has also been acknowledged that *tubular carcinomas* have better prognosis than well differentiated (grade 1) IBC-NSTs. However, it would be difficult not to perceive tubular carcinomas as one extreme end of differentiation of IBC-NST, where the better prognosis may simply stem from the fact that these tumors are required to score 1-1-1 or at most 1-2-1 (3 or 4 overall) on the gland/tubule formation, nuclear pleomorphism, adjusted mitotic rate scheme used for grading. (Highly atypical nuclei exclude the diagnosis, and low proliferation is a "non-defining" characteristic of tubular carcinomas and the luminal A category they belong to [5]). In contrast, grade I IBC-NSTs may score anything to make a grading sum of up to 5, and even their score 1 for gland/tubule formation needs only >75% glandular differentiation and not >90%. Therefore, tubular carcinomas are probably best viewed as the best differentiated carcinomas of the best differentiated (grade I) IBC-NSTs; nevertheless, they are worth being separated from the rest, due to their excellent prognosis and the possibility to omit adjuvant systemic and axillary treatment in most of them [5].

5. Mucous carcinoma [1] - Mucinous carcinoma [5]

Termed mucous carcinoma in the first edition [1] and preferentially mucinous in the subsequent ones [2-5], this type was characterised from the onset by substantial extracellular mucin formation. In the 3rd edition, this histological type became a part of a larger group of breast cancers characterized by mucin formation in general. The larger group also included tumors with intracellular mucin production like mucinous cystadenocarcinoma, its non cystic/solid variant, i.e. columnar cell mucinous carcinoma (featuring only in this edition with 2 cases previously reported) and signet-ring cell carcinoma, but did not include others like solid papillary carcinoma with extracellular mucin formation or mucoepidermoid carcinoma [3]. This was also the first classification to mention a hypocellular (type A by Capella et al.) and a cellular variant (type B by Capella et al.) of mucinous carcinoma, which remained in the subsequent editions [4,5], but no reference was made to indeterminate or transitional types labelled AB by Capella et al., which made up one fifth of their initial series [32]. Indeed, it is sometimes difficult to classify mucinous carcinoma into type A or B, but this matter does not seem to be of great importance, as this subclassification has no clinical relevance at present. As mentioned earlier, mucin forming DCIS has not received attention in the WHO classification of mucin forming carcinomas.

Two new subsets of IBC are discussed in the mucinous carcinoma chapter of the 5th edition.

One is the subset of carcinomas with both focal extracellular mucin formation and discohesive cells lacking E-cadherin expression, often showing an association with lobular neoplasia. These tumors are generally (but not unanimously) [33] presented as *ILC with extracellular mucin production* in the literature [9,30], but are not mentioned under the invasive lobular carcinoma heading.

The second is a subset mentioned under both the Mucinous carcinoma and the Invasive micropapillary carcinoma chapters, and is characterized by extracellular mucin and an inside-out reversed polarity of its cells, i.e. a micropapillary pattern. Probably first described as an entity in 2002 [34], *mucinous carcinoma with micropapillary features* (invasive micropapillary mucinous or mucinous micropapillary carcinoma) has been associated with a worse prognosis than pure (non-micropapillary) mucinous carcinoma [5]. The extent micropapillary architecture needs to be present for this

