INTERNATIONAL HISTOLOGICAL CLASSIFICATION OF TUMOURS

No. 10

HISTOLOGICAL TYPING OF URINARY BLADDER TUMOURS

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ALREADY PUBLISHED IN THIS SERIES:

No. 1. Histological typing of lung tumours, by Leiv Kreyberg in collaboration with A. A. Liebow and E. A. Uehlinger (1967)

No. 2. Histological typing of breast tumours, by R. W. Scarff and H. Torloni (1968)

No. 3. Histological typing of soft tissue tumours, by F. M. Enzinger in collaboration with R. Lattes and H. Torloni (1969)

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GENERAL PREFACE TO THE SERIES

Among the prerequisites for comparative studies of cancer are international agreement on histological criteria for the classification of cancer types and a standardized nomenclature. At present, pathologists use different terms for the same pathological entity and, furthermore, the same term is sometimes applied to lesions of different types. An internationally agreed classification of tumours, acceptable alike to physicians, surgeons, radiologists, pathologists, and statisticians, would enable cancer workers in all parts of the world to compare their findings and would facilitate collaboration among them.

In a report published in 1952,[1] *a subcommittee of the WHO Expert Committee on Health Statistics discussed the general principles that should govern the statistical classification of tumours and agreed that, to ensure the necessary flexibility and ease in coding, three separate classifications were needed according to (1) anatomical site, (2) histological type, and (3) degree of malignancy. A classification according to anatomical site is available in the* International Classification of Diseases.[2]

The question of establishing a universally accepted classification by histological type has received much attention during the last 20 years and a particularly valuable Atlas of Tumor Pathology*—already numbering more than 40 volumes—is being published in the USA by the Armed Forces Institute of Pathology under the auspices of the National Research Council. An* Illustrated Tumour Nomenclature *in English, French, German, Latin, Russian, and Spanish has also been published by the International Union Against Cancer (UICC).*

In 1956 the WHO Executive Board passed a resolution[3] *requesting the Director-General to explore the possibility that WHO might organize centres in various parts of the world and arrange for the collection of human tissues and their histological classification. The main purpose of such centres would be to develop histological definitions of cancer types and to facilitate the wide adoption of a uniform nomenclature. This resolution was endorsed by the Tenth World Health Assembly in May 1957*[4] *and the following month a Study Group on Histological Classification of Cancer*

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1952, No. 53, p. 45.

[2] World Health Organization (1967) *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*, 1965 revision, Geneva.

[3] *Off. Rec. Wld Hlth Org.*, 1956, 68, 14 (Resolution EB17.R40).

[4] *Off. Rec. Wld Hlth Org.*, 1957, 79, 467 (Resolution WHA10.18).

Types met in Oslo to advise WHO on its implementation. The Group recommended criteria for selecting tumour sites for study and suggested a procedure for drafting histological classifications and testing their validity. Briefly, the procedure is as follows:

1. For each tumour site, a tentative histopathological typing and classification is drawn up by a group of experts, consisting of up to ten pathologists working in the field in question.

2. An international reference centre and a number of collaborating laboratories are then designated by WHO to evaluate the proposed classification. These laboratories exchange histological preparations, accompanied by clinical information. The histological typing is then made in accordance with the proposed classification. Subsequently, one or more technical meetings are called by WHO to facilitate an exchange of opinions. If necessary, the classification is amended to take account of criticisms.

3. The international reference centre then prepares sets of microscope slides covering all the proposed histological types and sends these with the revised classification to other pathologists, usually not more than ten, for their comments and suggestions.

4. When replies have been received from all these reviewers, the classification is again revised in accordance with their comments. The international reference centre then prepares up to 100 sets of microscope slides of the various histological types and also drafts a text explaining the basis of the classification. In addition, photomicrographs are taken of the appropriate fields for the preparation of colour plates and 35-mm transparencies.

Since 1958, WHO has established 23 international reference centres covering tumours of the lung; breast; soft tissues; oropharynx; bone; ovaries; salivary glands; thyroid; skin; male urogenital tract; jaws; uterus; stomach and oesophagus; intestines; central nervous system; liver, biliary tract and pancreas; upper respiratory tract; eye; and endocrine glands; as well as oral precancerous conditions; the leukaemias and lymphomas; comparative oncology; and exfoliative cytology. This work has involved more than 200 pathologists from over 50 countries. The international reference centres for tumours of the lung; breast; soft tissues; oropharynx; bone; jaws; salivary glands; skin; and ovaries; and for leukaemias and lymphomas, have completed their work, and some of the classifications prepared by these centres have already been published (see page 6).

