Reference 5
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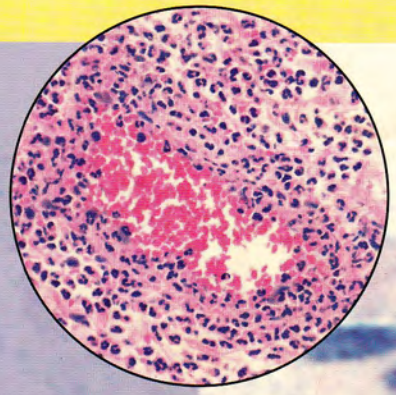
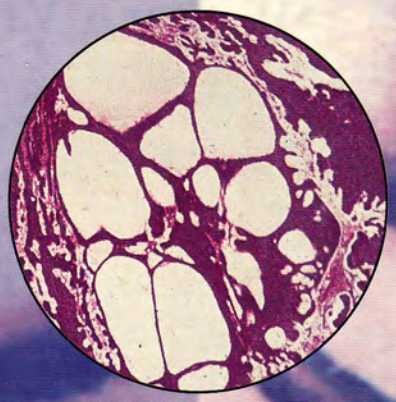
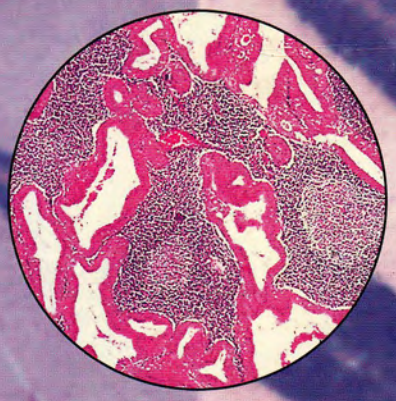
FOURTH EDITION

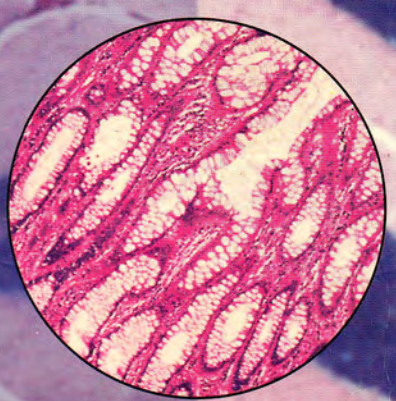
# WHEATER'S Basic HISTOPATHOLOGY

## a colour atlas and text









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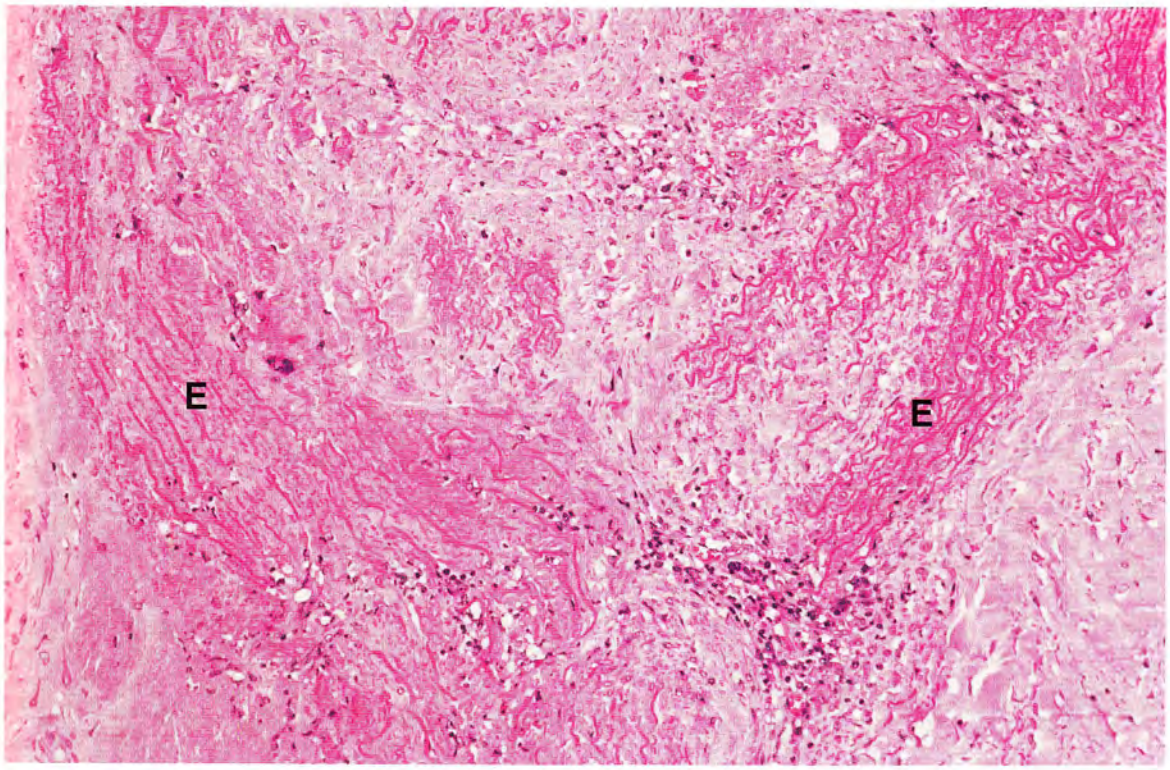



(b)

## Viral infections

Viruses cause disease in three main ways:

- By causing death of the cell they infect, either by a direct effect or by modifying the genome such that the host cell is recognised as foreign and is destroyed by the host's own immune system.
- By causing excessive proliferation of the infected cell line. This may be an important factor in the eventual development of malignant tumours in the affected cell line. Human papilloma virus (HPV) is important in this respect.
- By integrating themselves in the cell nucleus where they produce latent infection.

Although viral culture and the demonstration of rising titres of antibodies against the virus remain the mainstay of diagnosis, some viral infections can be diagnosed by characteristic histological appearances. Individual viruses are too small to be seen by light microscopy, but when congregating together in enormous numbers within the host cell, they are visible as viral inclusion bodies and may be either intranuclear, intracytoplasmic, or both. Inclusion bodies provide a histological clue to the causative virus, and this can be confirmed by electron microscopy and immunohistology.

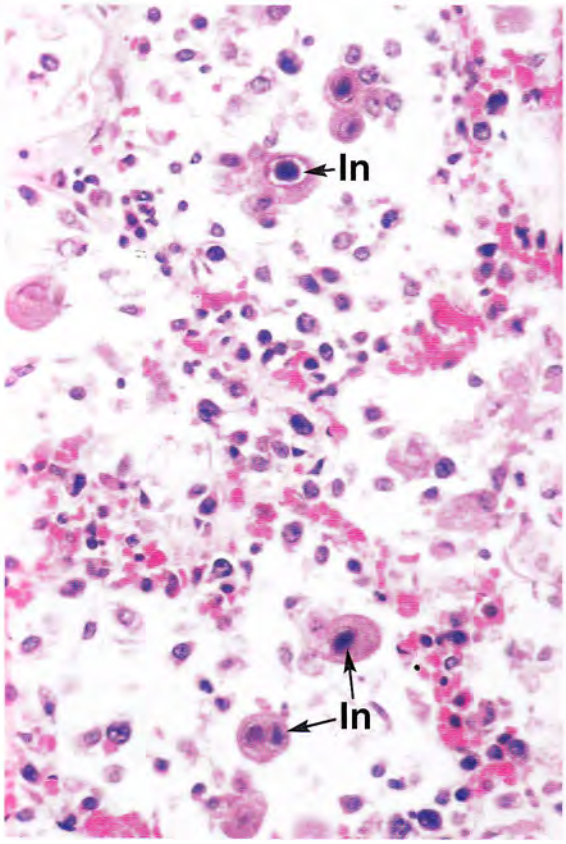



**Fig. 4.16** Cytomegalovirus infection (HP)

***Cytomegalovirus (CMV)***, another of the Herpes virus group, causes a mild, non-specific infection in immunocompetent individuals. Most adults will have been exposed to this virus by late middle age and will have specific serum antibodies. CMV infects white blood cells and may remain latent in leucocytes for many years. If the individual then becomes immunosuppressed for any reason, widespread systemic infection may result. Common sites of infection include the lungs, brain, retina, gastrointestinal tract and kidney.

CMV pneumonitis is shown in this micrograph. The characteristic feature is markedly enlarged cells with large dark-staining intranuclear inclusion bodies **In**. These are surrounded by a clear halo. Cytoplasmic inclusions are also sometimes seen but are not illustrated in this micrograph. Focal necrosis is also sometimes present but there is usually minimal, if any, inflammation. Cytomegalic inclusions are usually seen in epithelial cells, endothelial cells and in macrophages, and as is the case in other Herpes virus infections, they may be sparse.