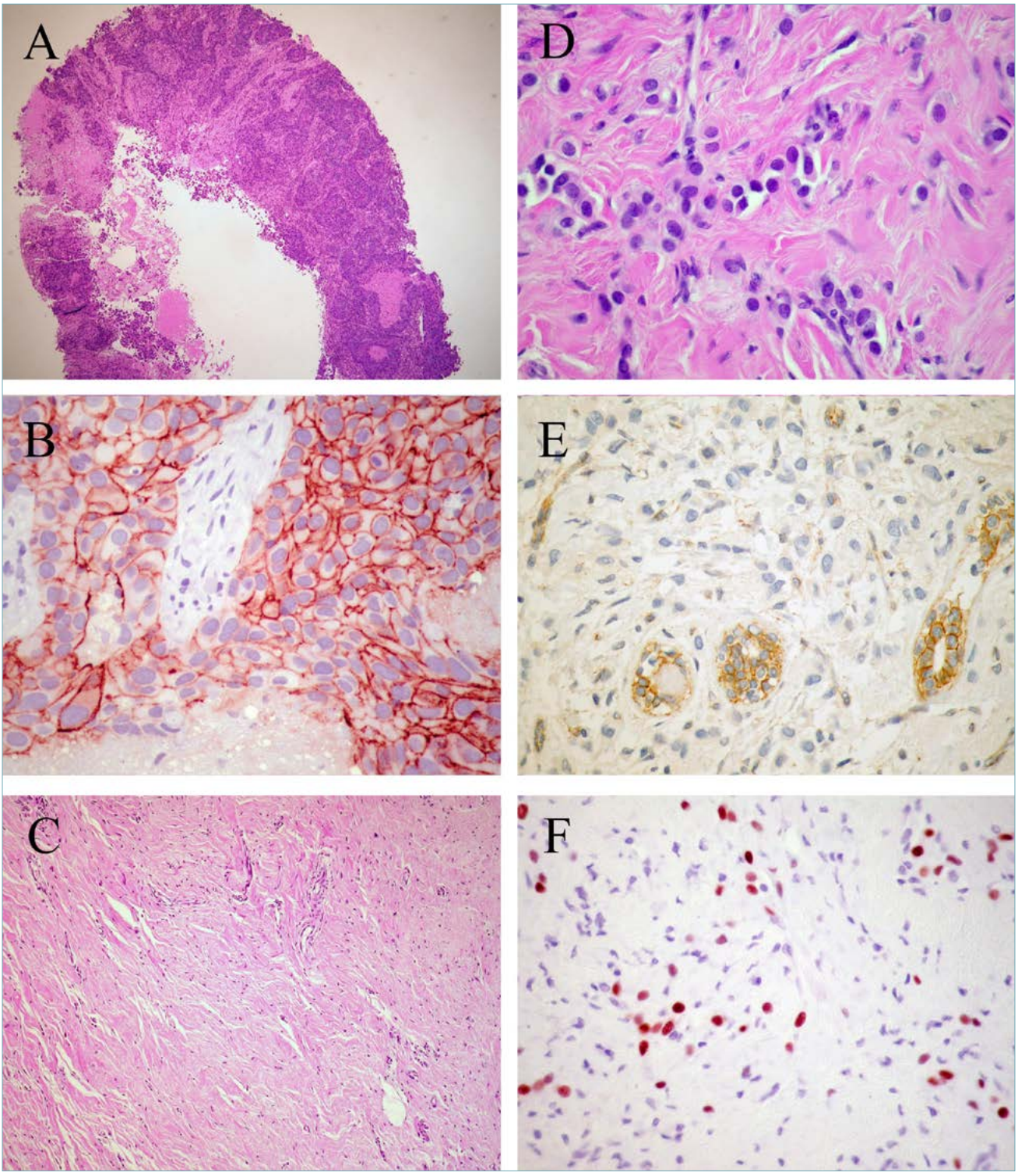

Figure 3. Mixed IBC-NST and lobular carcinoma or ductulolobular carcinoma? The illustrated tumor was diagnosed on core needle biopsy as IBC-NST (A, HE, x40) and had a HER2-positive (+) (B, HER2, x400), ER-negative (-), PR- phenotype (not shown). After primary systemic treatment with a taxan containing regimen and trastuzumab. Following this neoadjuvant therapy the tumor bed was suggestive of pathological complete regression (C, HE x100), except for about a 10% area where ILC was identified (D, HE x400) with the typical E-cadherin- (not shown), β-catenin- (E, β-catenin x400), ER+ (F, ER x400), PR+, HER2- phenotype, proving a well defined mixed tumor of different histological types and biomarker expression.

entity in order to qualify as such is not described in the WHO classification, >50% was used in some series [35-36]. Even the diagnostic criteria for reliably diagnosing this entity are less than perfectly described. The presence of reverted ("inside-out") pattern demonstrated by epithelial membrane antigen (MUC1) immunohistochemistry might not be sufficient, as this feature is seen in large numbers of pure mucinous carcinomas and fails to discriminate between the two entities [35-37]. It is therefore likely that series of pure mucinous carcinomas reported previously harbour a number of cases that would be diagnosed as micropapillary variants by Liu et al, and the good overall prognosis of mucinous carcinomas was derived from such aggregated series. However, when micropapillary mucinous cases are separated from the pure mucinous ones, they show a prognosis worse than that of pure mucinous carcinomas without a micropapillary pattern and better than that of invasive micropapillary carcinomas [36].