The World Health Organization is deeply indebted to the many pathologists who have participated and are participating in this large undertaking, especially to the heads of the international reference centres and of the collaborating laboratories. Grateful acknowledgement is also made to the many other international and national organizations whose pioneer work in

the field of histological classification of tumours has greatly facilitated the task undertaken by WHO. Finally, WHO wishes to record its appreciation of the valuable help it has received from the International Council of Societies of Pathology (ICSP) in proposing collaborating centres and in undertaking to distribute copies of the classifications, with corresponding sets of microscope slides, to national societies of pathology all over the world.

PREFACE TO HISTOLOGICAL TYPING OF URINARY BLADDER TUMOURS

The WHO International Reference Centre for the Histological Classification of Male Urogenital Tract Tumours was established in 1965 at the Armed Forces Institute of Pathology, Washington, D.C., USA.

At a meeting in Geneva in 1965, attended by Dr Mirghani Yousif Ali, Singapore; Dr J. Chomé, Versailles; Dr E. Dahme, Munich; Dr M. Gazayerli, Alexandria; Dr V. McGovern, Camperdown, New South Wales; Dr R. C. B. Pugh, London; Dr H. Usizima, Nagoya; Dr J. G. Moberger, Stockholm; Dr F. K. Mostofi, Washington; and Dr H. Torloni, WHO, a tentative classification of urinary bladder tumours was drafted. This was then evaluated by the International Reference Centre and its collaborating centres, a list of which will be found on page 5.

The International Reference Centre prepared and distributed material (clinical information and microscope slides) from selected cases of urinary bladder tumours to the collaborating centres for histological typing according to the tentative classification. In all, 500 cases were thus studied by the centres and were reviewed at a meeting held in 1968 and attended by the heads of the centres. The classification was reviewed by nine pathologists who had been designated by WHO (see page 5) and the final version was then adopted.

The authors then prepared the accompanying text and colour photomicrographs. The latter are reproduced as colour plates in this book and are also available as a collection of transparencies intended especially for teaching purposes. To help pathologists who might wish to know the corresponding terms in French, Russian, and Spanish, translations of the classification into these languages are also given, immediately following the English version.

It will, of course, be appreciated that the classification reflects the present state of knowledge and that modifications are almost certain to be needed as experience accumulates. Furthermore, it necessarily represents a majority view, from which some pathologists may wish to dissent. It is nevertheless hoped that, in the interests of international cooperation, all pathologists will try to use the classification as put forward. Criticisms and suggestions for its improvement will be welcome.

The publications in the series International Histological Classification of Tumours *are not intended to serve as textbooks but rather to promote*

the adoption of a uniform terminology and categorization of tumours that will facilitate and improve communication among cancer workers. For this reason, the literature references have been intentionally kept to a minimum and readers are referred to standard works on the subject for extensive bibliographies.

INTRODUCTION

Although the normal histological characteristics of the urinary bladder are simple and most of the tumours that may affect it are of epithelial origin, there is no agreement on a standard classification and nomenclature of these tumours, nor any generally accepted pathological criteria for the diagnosis of malignancy. One pathologist may designate a lesion as a papilloma, whereas others may call the same lesion a urothelioma; urothelial, transitional, or squamous cell carcinoma; epithelioma; or papillary tumour. Obviously this lack of agreement on histological criteria for tissue typing, malignancy, and classification makes it extremely difficult to assess the results of various forms of therapy or to compare epidemiological data.

Criteria for the diagnosis of carcinoma of the bladder

Since over 95% of the tumours encountered in the bladder are of the epithelial type, the primary concern here is to emphasize the criteria for the histological diagnosis and classification of epithelial tumours.