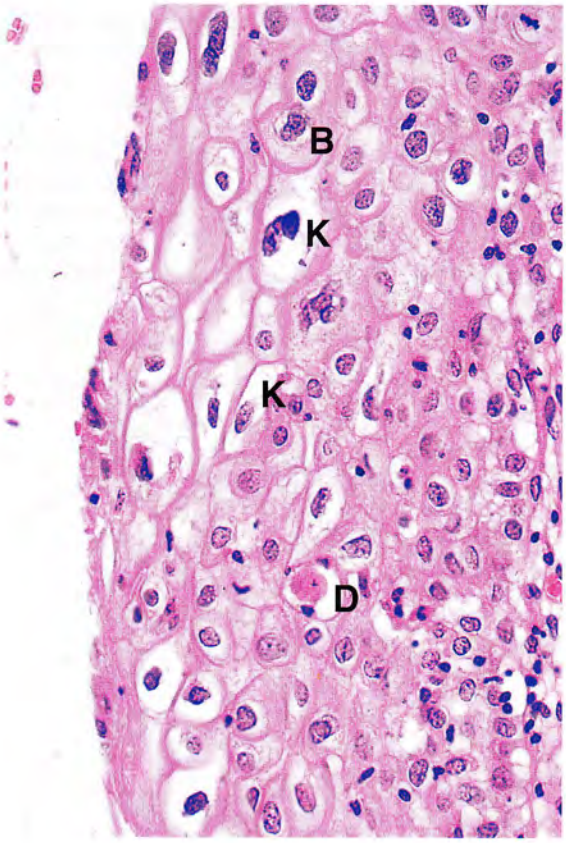



**Fig. 4.17** Human papilloma virus (HP)

***Human papilloma virus (HPV)*** is the causative agent of the common viral warts on the skin and genital warts. It has also been shown to be very closely associated with ***cervical intraepithelial neoplasia*** (**CIN**) and with invasive squamous cell carcinoma of the cervix, vagina, vulva and other sites.

HPV infects squamous epithelial cells and causes characteristic changes in the epithelial morphology. The epithelium is usually thickened (acanthotic) or may have the papillary appearance of an exophytic wart (***condyloma acuminatum***). Infection of cells in the upper layers of the epithelium produces enlargement of the nuclei which are hyperchromatic and have a folded appearance. A prominent cytoplasmic halo is also seen. These cells are called ***koilocytes*** **K**. In addition, the epithelium contains binucleate cells **B** and dyskeratotic cells **D** (i.e. individual cell keratinisation).

Such changes as those above are usually seen in association with low grade CIN, as in this specimen from a woman with CIN I. In high-grade CIN, these changes are not usually apparent, being overshadowed by more advanced dysplastic changes; HPV infection can, however, be demonstrated by molecular techniques in almost all high grade CIN lesions (see also Fig. 17.4).

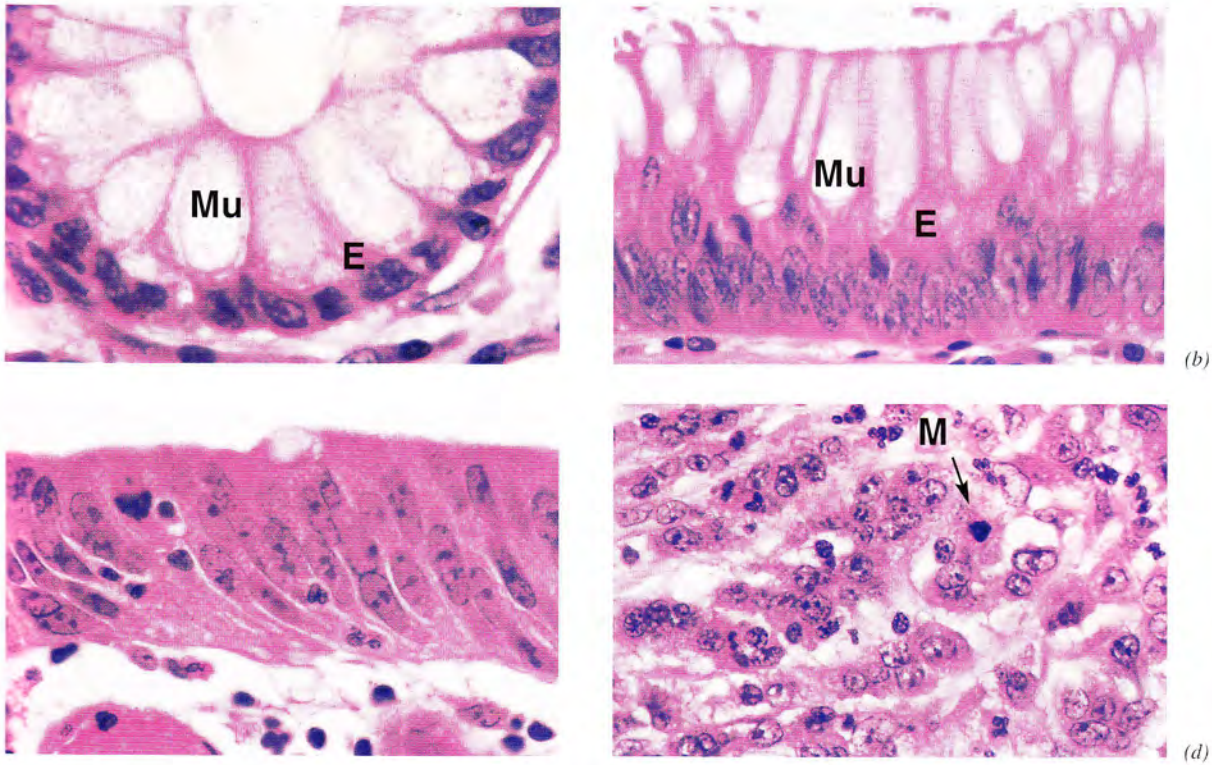
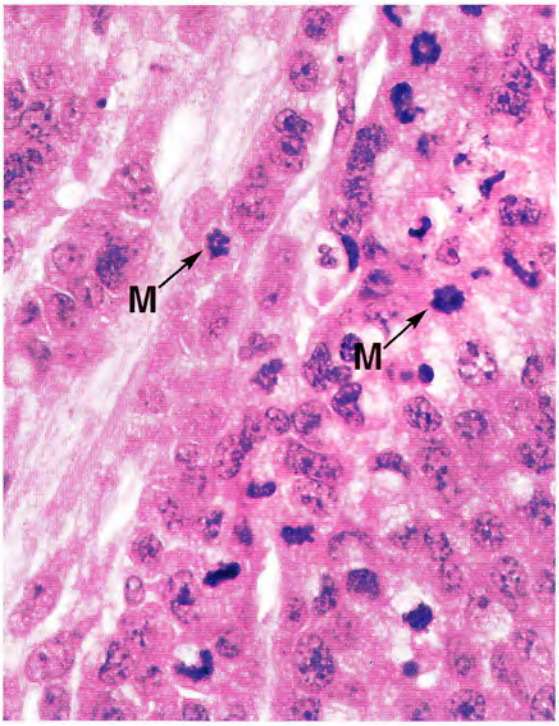
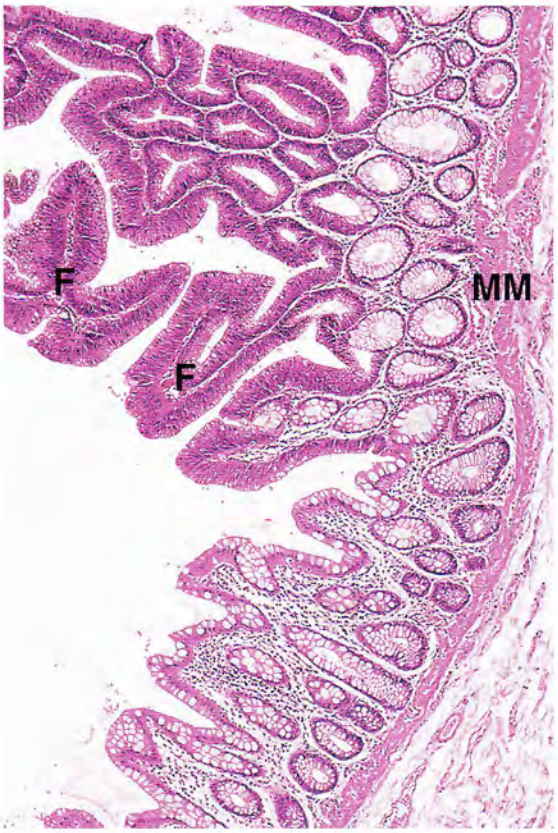



**Fig. 7.1** **Degrees of tumour differentiation: colon** *(caption opposite)*

**Fig. 7.2** **Cytological features of malignancy**

Pleomorphism, nuclear hyperchromicity and abnormal mitotic activity are features of malignant neoplasms and are not usually seen in benign neoplasms. The malignant tumour illustrated shows considerable variation in cell size and shape (***cellular pleomorphism***) and nuclear size and shape (***nuclear pleomorphism***); in addition, many nuclei are very darkly stained (***nuclear hyperchromatism***). The chromatin pattern in nuclei is typically coarsely clumped. Nucleoli are also prominent and some cells may have multiple nucleoli. Large numbers of cells in mitosis are seen in many conditions in which there is excess cellular proliferation (e.g. hyperplasia), but in malignant lesions many of the mitotic figures are abnormal; note two ring mitotic figures **M**. Multiple mitoses may also be seen in malignant tumours.