6. Medullary carcinoma [1] - IBC-NST with medullary pattern [5]; the rise and fall of a type with favourable outcome

This entity was already present in the 1st edition of the classification [1]. In general, pathology *medullary carcinoma* reflected a carcinoma with dominant tumor parenchyma in contrast to scirrhous carcinoma where the stroma and desmoplasia predominated over parenchyma, the first being soft, the other hard on palpation. In breast pathology, medullary carcinoma partially reflected this aspect, but also syncytial arrangement of the tumor cells. In the 1st edition, the exaggerated lymphoid stroma was not a necessary prescription for this histological type, and there was a notion that the tumor could be of good prognosis even in the absence of a lymphoid stroma. This is in contrast with the analysis of Ridolfi et al, where the lymphoid infiltrate was found to be of prognostic value: medullary carcinomas with pronounced mononuclear infiltrate had 91% 10-year-survival in opposition to 71% for the cases with fewer mononuclears [38]. The prominent lymphocytic stroma became a defining feature in the 2nd edition and remained as such in the 3rd [2,3], which was the first to give further stringent criteria for this special type: at least 75% syncytial architecture; lack of glandular structures; cells with abundant cytoplasm, vesicular, generally rounded nuclei with marked (or at least moderate) pleomorphism; circumscription. The classification was inconclusive with regards to DCIS component, stating it as a possible exclusion criterion [3]. *Atypical medullary carcinomas* were defined for the first time in this edition of the blue book as having the syncytial architecture and 2 or 3 of the other type defining criteria on lymphoid stroma, circumscription, nuclear morphology and lack of glandular structures. *Infiltrating ductal carcinoma with medullary features* also made its way to the classification in the 3rd edition, to replace atypical medullary carcinoma, and keep the medullary carcinoma type as clear as possible, and avoid confusion with it. With the 4th edition, medullary carcinoma vanished from the chapter headings and was lumped together with atypical medullary carcinoma and invasive carcinoma NST with medullary features under the heading of *carcinomas with medullary features* [4]. This change in policy was partly due to the suboptimal reproducibility of medullary carcinoma as a special type, and the fact that tumors with some but not all features of medullary carcinoma shared many aspects (like association with BRCA1 germline mutation or a common triple-negative phenotype) with it. Unfortunately, there remained three different ICD-O codes for the entities listed, and therefore many statistics based on these codes did not account for the change in policy towards the diagnosis of medullary carcinoma [4]. Finally, the 5th edition eliminated medullary carcinoma as a distinct histological type of breast carcinoma, and made it a distinct pattern of IBC-NST that is characterized by predominance of stromal tumor infiltrating lymphocytes (sTILs) and high grade [5]. This is in line with the early observation by Ridolfi et al, and contemporary reports and meta-analyses that large numbers of sTIL are of prognostic importance [39,40], and may explain the better prognosis of not only the former pure medullary carcinoma group, but also other high grade carcinomas with a lymphocyte predominant morphology.

7. Squamous carcinoma [1] - Metaplastic carcinoma [5]

Of the full range of metaplastic carcinomas, only *squamous carcinoma* was recognized as a separate entity in the 1968 classification [1], to stepwise get to all the types recognized by the 5th edition (Tab. II). The >90% purity rule is not mentioned in the related chapter. A *mixed metaplastic carcinoma* category is also defined with either different metaplastic components being present or the admixture of metaplastic and non-metaplastic adenocarciomatous components, where the percentage of each component requires reporting. According to the description with no percentage requirement, it seems that any amount of metaplasia qualifies a breast carcinoma as metaplastic. However, the last sentence of the histopathology section on metaplastic carcinoma states that IBC-NSTs may have a very tiny metaplastic component, which should be noted in the report, and this is probably best interpreted as an allusion to what is described under mixed carcinomas: if <10% is of special type,

this should be noted, but the carcinoma is classified as IBC-NST [5]. This might be in agreement with the statement (made under a different WHO classification in effect) that basal-like grade III *invasive ductal (NST) carcinomas* often demonstrate squamous metaplasia [41]; should they now be (mixed) metaplastic carcinomas if this feature exceeds 10%? – according to the rule, they should.

When one speaks about metaplasia in the breast, the most obvious term that comes to mind is *apocrine metaplasia*. Nevertheless, apocrine carcinoma or carcinomas with apocrine features have never been part of the metaplastic carcinoma group. As they were not even represented in the 1st edition, they are discussed separately, after the entities appearing in the 1968 edition.