In many organs of the body the diagnosis of malignancy is based on cellular anaplasia, invasion, or metastasis. Metastasis is a late phenomenon in carcinoma of the bladder. Invasion of the muscularis is readily identifiable in bladder tumours but it is sometimes difficult to recognize a break in the basement membrane and invasion of the lamina propria. This is because a distinct basement membrane has not been demonstrated in the vesical mucosa. In addition, the true lamina propria of the bladder wall is often not included in the biopsy specimen. Furthermore, invaginations of surface epithelium into the subjacent lamina propria, sometimes indistinguishable from invasion, may occur in benign conditions—e.g., von Brunn's nests.

Since many bladder tumours are papillary, showing neither invasion nor metastasis, the diagnosis of carcinoma must depend on cellular anaplasia. The lack of agreed standard criteria for the recognition of anaplasia in bladder tumours is reflected in the great discrepancy in the incidence of papilloma reported from various parts of the world.

Normally the bladder is lined with a layer of transitional epithelial cells [1] which varies from 3 to 6 layers in thickness. A number of epithelial

[1] The term " urothelium " is used in some departments for this type of epithelium; likewise, transitional cell carcinoma is called " urothelial carcinoma ".

abnormalities, some or all of which may be present in a single specimen, are adopted here as evidence of anaplasia; these include increased cellularity, nuclear crowding, disturbances of cellular polarity, failure of differentiation from the base to the surface, polymorphism, irregularity in the size of cells, variations of shape and chromatin pattern of the nuclei, displaced or abnormal mitotic figures, and giant cells. In this classification, any cytological anaplasia as defined above is considered as evidence of malignancy. However, it must be recognized that certain inflammatory, reactive, or regenerative conditions may result in the appearance of some of these changes. The diagnosis of carcinoma can and should be made on the basis of such anaplastic changes even in the absence of any evidence of invasion.

It should be emphasized that these criteria for diagnosing carcinoma are arbitrary. They are justified as a means of providing reproducibility for comparing the results of therapy and of epidemiological studies.

Benign epithelial tumours of the bladder certainly exist, but it must be recognized that a significant proportion of histologically benign papillomas may be followed by carcinoma. In this histological classification, tumours without any evidence of anaplasia are called " benign ", but they may be potentially malignant. On the other hand, it is also likely that, with these same criteria for malignancy, some tumours labelled as carcinoma may, in fact, not behave as such. Until a more sound scientific basis is found for distinguishing between benign and malignant epithelial tumours of the urinary bladder, these histological criteria must be used.

Bases of classification

This classification is based primarily on the type of cell or tissue appearing in each tumour. It is descriptive rather than histogenetic.

When dealing with epithelial tumours of the urinary bladder, however, the following features must also be taken into consideration.

Growth pattern

The pathologist must report on the growth pattern of the tumour as determined macroscopically and microscopically. There are four main patterns:

(1) Papillary, in which the tumour is growing into the lumen of the bladder;

(2) Infiltrating, in which it is growing into the wall of the bladder;

(3) Papillary and infiltrating, in which it is doing both;

(4) Non-papillary and non-infiltrating, in which the tumour is confined to the surface—i.e., *in situ.*

This information is particularly important because of its relationship to prognosis. Papillary carcinomas have a much better prognosis than

infiltrating carcinomas, and carcinomas that are both papillary and infiltrating lie somewhere in between.

Histological grading

Grading is one of the methods used by pathologists for evaluating the degree of anaplasia of tumour cells. Several systems of grading are in use. The method proposed here is a simple one in which three grades are employed. Grade 1 applies to the tumours that have the least degree of cellular anaplasia compatible with a diagnosis of malignancy; grade 3 applies to tumours with the most severe degrees of cellular anaplasia; and grade 2 lies in between. Pathological grading is of value clinically because it has been demonstrated to be related to the survival rate of patients.

Pathological staging

Another criterion for assessing the behaviour of a tumour is to determine the depth of its infiltration into the bladder wall or adjacent tissue. This is designated as " staging " and may be clinical or pathological. Clinical staging is an estimate by the urologist of the extent of local spread in the bladder wall and is based on cystoscopic examination and bimanual examination under anaesthesia. Pathological staging is carried out through the histological examination of tissue by determining, with the use of the microscope, the precise depth of extension of the tumour into the bladder wall. In pathological staging, one should mention where the tumour has infiltrated to its deepest extent—e.g., mucosa (PIS),[1] lamina propria (P1), superficial muscle (P2), deep muscle or perivesical tissue (P3), or the adjacent organs or other structures (P4). It should be stressed that the depths of vascular and/or lymphatic invasion (which may be greater than that of the tumour itself) are not taken into account in determining the stage. Grading, or the degree of anaplasia, should not be confused with the depth of infiltration into the bladder wall. Whereas there is a high correlation between the two—most of the infiltrating tumours are of grade 3—they are totally separate entities.