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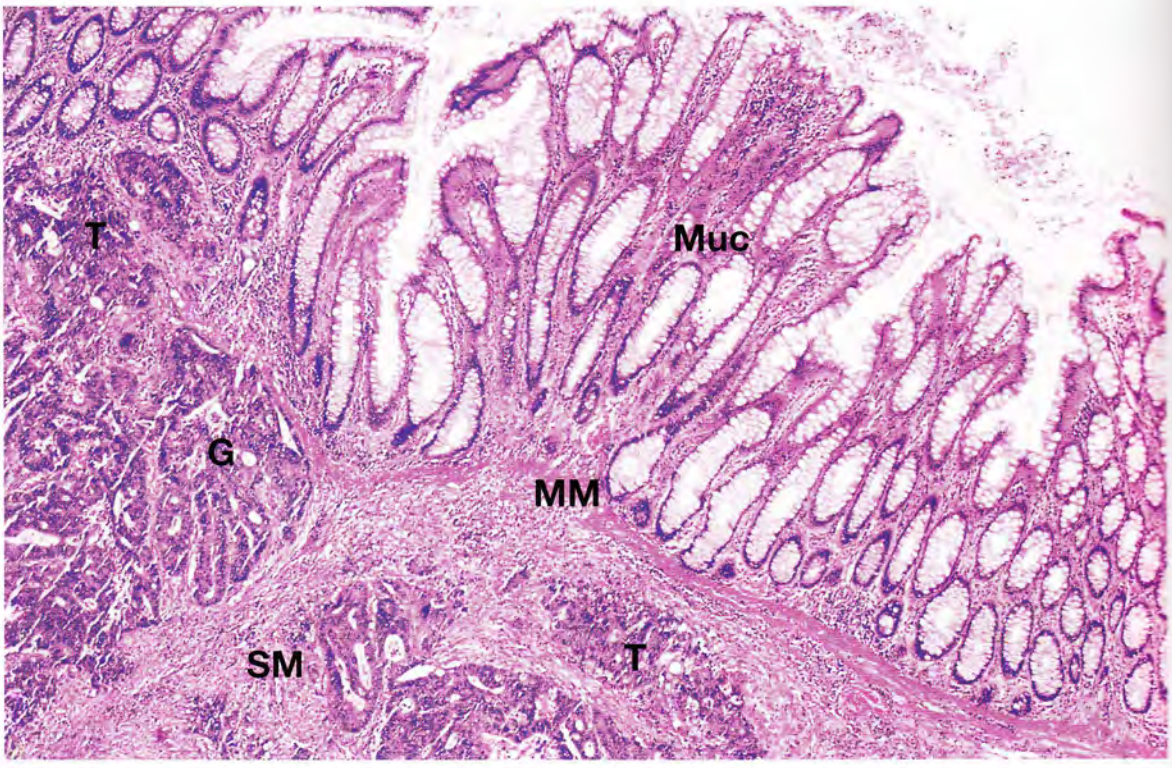



(b)

**Fig. 7.4 Invasive characteristics of surface neoplasms: colon**

**(a) Benign neoplasm: villous adenoma (MP)**

**(b) Malignant neoplasm: adenocarcinoma (LP)**

Benign neoplasms of surface epithelia usually grow in the form of warty, papillary or nodular outgrowths and show no tendency to infiltrate downward into the submucosa. Micrograph (a) shows one form of benign colonic neoplasm; this ***villous adenoma*** has grown into the lumen in the form of papillary fronds **F** with a stromal core covered by moderately dysplastic epithelial cells. The underlying muscularis mucosae **MM** is intact and there is no downward tumour spread.

Malignant neoplasms not only form a mass in the lumen, but also spread across the epithelial basement membrane into subepithelial tissues. In micrograph (b) of a colonic ***adenocarcinoma***, the tumour cells **T** have grown in complex, abnormal gland formations **G** within the mucosa; malignant glands are also seen invading into the submucosa **SM**, having breached the muscularis mucosae **MM**, and have spread beneath the adjacent normal mucosa **Muc**. Even at low power, it is obvious that the malignant cells are disorganised, crowded together and are less differentiated than are the cells of the benign adenoma. Note the nuclear hyperchromatism of both benign and malignant lesions in comparison to the normal. Higher power micrographs of similar neoplasms are shown in Figure 7.1.

## Staging of malignant tumours

The extent of local, regional and distant tumour spread is an important determinant of tumour management and prognosis. Several systems have been devised for defining these characteristics in a standardised fashion; this is known as ***staging*** of a tumour. The ***TNM system*** is the most widely used method and involves scoring the extent of local **T**umour spread, regional lymph **N**ode involvement and the presence of distant **M**etastases. Despite advances in diagnostic techniques, the stage of a tumour is generally a very good indicator of likely prognosis. Tumour stage assessment is also important in planning therapy; tumours at an advanced stage (extensive spread) may require aggressive treatment, while early stage tumours (localised) can be treatable by more conservative measures such as surgical excision alone. Staging is usually performed by a combination of histopathology, radiology and clinical assessments.

By way of example, the TNM method of breast cancer staging is as follows:

| | | |
|---|---|---|
| T0 = breast free of tumour | N0 = no axillary nodes involved | M0 = no metastases |
| T1 = local lesion < 2 cm in size | N1 = mobile nodes involved | M1 = demonstrable metastases |
| T2 = lesion 2–5 cm in diameter | N2 = fixed nodes involved | MX = suspected metastases |
| T3 = lesion >5 cm in diameter | N3 = ipsilateral internal mammary node involved | |
| T4 = skin and/or chest wall involved | | |

## Histological assessment of neoplasms

Histological assessment of a tumour provides a useful guide to tumour behaviour, i.e. whether the tumour is benign or malignant, and provides a rational basis for treatment. Histological assessment should establish the following features:

- The type of tumour. This is based on the presumed tissue of origin and/or differentiation of the tumour.
- The degree of differentiation. This is known as ***grading*** and takes into account some or all of the following features:
  — the similarity of the tumour to the supposed tissue of origin both architecturally and cytologically (***differentiation***)
  — the degree of variability of cellular shape and size (***pleomorphism***)
  — the proportion of mitotic figures (dividing cells).
- The extent of spread of tumour (***staging***) is partly assessed histologically, particularly:
  — size of the primary tumour
  — histological assessment of local invasion, and vascular, lymphatic and perineural invasion
  — the presence of metastatic tumour deposits, for example in lymph nodes and bones.
- The presence or absence of other prognostic factors; for instance, the presence of oestrogen receptors in breast carcinoma cells confers an improved prognosis. The expression of certain oncogenes is increasingly being related to prognosis in some tumours.

The histological features which distinguish benign and malignant tumours are summarised in Figure 7.10.

**Fig. 7.10 Summary of histological features of neoplasms**

| | Benign | Malignant |
|---|---|---|
| *Behaviour* | Expansile growth only; grows locally<br>Often encapsulated | Expansile and invasive growth; may mestastasise<br>Not encapsulated |
| *Histology* | Resembles cell of origin (well differentiated)<br>Few mitoses<br>Normal or slight increase in ratio of nucleus to cytoplasm<br>Cells are uniform through the tumour | May show failure of cellular differentiation<br>Many mitoses, some of which are abnormal forms<br>High nuclear to cytoplasmic ratio<br>Cells vary in shape and size (cellular pleomorphism) and/or nuclei vary in shape and size (nuclear pleomorphism) |

## In situ neoplasia (carcinoma in situ)

These terms are used when an epithelial tissue shows the cytological and histological features of a carcinoma (architectural and cytological abnormalities, such as cell crowding, pleomorphism, increased and abnormal mitotic activity, i.e. severe dysplasia, see Ch. 6), but there is no evidence of any invasion. The basement membrane bounding the abnormal epithelial tissue is intact, and there is no encroachment of the atypical cells into underlying stroma. Thus, the epithelial cells show the cytological, but not the behavioural, characteristics of malignancy. However, many forms of ***in situ carcinoma*** will become invasive if left untreated.

Certain benign epithelial tumours may progress to form an invasive malignant tumour by development and selective persistence of mutations in key oncogenes. A sequence from benign neoplasm through increasing dysplasia to in situ carcinoma, and on to invasive carcinoma is well recognised in certain sites (e.g. the colon).

In situ neoplasia occurs particularly in skin (intra-epidermal carcinoma, see Fig. 2.15), uterine ectocervix (cervical intra-epithelial neoplasia, CIN III, see Fig. 17.6), vulval skin and mucosa (VIN), and other sites. In situ neoplasia also occurs in solid glandular organs, most notably the breast (see Fig. 18.9).

Two other terms are used in this context: some ovarian carcinomas, which show the cytological features of malignancy but no histological evidence of invasion, are said to be '***of borderline malignancy***', and some soft tissue tumours, which show limited cellular and nuclear pleomorphism with increased mitotic activity, yet are bounded with a discrete capsule, are said to be '***of low malignant potential***'.