8. Papillary carcinoma [1] - carcinomas with a papillary morphology

The papillary pattern is easy to discern, and several organs (like the thyroid gland, kidneys, ovaries… etc.) have papillary carcinomas. (Benign and borderline papillary tumors are also well recognized, and the gastrointestinal tract features villous tumors with similar architectural patterns). The papillary carcinoma structure requires fibrovascular cores covered by neoplastic cells, in contrast to "micropapillae" which is a misnomer and does not refer to small papillae, but to epithelial outgrowths without fibrovascular cores. The breast has a number of papillary carcinomas, and the use of papillary carcinoma without further qualifiers is improper. These tumors are also classified as part of mammary *papillary lesions*, which can be hyperplastic, neoplastic and in the latter category benign, in situ and invasive.

The 1st edition of the blue book mentions intracystic and intraductal papillary carcinomas with a proliferation similar to intraductal papilloma but with cellular atypia and features of malignancy as well as infiltration of the stroma at the base of the papillary growth. The illustrations appear more micropapillary (epithelial cell outgrowths without fibrovascular cores) than papillary [1]. The second edition stressed the papillary structures of the invasive component [2], and a carcinoma with papillary lymph node metastasis is also illustrated. Tumors with >90% papillary invasive component are admittedly extremely rare [3-5], and although invasive papillary carcinoma has been part of the classification since the beginning (with the described alteration in what was meant by the term), other special forms of papillary carcinomas are more common. In the 5th edition, *papillary DCIS* stands alone (separated from the DCIS category where it is also mentioned as a pattern of growth), and together with *encapsulated papillary carcinoma*, *solid papillary carcinoma* (in situ and invasive) and *invasive papillary carcinoma*, it forms the group of carcinomas listed under papillary neoplasms.

However, other carcinomas like the *mucinous cystadenocarcinoma* and the *tall cell carcinoma with reversed polarity* may have papillary areas. The latter is a new entity in the classification, first described under the lengthy name of *breast tumor resembling the tall cell variant of papillary thyroid carcinoma* [42], and also mentioned as a variant of *solid papillary carcinoma* [43], with relatively few cases and several alternative names in the literature. Although many of these names had reference to the common papillary architecture of the tumor, the final name adopted by the WHO classification has omitted this. To many, reversed polarity in breast pathology is associated with the image of the first morphology described as such, and this is the inside-out pattern of invasive micropapillary carcinoma, where the reversal of polarity seems complete, according to our current understanding of this structural phenomenon [44]. Despite the search for a good name, reversed polarity in *tall cell carcinoma with reversed polarity* does not always adequately describe the phenomenon of the nuclei being placed towards the centre or apical pole of the cells from the common basal location. Reversed polarity (like in inside-out or upside-down) would suggest that all nuclei are at the top of the cells (and this is often the case, but not always; nuclei may be more central in location), and therefore altered polarity might have been more descriptive.

In contrast to the rarity of invasive papillary carcinoma, *invasive micropapillary carcinomas* (described in a number of other organs too), not demonstrating fibrovascular coreless epithelial outgrowths (like in DCIS), but rather showing an inside-out reverted polarity pattern with a typical cuticule-like microvillous secretory surface towards the stroma and therefore a gap between the stroma and the neoplastic epithelial cells, is not uncommon, especially in its mixed form. It has made its first inclusion into the classifications in the 3rd edition and has remained thereafter without great alterations [3-5]

9. Apocrine carcinomas [1] - carcinomas with apocrine differentiation [5]

As carcinomas with predominant cells having abundant eosinophilic cytoplasm are reminiscent of apocrine metaplasia, they made their way to the classification in the 2nd edition [2]. Carcinomas with cytologically and immunohistochemically apocrine cells in >90% of the tumors were classified as apocrine in the 3rd edition [3]; according to the description the immunoprofile

is typically GCDFP15 positive (+), bcl2 negative (-), usually estrogen receptor (ER)- and progesterone receptor (PR)- and often androgen receptor (AR)+. The 4th and 5th editions discuss these tumors under the heading of "*Carcinomas with apocrine differentiation*", recognizing that several histological types may show apocrine morphology and immunophenotype: those listed beside *IBC-NST* include *invasive micropapillary*, *lobular* and *mucinous carcinomas*. Furthermore, *encapsulated papillary carcinoma* of apocrine differentiation has also been reported [45,46]. The 5th edition defines apocrine differentiation by light microscopic morphology as cells with distinct cell borders, abundant granular eosinophilic or vacuolated cytoplasm, large round to oval nuclei and prominent nucleoli and a GCDFP-15+, ER- PR- AR+ immunophenotype [5]. Nothing is said about the classification of tumors having light microscopic apocrine features with some deviation from the described immunophenotype. The earlier wording [3,4] allowed these to be classified as apocrine.