Mode and location of local spread

The manner in which a carcinoma spreads in the wall of the bladder also provides information on the behaviour of the tumour. We recommend the recognition of three types of spread:

(1) Tentacular invasion, by which the tumour infiltrates in strands, nests, and individual cells, insinuating themselves between normal structures.

[1] International Union Against Cancer, Committee on TNM Classification (1968) *TNM classification of malignant tumours*, Geneva.

(2) *En bloc* invasion, in which the tumour appears to advance on a broad front;

(3) Lymphatic and vascular invasion, in which the tumour spreads by means of these vessels.

Assessment of the means of spread is important to the prognosis, which is much more ominous for tentacular invasion and lymphatic and vascular invasion than for *en bloc* invasion. The search for invasion of superficial lymphatic channels is essential in superficial carcinomas.

It must be noted that carcinomas of the bladder usually spread to subjacent areas of the bladder wall, immediately under the mucosal site of origin, but that some carcinomas of the bladder tunnel under the intact, apparently normal mucosa and may therefore be missed on cystoscopic examination and even on biopsy.

" Unstable mucosa " (" Maladie de la muqueuse ")

It should be recognized that under certain conditions the bladder mucosa may appear histologically to be in an unstable condition.

The mucosa is often not normal cystoscopically, yet a definite diagnosis of a tumour cannot be made either cystoscopically or microscopically. The changes may remain stationary, regress, or progress to a tumour. Such a mucosa may manifest a number of alterations: various types of cystitis, the formation of von Brunn's nests, or squamous or glandular metaplasia. These conditions are benign, but, because of the polypoidal or abnormal appearance of the mucosa, or apparent infiltration, they may be mistaken for carcinomas. Because these changes as well as papillomas sometimes precede the development of carcinomas, are observed adjacent to carcinomas, are encountered in the early stages of industrial carcinogenesis in man, and are an almost constant finding in the course of experimental carcinogenesis in animals, they have been considered potentially malignant and therefore require follow-up of the patient. It is worth noting that whether carcinomas are industrial or apparently nonindustrial in origin they have essentially the same histological appearance.

Carcinoma *in situ*

This term is employed for lesions in which there is definite anaplasia of surface epithelium without the formation of papillary structures and without infiltration. In contrast to papillary carcinomas, many of which show slight or moderate cellular anaplasia, carcinoma *in situ* often displays marked anaplasia, so that these tumours are more easily recognizable on cytological examination than many papillary carcinomas are. The pathologist often encounters difficulty in detecting these lesions because the neoplastic

layer tends to become detached during tissue processing, leaving only a denuded mucosa.

Ureter and renal pelvis

The histological classification outlined here as well as the other criteria by which urinary bladder tumours should be assessed apply equally to tumours occurring in the ureter and renal pelvis. It should be stressed that these tumours are often multifocal and may affect more than one site in the urinary tract.

Synonyms are given only where they have been widely used in the literature; the preferred term is given first, followed by the synonym in square brackets.