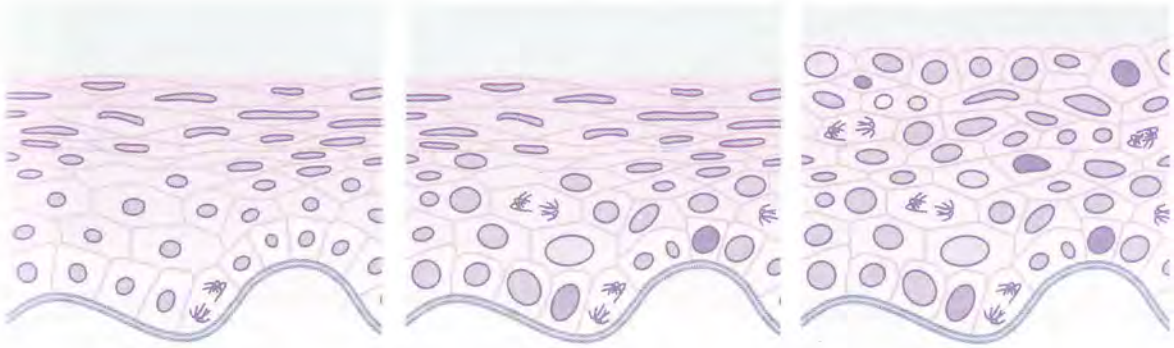



**Fig. 7.11** **In situ neoplasia**

Diagram (a) shows the regular architecture of a normal stratified squamous epithelium. The layered epithelium is formed by mitotic replication of the basal layer, producing layers of regular cells which differentiate and flatten as they get near the surface (stratification). The cells are regular in shape and size, as are the nuclei, and mitotic activity is confined to the basal layer.

Diagram (b) shows an epithelium in which there is dysplasia in the lower layers. The cells and their nuclei are irregular in shape and size, and the nuclei occupy more of the cell. Mitoses are present in layers other than the basal layer. The cells still differentiate and mature, eventually, near the surface.

Diagram (c) shows fully developed in situ neoplasia. The dysplastic epithelial cells now occupy the full thickness of the epithelium, and stratification and differentiation are largely lost; mitoses can be present in any of the layers, even in surface cells. Although all the cells in this epithelium show cytological characteristics of malignancy (cellular and nuclear pleomorphism, high nucleus/cytoplasm ratio, nuclear hyperchronicity and increased abnormal mitotic activity), the epithelial cells as yet show no tendency to invade across the basement membrane into the stroma.

The changes shown in (b) are regarded as an early stage in the development of in situ neoplasia. In certain locations, this is acknowledged by applying a numerical value. Hence, in the squamous epithelium of the uterine cervix, the changes in (c) would be called CIN III (cervical intra-epithelial neoplasia III), whereas those in (b) would be called CIN II. A similar scheme exists in the nomenclature of dysplastic/in situ neoplastic changes in the vulva (VIN), anus (AIN) and vagina (VAIN), with gradings of I, II and III.

## Acute inflammation of the liver

Hepatocytes, with their high degree of metabolic activity, are readily disturbed by toxins and demonstrate the histological cellular responses known as cloudy swelling, fatty change and necrosis as described in Chapter 1. Acute inflammation of the liver parenchyma is usually marked by focal accumulations of inflammatory cells usually in relation to the site of necrotic hepatocytes. The exception to this is in the formation of ***hepatic abscesses*** which usually develop either as a result of bacterial infections from the biliary tract or from a septic focus in the abdomen drained by the portal venous system to the liver.

***Acute hepatitis*** is a general term for inflammation of the liver parenchyma which can then be further classified according to aetiology. The four most important groups of conditions causing acute hepatitis are:

- **Viral hepatitis** (outlined in Fig. 14.3) – histological appearance shown in Figure 14.2.
- **Toxins** – alcohol is the most common hepatic toxin (Fig. 14.4).
- **Drugs** – hepatitis may be caused by the anaesthetic gas ***halothane***, particularly after repeated exposure. ***Isoniazid***, a drug commonly used in the treatment of tuberculosis, results in acute hepatitis in a small proportion of cases. Many other drugs occasionally cause acute hepatitis.
- **Systemic infections** – infections caused by *Leptospira* and *Toxoplasma* usually involve the liver as part of disseminated disease. Other systemic infections may cause multiple minute infective lesions as in bacterial septicaemia and miliary tuberculosis.

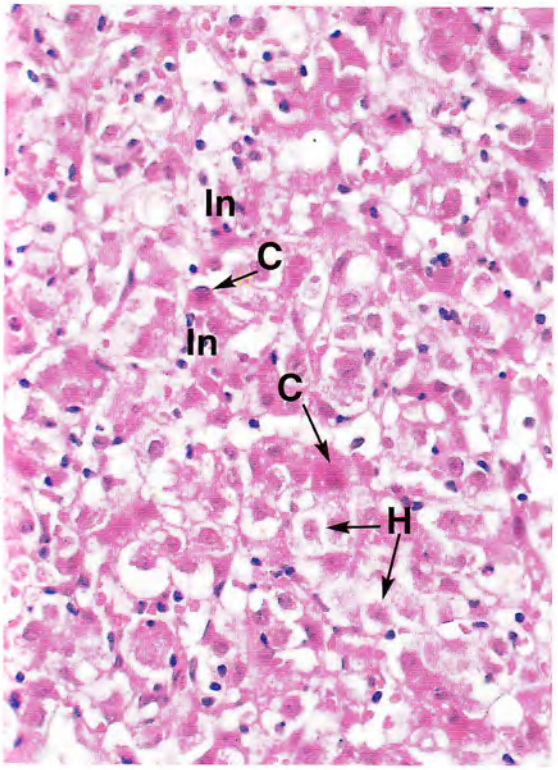



**Fig. 14.2 Acute viral hepatitis (HP)**

The viral agents causing acute hepatitis all produce a similar histological picture in the acute phase.

There is widespread swelling and ballooning of hepatocytes owing to hydropic degeneration **H** and this progresses to focal or ***spotty necrosis*** throughout the lobule; the areas of necrosis are identified by aggregates of inflammatory cells **In** surrounding eosinophilic (pink-stained) bodies called ***Councilman bodies*** **C**, representing the cytoplasm of necrotic liver cells. The Kuppfer cells are very active and within portal tracts there are increased numbers of chronic inflammatory cells (not illustrated here).

In time, regeneration of the dead hepatocytes occurs. In hepatitis A and E, complete resolution is the rule but in hepatitis B, C and D, activity may persist or progress to chronic hepatitis (Fig. 14.7).

Rare cases of viral hepatitis occur in which there is massive liver necrosis instead of the focal type seen here. This is particularly seen with hepatitis E in pregnancy; such fulminant cases are usually fatal.

**Fig. 14.3 Viral causes of hepatitis**

| Virus Type | Mode of transmission | Acute hepatitis | Chronic hepatitis | Chronic carrier | Notes |
|---|---|---|---|---|---|
| Hep A | Faeco-oral | Yes | No | No | Mild, self-limiting (rarely fulminant) |
| Hep B | Blood, saliva, semen | Yes | 5-10% | Yes | Transmission – 'needle sharing', sexual, transfusion |
| Hep C | Blood, saliva, semen | Yes | 50% | Yes | Transmission – 'needle sharing' transfusion |
| Hep D | Blood, saliva, semen | Yes | Yes | Yes | Only in association with hepatitis B |
| Hep E | Faeco-oral | Yes | No | No | Usually mild, self-limiting (rarely fulminant) |

## Aetiology and classification of dysplasia of the vulva, vagina and cervix

The vulva, vagina and ectocervix are lined by stratified squamous epithelium which is prone to sexually transmitted infection by ***human papillomavirus (HPV)***. This virus has long been known to be associated with common skin warts, ***verruca vulgaris*** (Fig. 21.9) and venereal warts, ***condyloma acuminatum***.

There are a large number of serotypes of HPV and recent evidence has shown a very close association between infection with certain serotypes and the presence of dysplasia and invasive carcinoma of squamous epithelia. The association was first discovered in the cervix where high risk HPV serotypes are associated with approximately 85% of invasive cancers but has also been shown to apply to the vagina, the vulva and to squamous lesions at other sites.

Infection with certain ***low risk serotypes*** of HPV, namely serotypes 6, 11, 42 and 44, results in condyloma acuminatum and low grade dysplasia. The ***high risk serotypes***, serotypes 16, 18, 31, 33 and 35, are more likely to result in high grade dysplasia or invasive carcinoma. High risk serotypes are more likely to integrate their DNA into the host genome thereby introducing ***viral oncogenes (v-oncogenes)*** and allowing their transcription. The progression from latent infection to invasive carcinoma is also dependent on host factors such as the immune status of the host, nutritional factors and cigarette smoking, and only a small proportion of women infected with high risk serotypes progress to invasive carcinoma.

In the cervix, intraepithelial dysplasia is termed ***cervical intraepithelial neoplasia*** or ***CIN*** and graded as I, II or III (see Fig. 17.5). Similarly, ***vulval intraepithelial neoplasia*** is graded ***VIN I, II*** or ***III*** and ***vaginal intraepithelial neoplasia*** as ***VAIN I, II*** or ***III***.