10. Other special types

A number of other types or clinical presentations (e.g. inflammatory breast carcinoma or male breast cancer) not specifically listed in the previous paragraphs are represented in the classifications and Table II. The examples detailed above serve as illustration to changes, rules of classification, and/or represent the most frequent types of breast cancers encountered.

Although we as pathologists are much concerned about an as precise as possible classification of breast tumors, our clinical colleagues are more pragmatic in their approaches, generally distinguishing between ductal, lobular, sometimes a mixed ductal and lobular, and *other types* as examplified by the reports of some of their clinical trials [47,48].

Concluding remarks about histological typing

There has clearly been a development in understanding breast carcinoma, its development, morphology and molecular/genetic backgrounds. For example, the early belief that usual type ductal hyperplasia (UDH) precedes atypical hyperplasia (ADH) which then progresses to DCIS and invasive carcinoma has been refuted, and UDH is now considered a hyperplastic proliferation, whereas ADH is a neoplastic one. Starting from 10 types of noninvasive and invasive carcinomas, of which one (carcinoma arising in cellular intracanalicular fibroadenoma) has practically disappeared, some half a hundred distinct or overlapping or encompassing entities are recognized now and form the basis of the classification which – as it is often the case – achieves goals but fails to make an idealistic absolute order. The WHO blue books have always been written by some of the most prominent experts in the field, and having been part of the process was a rewarding experience to be remembered. The present edition, 51 years after the first one, is probably the best that could be achieved at this point, but there is still ground for improvement.

Theoretically, a classification should allow all cases to be allocated to one class or the other, but in practice there always seem to be cases that defeat the artificial categories created. Therefore, it seems that there is no proper classification without an "others" category, which in the case of invasive breast carcinomas is the *IBC-NST without distinct patterns*.

Optimally, a tumor should be only classified (and coded) as belonging to one class, and this would require easily reproducible and obvious categories defined on the basis of unique features. "It is unknown whether these tumors represent a subtype of ILC or mucinous carcinoma" – write the authors of the chapter on mucinous carcinoma when they deal with the lobular carcinomas that form extracellular mucin [5], and they are right, as these tumors fit both the definitions of lobular carcinomas (defined principally by their discohesive cells) and of mucinous carcinomas (defined principally by the presence of extracellular mucin). The same overlaps are acknowledged or may arise in carcinomas with apocrine differentiation, a micropapillary and a mucinous look, a papillary architecture and a metaplastic trait… etc. A person can be of short stature and obese together and the presence or color of his/her hair will depend on neither of these features. Therefore, a classification that includes e.g. overweight/obese – deviating from normal height – bold as categories, will allow several proper classifications, but none of which would be "the ideal".

If we are to have obvious categories for classification, we should have obvious none overlapping features to allow us to properly allocate tumors into categories and further similar organizing principles to subdivide the larger categories into subcategories, like the kingdoms, phyla, classes, orders, families, genera in taxonomy. Even the biologic behaviour of tumors is difficult to segregate into categories: it would seem obvious to have benign (white) and malignant (black) as two major categories (as done by the 1st edition of the WHO classification), but there are so many shades of gray in between (carcinomas of better and worse outcome) and even some entities with unknown behaviour, that even such an organization would not be as obvious as initially believed. Lumping as many as

possible into two categories at one extreme or splitting each tumor into an individual place in the system – something that personalized treatment would perhaps wish to achieve – are not what a usable classification at human scales can do, especially if it wishes to be congruent with traditions.

We now have a system with diagnostic categories of carcinomas that are still based on morphologies with possible overlaps (histological types) [5]. Some entities share the name of previously differently defined diseases (e.g. mixed carcinomas, cribriform carcinoma) and alert to caution when reading papers from the past, using alternative definitions. Some entities that have been described by others (e.g. tubulopapillary carcinoma [49] in addition to those already mentioned) are not recognized by the WHO classification as separate entities, and are therefore not part of the system, just as IBC-NSTs (the "Others" category). We also have treatment influencing stratifications on the basis of e.g. histological grade or biomarker expression (ER, PR, human epidermal growth factor receptor 2 – HER2, stromal tumor infiltrating lymphocytes – sTILs, targetable driver mutations, gene expression profiles… etc.), and this seems to be the way our clinical colleagues would like to simplify their approaches to breast cancer, where histological typing is simply missing from the results of some recent milestone clinical trials [50,51]. However, as stated in the introduction, histological types matter, have clinico-pathological correlations worth knowing for optimal management and add to the art of pathology.

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