HISTOLOGICAL CLASSIFICATION OF URINARY BLADDER TUMOURS

I. EPITHELIAL TUMOURS

A. Transitional cell papilloma

B. Transitional cell papilloma, inverted type

C. Squamous cell papilloma

D. Transitional cell carcinoma

E. Variants of transitional cell carcinoma

1. With squamous metaplasia
2. With glandular metaplasia
3. With squamous and glandular metaplasia

F. Squamous cell carcinoma

G. Adenocarcinoma

H. Undifferentiated carcinoma

II. NON-EPITHELIAL TUMOURS

A. BENIGN

B. MALIGNANT

1. Rhabdomyosarcoma
2. Others

III. MISCELLANEOUS TUMOURS

A. Phaeochromocytoma

B. Lymphomas

C. Carcinosarcoma

D. Malignant melanoma

E. Others

IV. METASTATIC TUMOURS AND SECONDARY EXTENSIONS

V. UNCLASSIFIED TUMOURS

VI. EPITHELIAL ABNORMALITIES

A. Papillary [polypoid] " cystitis "

B. Von Brunn's nests

C. " Cystitis " cystica

D. Glandular metaplasia

E. " Nephrogenic adenoma "

F. Squamous metaplasia

VII. TUMOUR-LIKE LESIONS

A. Follicular cystitis

B. Malakoplakia

C. Amyloidosis

D. Fibrous [fibroepithelial] polyp

E. Endometriosis

F. Hamartomas

G. Cysts

CLASSIFICATION HISTOLOGIQUE DES TUMEURS DE LA VESSIE

I. TUMEURS ÉPITHÉLIALES

A. Papillome à cellules transitionnelles [paramalpighiennes]

B. Papillome à cellules transitionnelles de type inversé

C. Papillome épidermoïde

D. Carcinome * à cellules transitionnelles [paramalpighiennes]

E. Variantes des carcinomes à cellules transitionnelles

1. Avec métaplasie épidermoïde
2. Avec métaplasie glandulaire
3. Avec métaplasie épidermoïde et glandulaire

F. Carcinome épidermoïde

G. Adénocarcinome

H. Carcinome indifférencié

II. TUMEURS NON ÉPITHÉLIALES

A. BÉNIGNES

B. MALIGNES

1. Rhabdomyosarcome
2. Autres

III. TUMEURS DIVERSES

A. Phéochromocytome

B. Lymphomes

* Carcinome et adénocarcinome sont synonymes d'épithélioma et d'épithélioma glandulaire.

C. Carcinosarcome

D. Mélanome malin

E. Autres

IV. TUMEURS MÉTASTATIQUES ET ENVAHISSEMENTS SECONDAIRES

V. TUMEURS NON CLASSÉES

VI. ANOMALIES ÉPITHÉLIALES

A. " Cystite " papillomateuse

B. Nids de von Brunn

C. " Cystite " kystique

D. Métaplasie glandulaire

E. " Adénome néphrogène "

F. Métaplasie épidermoïde

VII. LÉSIONS PSEUDO-TUMORALES

A. Cystite folliculaire

B. Malacoplasie

C. Amyloïdose

D. Polype fibreux [polype fibreux épithélial]

E. Endométriose

F. Hamartomes

G. Kystes

ГИСТОЛОГИЧЕСКАЯ КЛАССИФИКАЦИЯ ОПУХОЛЕЙ МОЧЕВОГО ПУЗЫРЯ

I. ЭПИТЕЛИАЛЬНЫЕ ОПУХОЛИ

А. Переходноклеточная папиллома

Б. Переходноклеточная папиллома, инвестированный тип

В. Плоскоклеточная папиллома

Г. Переходноклеточный рак

Д. Варианты переходноклеточного рака

1. С плоскоклеточной метаплазией
2. С железистой метаплазией
3. С плоскоклеточной и железистой метаплазией

Е. Плоскоклеточный рак

Ж. Аденокарцинома

З. Недифференцированный рак

II. НЕЭПИТЕЛИАЛЬНЫЕ ОПУХОЛИ

А. Доброкачественные

Б. Злокачественные

1. Рабдомиосаркома
2. Другие

III. СМЕШАННЫЕ ОПУХОЛИ

А. Феохромоцитома

Б. Лимфомы

В. Карциносаркома

Г. Злокачественная меланома

Д. Другие

IV. ВТОРИЧНЫЕ ОПУХОЛИ

V. НЕКЛАССИФИЦИРОВАННЫЕ ОПУХОЛИ

VI. НЕОПУХОЛЕВЫЕ НАРУШЕНИЯ ЭПИТЕЛИЯ

А. Сосочковый «цистит»

Б. Гнезда фон Брунна

В. Кистозный «цистит»

Г. Железистая метаплазия

Д. «Нефрогенная аденома»