## Cervical dysplasia and carcinoma

The vagina and the vaginal aspect of the cervix are covered by stratified squamous epithelium, which is well adapted to withstand the normal vaginal environment. The endocervical canal, on the other hand, is lined by a simple columnar, mucin-secreting epithelium; at a microscopic level, this is deeply folded so as to form gland-like invaginations into the cervical stroma, the endocervical glands, which are responsible for the elaboration of normal cervical mucus.

The junction between stratified squamous and columnar epithelium normally lies at the external os. The volume of the cervical stroma expands under the influence of hormones during each menstrual cycle, at menarche and during pregnancy, and this causes eversion of the vaginal end of the endocervical canal thus exposing some of the simple columnar epithelium to the vaginal environment. This exposed epithelium appears red in relation to the surrounding stratified squamous epithelium and hence became inaccurately known as a ***cervical erosion***; more appropriate is the term ***cervical ectropion***. Under the influence of the vaginal environment, the ectropic columnar epithelium may undergo squamous metaplasia (see Fig. 6.6a) to form stratified squamous epithelium indistinguishable from the lining epithelium native to the vagina. This metaplastic area, described as the ***transformation zone***, appears to be unstable and susceptible to dysplastic changes induced by external factors. As described above, infection with certain HPV serotypes, as well as cigarette smoking and large numbers of sexual partners, is associated with a higher incidence of cervical dysplasia and carcinoma. The dysplastic changes may well regress if these predisposing factors are eliminated; however, it is believed that some undergo irreversible neoplastic change with the development of ***CIN III***. Furthermore, a small proportion of untreated cases of CIN III progress to frank ***invasive squamous cell carcinoma***.

The development of invasive squamous carcinoma may thus be prevented by intercepting the dysplastic process at an early stage and ***cervical cytology*** has been developed as a method of screening and monitoring this process in the population of women at risk. Once significant dysplasia has been demonstrated cytologically, histological examination of biopsy specimens taken at ***colposcopy*** is used to define accurately the degree of dysplasia and to plan appropriate treatment.

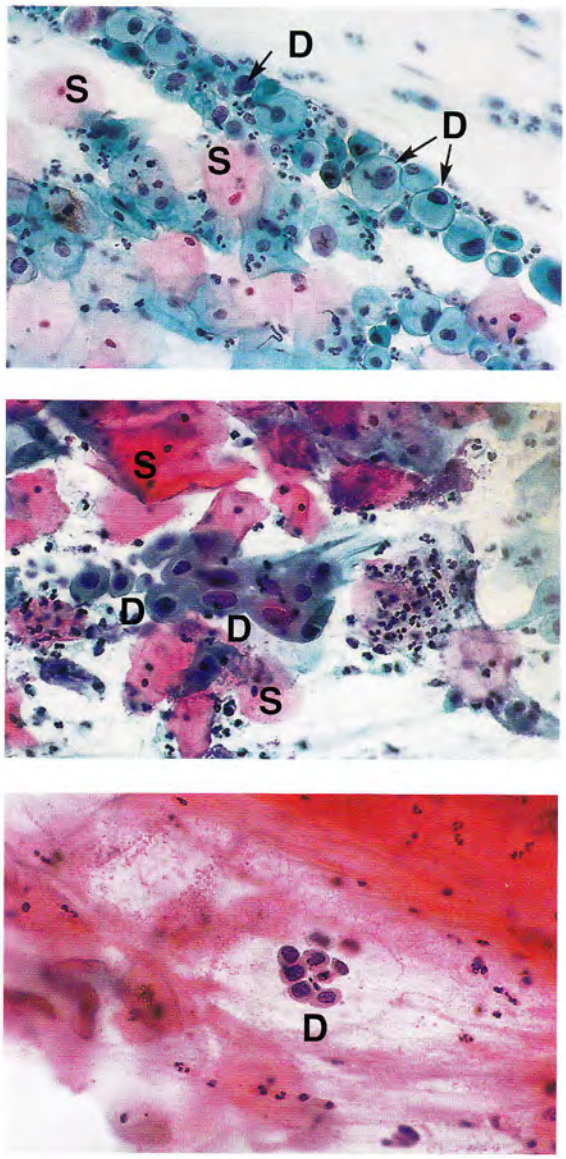



**Fig. 17.4 Cervical smear cytology**
**(a) CIN I (b) CIN II (c) CIN III (Pap stain) (HP)**

These micrographs are from preparations obtained by cervical smear stained by the ***Papanicolaou method*** (***Pap***). Micrograph (a) of CIN I (***low grade squamous intraepithelial lesion (SIL)***) exhibits both normal cervical squamous cells **S** and clumps of mildly dysplastic cells **D** which have large dark-stained nuclei, a slightly irregular nuclear contour and a coarse pattern of nuclear chromatin.

Micrograph (b) shows CIN II (***high grade SIL***). In this smear, the abnormal epithelial cells **D** have larger nuclei and a higher nuclear to cytoplasmic ratio than in CIN I with coarser, more hyperchromatic nuclei. Normal epithelial cells are marked **S**. In CIN III (***high grade SIL***) as shown in micrograph (c), the nuclear to cytoplasmic ratio is even greater although the cells overall are smaller **D**. This corresponds to total lack of surface maturation so that cells resembling the basal layer cells are exfoliated at the surface. ***Koilocytes*** (virus-infected cells) may also be detected on cervical smears (see Fig. 17.6).

The abnormal surface cells of dysplastic epithelium are scraped off when a Pap smear is taken. Most dysplasia occurs at the transformation zone, which is an area of metaplastic squamous epithelium found at the squamocolumnar junction in most women of reproductive age; clinically, the transformation zone is correctly described as an ectropion or more colloquially as an 'erosion'. It is therefore important that endocervical cells are seen in the Pap smear to ensure that the correct area has been sampled.

Many pathologists use the Bethesda classification system when grading cervical cytology specimens. This system groups human papillomavirus-induced changes and CIN I into the category of ***low grade squamous intraepithelial lesion (SIL)*** and CIN II and III into ***high grade SIL***. These slightly confusing grading systems are compared in Figure 17.5 below.

**Figure 17.5 Comparison of grading systems for cervical dysplasia**

| Histological features | Traditional system | WHO system | Bethesda system |
|---|---|---|---|
| Koilocytes plus mild atypia | HPV infection | HPV infection | Low grade SIL |
| Dysplasia limited to lower third of epithelium | Mild dysplasia | CIN I | Low grade SIL |
| Dysplasia limited to lower two thirds of epithelium | Moderate dysplasia | CIN II | High grade SIL |
| Dysplasia extending into upper third of epithelium | Severe dysplasia | CIN III | High grade SIL |
| Dysplasia of full thickness of epithelium | Carcinoma in situ | CIN III | High grade SIL |

# 18. Breast

## Introduction

The female breast is dependent for its normal activity on oestrogen and progestogens and thus exhibits considerable structural and functional variation throughout life. Apart from the overt changes occurring at puberty, pregnancy, lactation and menopause, more subtle changes also occur within the normal menstrual cycle. As a corollary, hormonal disturbances probably underlie various disorders of the breast, notably ***benign breast disease***, but probably also play some part in the pathogenesis of more serious conditions such as ***breast cancer***. Likewise, the male breast normally remains rudimentary unless breast enlargement, ***gynaecomastia*** (Fig. 18.5), is induced by exogenous or endogenous hormone imbalance; it may also result from the use of certain drugs, for example spironolactone.

Most clinically significant breast disorders present as a lump and the major imperative is to identify those which are malignant tumours so that the patient may be treated promptly. Several national screening programmes now use radiological techniques (***mammography and/or ultrasound***) to identify early suspicious breast lesions, including abnormal calcifications. A tissue diagnosis is then made by ***fine needle aspiration biopsy (FNAB)***, ***core biopsy*** or ***excision biopsy*** before definitive treatment is undertaken. It is expected that early removal of very small tumours will be curative.

## Inflammatory disorders of the breast

Infections of the breast are uncommon and mainly occur during lactation; the organisms (usually *Staphylococcus aureus*) gain access through cracks and fissures in the nipple and areola. Without early antibiotic therapy, the resulting ***bacterial mastitis*** may be followed by the development of a ***breast abscess*** that may require surgical drainage. More commonly, localised areas of inflammation of the breast follow trauma, which may be of sufficient severity to produce a condition known as ***fat necrosis*** (Fig. 18.1).