Е. Метаплазия плоского эпителия

VII. ОПУХОЛЕПОДОБНЫЕ ИЗМЕНЕНИЯ

А. Фолликулярный цистит

Б. Малакоплакия

В. Амилоидоз

Г. Фиброзный [фиброэпителиальный] полип

Д. Эндометриоз

Е. Гамартомы

Ж. Кисты

CLASIFICACION HISTOLOGICA DE LOS TUMORES DE LA VEJIGA URINARIA

I. TUMORES EPITELIALES

A. Papiloma de células de transición

B. Papiloma de células de transición, tipo invertido

C. Papiloma de células escamosas

D. Carcinoma de células de transición

E. Variedades del carcinoma de células de transición

1. Con metaplasia escamosa
2. Con metaplasia glandular
3. Con metaplasia escamosa y glandular

F. Carcinoma de células escamosas

G. Adenocarcinoma

H. Carcinoma indiferenciado

II. TUMORES NO EPITELIALES

A. BENIGNOS

B. MALIGNOS

1. Rabdomiosarcoma
2. Otros

III. TUMORES VARIOS

A. Feocromocitoma

B. Linfomas

C. Carcinosarcoma

D. Melanoma maligno

E. Otros

IV. TUMORES METASTATICOS Y PROPAGACIONES SECUNDARIAS

V. TUMORES NO CLASIFICADOS

VI. ANOMALIAS EPITELIALES

A. « Cistitis » papilar [polipoide]

B. « Nidos » de von Brunn

C. « Cistitis » quistica

D. Metaplasia glandular

E. « Adenoma nefrogénico »

F. Metaplasia escamosa

VII. LESIONES SEUDOTUMORALES

A. Cistitis folicular

B. Malacoplaquia

C. Amiloidosis

D. Pólipo fibroso [fibroepitelial]

E. Endometriosis

F. Hamartomas

G. Quistes

DEFINITIONS AND EXPLANATORY NOTES

I. EPITHELIAL TUMOURS

A. *Transitional cell papilloma* (Fig. 1–2): A papillary tumour with a delicate fibrovascular stroma covered by regular transitional epithelium indistinguishable from that of the normal bladder and not more than six layers thick.

The individual cells are slender and lie parallel to each other at right angles to the basement membrane. Mitotic figures, both normal and abnormal, are either extremely rare or entirely absent. If present, they are located in the basal region. The nuclei are of uniform size and show a normal distribution of chromatin.

It must be emphasized that the designation transitional cell papilloma is based on purely histological considerations and is not intended to imply innocent biological behaviour, particularly as such epithelial tumours may recur and may behave in a malignant manner.

Diffuse papillomatosis is a special category of epithelial tumour of the bladder in which all or the greater part of the mucosa is replaced by delicate papillary processes producing a velvety appearance. Histologically the papillae are covered by transitional epithelium which may have the characteristics of papilloma or papillary carcinoma. The basement membrane is usually intact. The tumour may be present throughout the urinary tract.

B. *Transitional cell papilloma, inverted type* (Fig. 3): A tumour with the characteristics of a transitional cell papilloma but with an endophytic rather than an exophytic growth pattern.

This type of papilloma must be distinguished from von Brunn's nests and infiltrating carcinoma.

C. *Squamous cell papilloma*: A papillary tumour with a delicate fibrovascular stroma covered by regular squamous epithelium.

Some of these tumours may be condylomata acuminata that have extended into the bladder from the urethra.

D. *Transitional cell carcinoma* (Fig. 4–12): A tumour of transitional epithelium showing evidence of anaplasia or invasion.

The criteria for anaplasia are: increased cellularity, nuclear crowding, disturbances of cellular polarity, failure of differentiation from the base to the surface, polymorphism, irregularity in size of cells, variations of shape and chromatin pattern of the nuclei, displaced or abnormal mitotic figures, and giant cells. It must be emphasized that some of these features may be present in certain inflammatory, reactive, or regenerative conditions, without signifying malignancy.

Except for papillary cystitis, any papillary lesion showing any degree of anaplasia as defined above should be diagnosed as carcinoma. This diagnosis can and should be made on the basis of such anaplastic changes, even in the absence of any evidence of invasion.

The degree of cellular anaplasia forms the basis of grading of these tumours (see page 17).

Whereas it is desirable to examine the basement membrane carefully, it is difficult and may sometimes be impossible to establish the fact of the invasion of lamina propria in routine sections of the bladder. Invasion should be looked for and, if present, it should be reported, since the prognosis is undoubtedly worse with invasive tumours. However, the absence of invasion should not preclude a diagnosis of cancer.