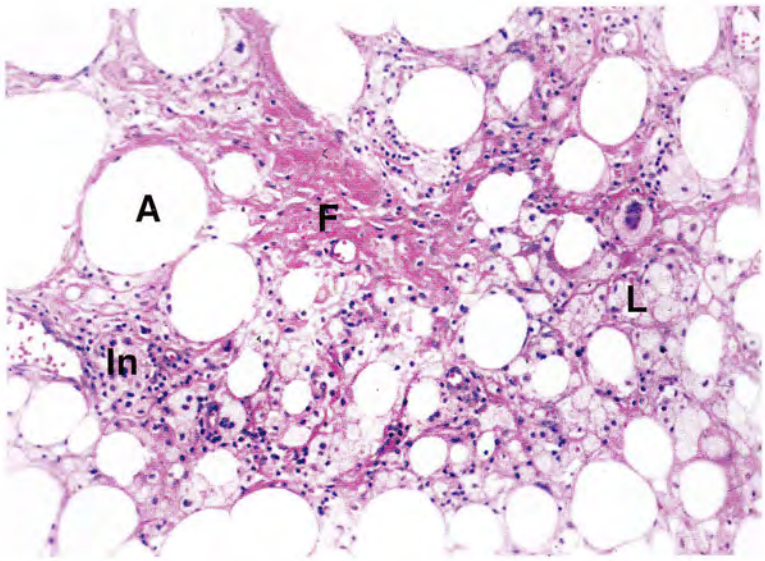
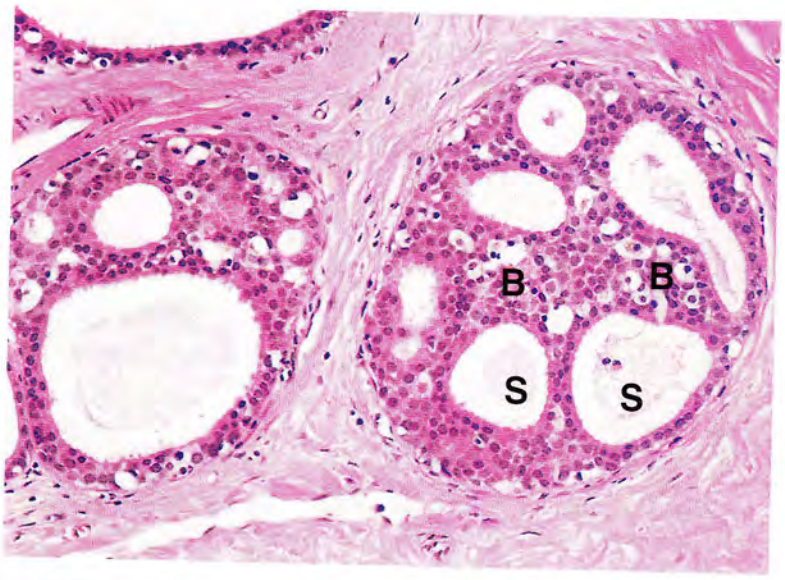
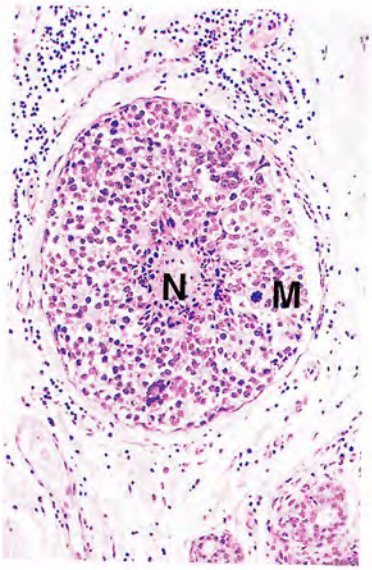



**Fig. 18.1** Fat necrosis (MP)

Trauma to the breast, sometimes apparently quite trivial, may result in necrosis of mammary adipose tissue. The presence of necrotic adipose tissue **A** excites a chronic inflammatory cell infiltrate **In**, in which lipophages **L** (macrophages containing lipid giving their cytoplasm a foamy appearance) and plasma cells may be present in large numbers. Fibrosis **F** of the damaged area produces a hard, often irregular, breast lump, which may resemble a breast carcinoma on palpation. Similar, more localised, changes may be seen in the breast following FNAB, core biopsy or other surgical procedures.




(a)




(b)

**Fig. 18.9 Ductal carcinomas of the breast**
**(a) Low grade ductal carcinoma in situ (MP)**
**(b) High grade ductal carcinoma in situ (MP)**
**(c) Invasive ductal carcinoma (MP)**

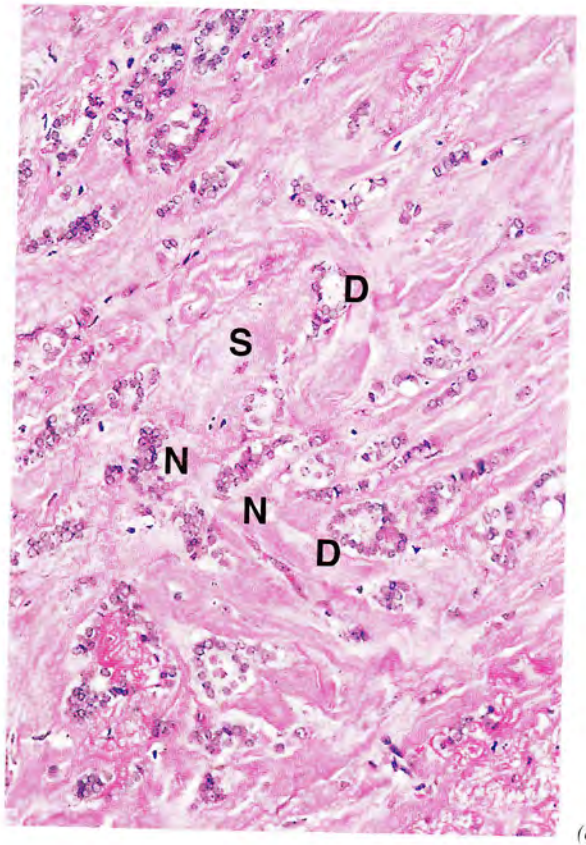
Ductal carcinoma is divided into invasive and in situ types depending on whether the malignant cells have breached the basement membrane of the duct and invaded the stroma. Both invasive and in situ carcinomas may be associated with abnormal calcifications that may provide the only mammographic clue to the presence of small tumours.

***Ductal carcinoma in situ (DCIS)*** is graded according to the cytological and architectural features of the lesion, with low grade lesions conferring a moderate increase in the likelihood of invasive carcinoma while high grade lesions are associated with a marked increase in the likelihood of invasive carcinoma. Micrograph (a) shows an example of low grade DCIS. The epithelial cells fill and expand the ducts forming sharply defined glandular spaces **S** separated by 'rigid' bridges **B** of cells; this is also known as the ***cribriform pattern***. The cells are very uniform in size and very regularly placed in relation to each other. Another low grade variant is the ***micropapillary pattern*** (not illustrated here) which commonly occurs in association with the cribriform pattern.

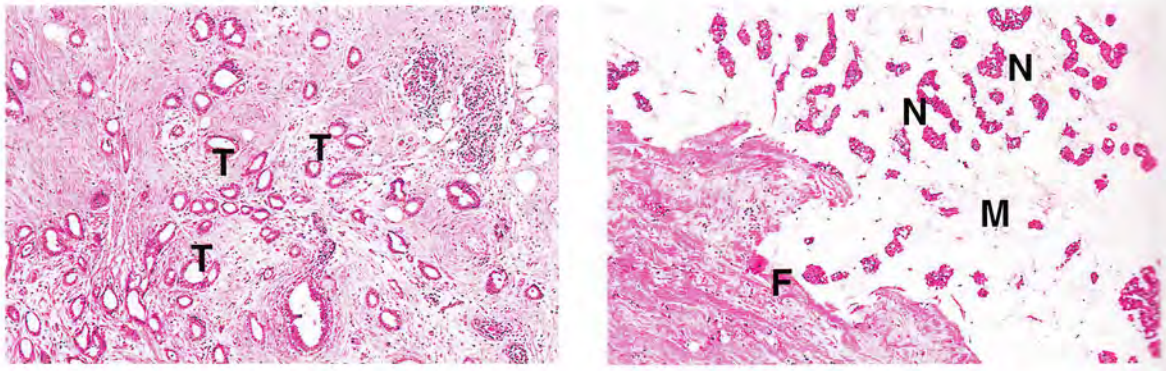
In contrast, in high grade ductal carcinoma in situ, the duct is expanded by a proliferation of large highly pleomorphic cells. As seen in micrograph (b), mitotic figures **M** are common as is central necrosis **N** (often called ***comedo necrosis***), which may be calcified (not in this example). DCIS is usually detected by mammographic screening programmes and only gives rise to a palpable mass when extensive.

***Invasive ductal carcinoma*** (often called ***ductal carcinoma, NOS***, i.e. ***N***ot ***O***therwise ***S***pecified) is the most common form of invasive carcinoma and has the worst prognosis. As seen in micrograph (c), the invading malignant epithelial cells form small ductal structures **D**, solid nests **N** and even solid sheets of cells. The stroma **S**, as in this example, is frequently very fibrotic which gives the characteristic firm texture on palpation. Another example of invasive ductal carcinoma is shown in Figure 7.3.

Several grading schemes have been developed over the years to help predict the clinical behaviour of invasive breast carcinomas. The most commonly used scheme assigns a numerical grade to each of three features of the tumour; namely, the degree of gland formation, the nuclear features of the tumour cells and the frequency of mitotic figures. The sum of these grades is then converted to a numerical grade 1,2 or 3, with grade 1 being a low grade lesion with a better prognosis and grade 3 being a high grade lesion.




(c)




(a)

**Fig. 18.10** **Variants of invasive ductal carcinoma**
**(a) Tubular carcinoma (MP) (b) Mucinous (colloid) carcinoma (MP)**

Certain variants of invasive ductal carcinoma have a much better prognosis than invasive ductal carcinoma, NOS. These are much less common than invasive ductal carcinoma, NOS but two of the commoner types are invasive ***tubular carcinoma*** and ***mucinous*** or ***colloid carcinoma***. Tubular carcinoma, as shown in micrograph (a), consists of malignant epithelial cells which form well-defined tubular or ductal structures **T** with no solid nests of cells or single cell invasion. The tubules are lined by a single layer of mildly pleomorphic cells and invade into the surrounding fat with no evidence of an overall lobular architecture; this is in contrast to sclerosing adenosis (Fig. 18.3) which may be confused with tubular carcinoma.

Mucinous carcinoma, as seen in micrograph (b), is characterised by pools of mucin **M** in which nests of malignant cells **N** are suspended. Mucinous carcinoma is characteristically soft to palpation and has a well-defined margin of fibrous tissue **F**.

Other ductal carcinoma variants with a good prognosis that are not illustrated here include invasive ***cribriform carcinoma*** and ***medullary carcinoma***.

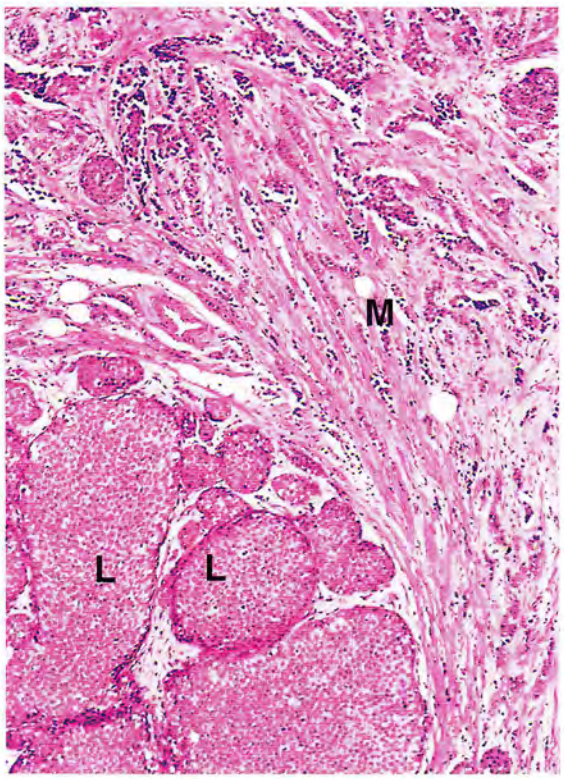



**Fig. 18.11** **Lobular carcinoma of the breast (MP)**

Like their ductal counterparts, cancers arising from breast lobules are divided into in situ and invasive forms; both are often present in the same lesion. This micrograph shows ***lobular carcinoma in situ (LCIS)*** at the lower left adjacent to an area of invasive carcinoma.

In the in situ area, the lobules **L** are expanded and filled by small, evenly spaced epithelial cells that do not form ducts. In the upper right part of the micrograph, ***invasive lobular carcinoma*** consists of similar malignant cells **M** infiltrating the stroma in rows of cells (often described as ***Indian files***) and as single cells which do not form ducts.

Lobular carcinoma in situ is often found incidentally in biopsies taken for another purpose as it usually does not give rise to a mammographic or palpable lesion. LCIS is often multifocal and is considered as a marker lesion for invasive carcinoma rather than a premalignant lesion. Invasive lobular carcinoma carries a better prognosis than invasive ductal carcinoma NOS, but is more likely to be bilateral.

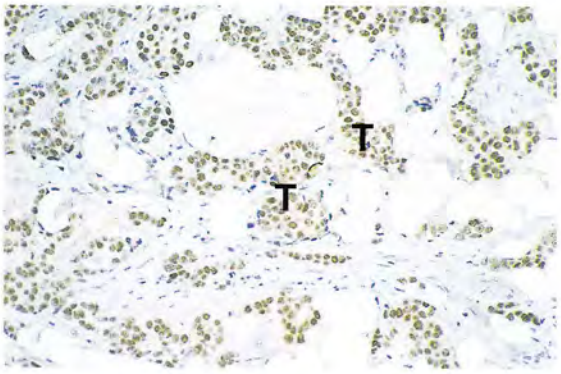



**Fig. 18.12 Oestrogen receptors in breast carcinoma (MP)**

Many factors influence the prognosis of patients with breast carcinoma. Most important among these are the histological type of the tumour, the histological grade of the tumour, tumour size, lymphatic or vascular invasion and the presence and number of lymph node metastases. Tumours that express receptors for oestrogen and/or progestogens also have a better prognosis and furthermore are more likely to respond to hormonal treatment.

This micrograph shows a section of invasive ductal carcinoma which has been stained by the immunoperoxidase method using a monoclonal antibody specific for oestrogen receptors. Most of the tumour cells **T** show strong brown staining of the nuclei indicating oestrogen receptor positivity and thus a relatively improved prognosis.

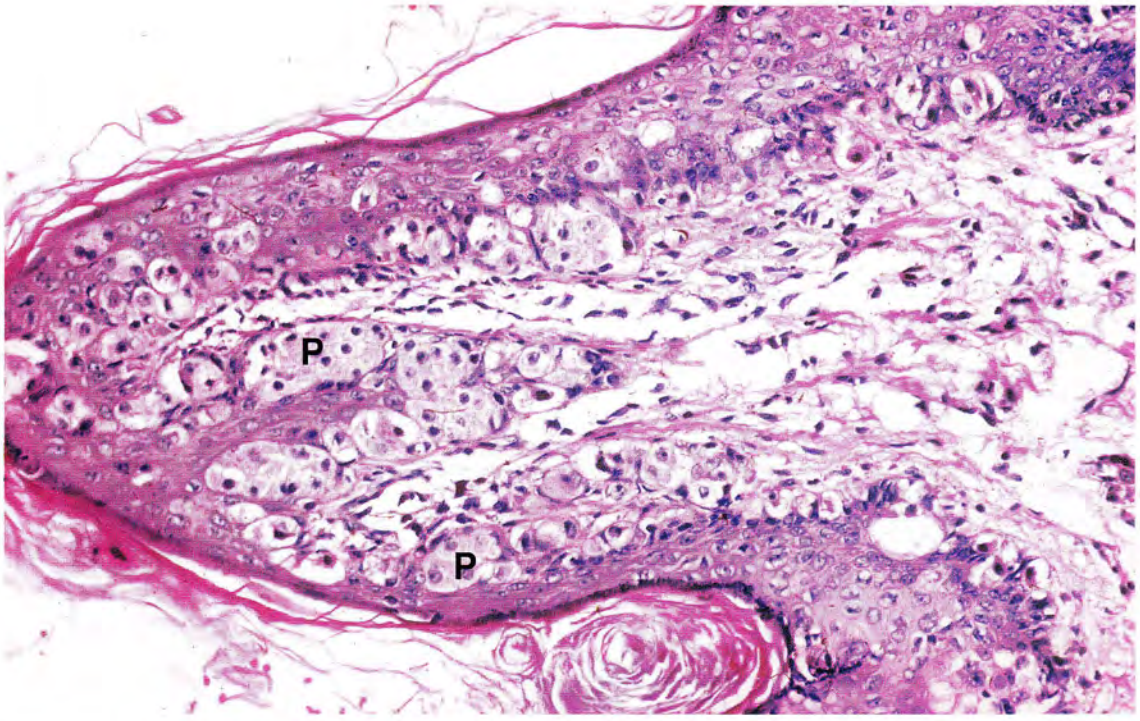
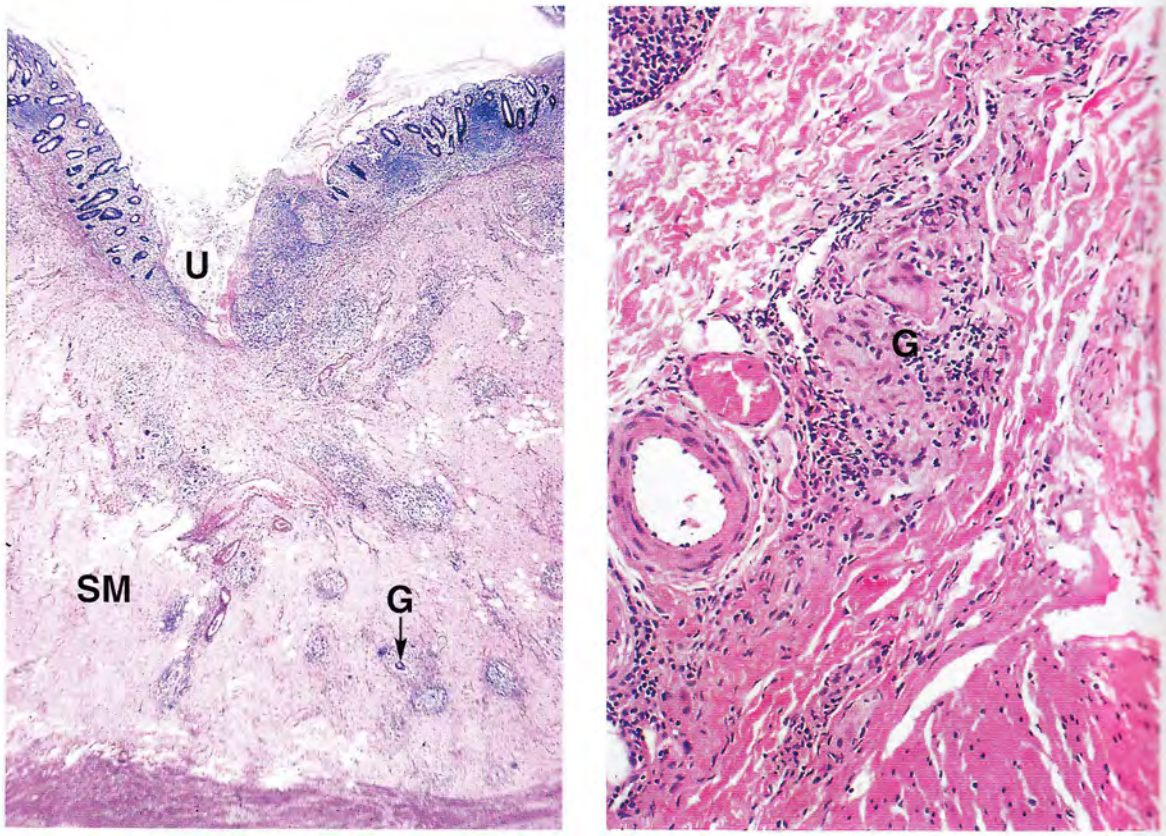



**Fig. 18.13 Paget's disease of the nipple (HP)**

Some patients with carcinoma of the breast (usually of ductal origin) develop reddening and thickening of the skin of the nipple and areola, occasionally followed by ulceration. The epidermis of the nipple and areola becomes infiltrated by malignant epithelial cells with hyperchromatic nuclei and pale cytoplasm. These cells, known as ***Paget's cells*** **P**, are breast carcinoma cells that have spread along the epithelium of the mammary and nipple ducts to the epidermis from an underlying in situ or invasive ductal carcinoma.




(a)

**Fig. 13.16** Crohn's disease
**(a) Fissured ulcer (MP) (b) Crohn's granuloma (HP)**

***Crohn's disease*** is a chronic inflammatory disease of unknown aetiology which mainly involves the small intestine, especially the terminal ileum, but which also often affects the large bowel and anus and occasionally the upper gastrointestinal tract. In the colon and anus, it may be confused clinically with ulcerative colitis and anal fissures and fistulae respectively. Crohn's disease is characteristically patchy in distribution, affecting short segments with lengths of normal small intestine in between (***skip lesions***).

As shown in micrograph (a), the affected segments of small intestine show gross thickening of the wall, mainly because of marked oedema and inflammation of the submucosa **SM.** This oedema produces the typical 'cobblestone' macroscopic appearance of the mucosa in which domed areas of swollen mucosa and submucosa are criss-crossed by linear depressions caused by narrow ***fissured ulcers***. A typical fissured ulcer **U** can be seen here in midfield. Micrograph (a) also demonstrates two other characteristic features of Crohn's disease. First, the chronic inflammatory changes are ***transmural*** (i.e. affect all layers from mucosa to serosa). Second, granulomas **G**, often containing giant cells, may be found in all layers. A granuloma in the submucosa is illustrated at higher magnification in micrograph (b). The granulomas in Crohn's disease are often loose aggregates of epithelioid macrophages and giant cells rather than the well-circumscribed granulomas found in tuberculosis or sarcoidosis. Granulomas such as these may also be found in lymph nodes draining the affected segment of bowel. The result of longstanding transmural inflammation is widespread fibrosis, which may cause bowel obstruction; the deep-fissured ulceration predisposes to the formation of fistulae, a common complication of Crohn's disease.

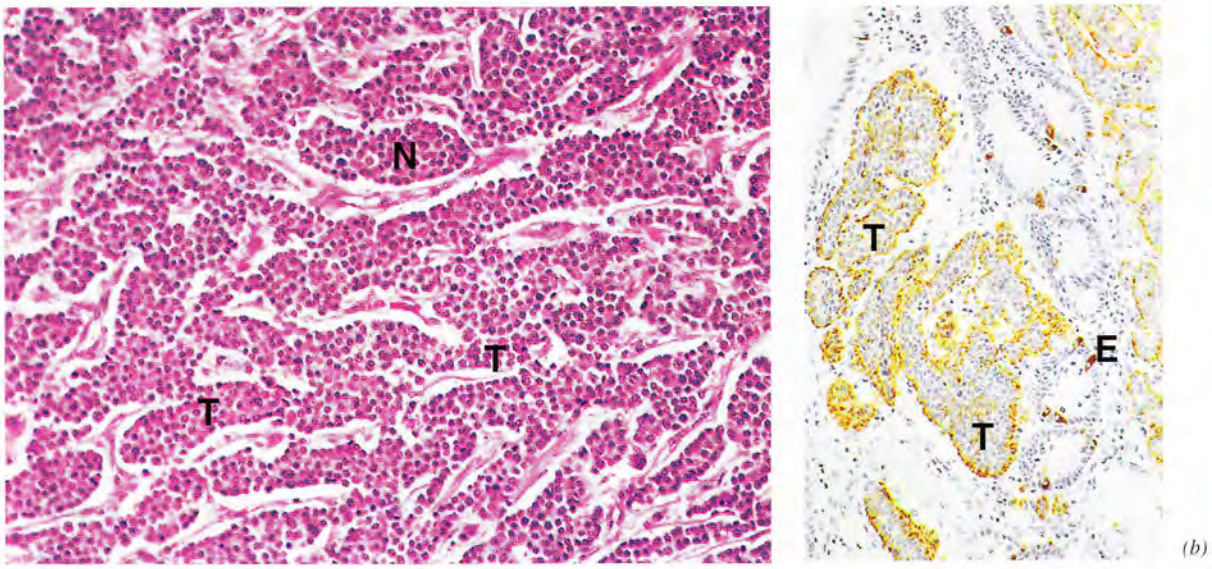



**Fig. 13.17** **Gastrointestinal neuroendocrine tumour (carcinoid)**
**(a) H&E (MP) (b) Chromogranin (HP)**

These tumours are found in the stomach, small intestine, appendix, pancreas and lung and, more rarely, the oesophagus, colon and biliary tract. Most are locally invasive but all may metastasise. They are derived from neuroendocrine cells and may secrete a variety of hormone products such as ***serotonin***, which may cause ***carcinoid syndrome***; insulin or glucagon are the usual secretory products of pancreatic lesions.

Whatever the location and secretory product, the histological appearance is very similar with tumour cells forming nests **N** and trabeculae **T** as in micrograph (a), glandular structures or diffuse sheets of cells. The cells characteristically are small and uniform with round nuclei, stippled chromatin and pinkish granular cytoplasm. Immunoperoxidase staining will often reveal the hormone products within the cells. Similarly, in micrograph (b) of duodenal mucosa, tumour cells **T** have been stained for ***chromogranin A***, a protein found in the secretory granules. Note also the positive staining of normal neuroendocrine cells scattered in the adjacent normal duodenal epithelium **E.**

## Diseases of the large intestine

The colon and rectum are subject to various viral, bacterial and parasitic infections that are usually short-lived and readily diagnosed by microbiological methods; an important exception is ***amoebic colitis*** (Fig. 4.25), which is often diagnosed only after histological examination of biopsy specimens. Of great importance is the chronic relapsing inflammatory disease of the large intestine known as ***ulcerative colitis*** (Fig. 13.19). More recently discovered causes of chronic diarrhoea include ***collagenous colitis*** and ***lymphocytic (microscopic) colitis*** (Fig. 13.18).

Raised intraluminal pressure in the colon, probably as a result of a low residue diet, commonly leads to saccular herniation of mucosa through the muscle layers of the bowel wall; the diverticula so formed may become inflamed giving rise to ***diverticulitis*** (Fig. 13.23) which may have serious sequelae.

The large intestine may undergo infarction either as a result of mesenteric artery occlusion by thrombus or embolus, or more commonly by venous infarction following hernial strangulation or ***volvulus***; this is shown in Fig. 10.5.

Colonic polyps are exceedingly common. By far the most common is the ***hyperplastic polyp*** (Fig. 13.20), a reactive rather than neoplastic lesion. Less common non-neoplastic polyps include ***inflammatory pseudopolyps*** as seen in ulcerative colitis (Fig. 13.19a) and polypoid hamartomas such as ***Peutz–Jeghers' polyps***. Neoplastic benign polyps include ***tubular adenomas***, ***villous adenomas*** and ***tubulovillous adenomas*** (Fig. 13.21), all of which have a definite risk of malignant transformation.

Malignant tumours of the colon and rectum are very common, and almost all are ***adenocarcinomas*** (Fig. 13.22); most appear histologically moderately differentiated with a clearly defined glandular pattern. The anal canal, being lined by squamous epithelium, is occasionally the site of ***squamous carcinoma*** (Fig. 7.14), although local invasion of the anal canal by adenocarcinoma of the lower rectum also occurs.