E. *Variants of transitional cell carcinoma* (Fig. 13–15): Tumours in which transitional cell carcinoma contains foci of squamous and/or glandular elements. They are:

1. Transitional cell carcinoma with squamous metaplasia
2. Transitional cell carcinoma with glandular metaplasia
3. Transitional cell carcinoma with squamous and glandular metaplasia

The most frequent mixture of cell types is that of squamous elements in a predominantly transitional cell carcinoma; somewhat less frequent is the presence of adenocarcinoma in a transitional cell tumour. Such tumours should not be classified by predominance but should be placed in one of the above-mentioned categories.

F. *Squamous cell carcinoma* (Fig. 16–18): A malignant epithelial tumour with cells forming keratin or having intercellular bridges. The tumour must be of one cell type.

Unlike transitional cell carcinomas, which are most often papillary and non-ulcerating, squamous cell carcinomas are typically sessile, nodular, and infiltrating, and may be ulcerated.

G. *Adenocarcinoma* (Fig. 19–25): A malignant epithelial tumour with cells forming glands, tubules, and/or mucus.

Most adenocarcinomas occur in the dome and anterior wall of the bladder and are considered to be urachal in origin. They are usually intramural and secondarily involve the mucosa.

Adenocarcinoma can also arise in glandular cystitis and exstrophy. In these cases it is predominantly located in the trigonal area or the posterior wall. Rarely, it occurs at the bladder base.

A rare variety of adenocarcinoma, characterized by tubular structures infiltrating the bladder wall, has been described as " mesonephric carcinoma " (Fig. 24 and 25).

H. *Undifferentiated carcinoma* (Fig. 26–30): A malignant tumour of epithelial structure that is too poorly differentiated to be placed in any of the other groups of carcinoma.

The term " undifferentiated " is used in a histological sense to denote primitive tissue and is not employed here as a synonym for anaplasia.

If a predominantly undifferentiated carcinoma contains rare, distinctly differentiated foci, the tumour should be classed in this category with a notation of the combination (Fig. 29 and 30).

This category should also include the rare variety of carcinoma composed of large, clear, but otherwise undifferentiated, cells described as " lipidic carcinoma " because of its lipid content.

II. NON-EPITHELIAL TUMOURS

Non-epithelial tumours are classified according to the scheme devised by the International Reference Centre for the Histological Classification of Soft Tissue Tumours.[1]

A. Benign

The most common types of benign mesenchymal tumours are leiomyoma, neurofibroma (Fig. 31), haemangioma (Fig. 32), and granular cell tumour.

B. Malignant

1. *Rhabdomyosarcoma* (Fig. 33–37)

This is the most frequent malignant tumour of the bladder occurring in children. The most commonly encountered type in the bladder is the embryonal variety; this is characteristically polypoid.

[1] Enzinger, F. M.. Lattes, R. & Torloni, H. (1969) *Histological typing of soft tissue tumours*, Geneva, World Health Organization (*International Histological Classification of Tumours*, No. 3).

2. *Others*

Leiomyosarcoma (Fig. 38), fibrosarcoma, and osteosarcoma (Fig. 39) are uncommon and occur mostly in older patients.

III. MISCELLANEOUS TUMOURS

A. *Phaeochromocytoma* (Fig. 40)

These may be functional or non-functional and may be composed of chromaffin or non-chromaffin cells; they are usually benign but may be malignant.

B. *Lymphomas* (Fig. 41)

Lymphomas have been described as being primary in the bladder; histologically, they may simulate undifferentiated carcinoma.

C. *Carcinosarcoma* (Fig. 42)

This very rare tumour contains malignant elements of distinctly epithelial and mesenchymal tissues.

The presence of spindle-shaped cells or of metaplastic bone or cartilage alone should not lead to a diagnosis of carcinosarcoma.

D. *Malignant melanoma*

These are extremely rare and the ones described have been mainly in the trigone and bladder neck.

E. *Others*

IV. METASTATIC TUMOURS AND SECONDARY EXTENSIONS

A primary extravesical tumour occasionally produces initial manifestations in the bladder. The primary cancers that most frequently affect the bladder are those arising in the prostate, cervix, and colon, spreading to the bladder by extension.

V. UNCLASSIFIED TUMOURS

These are primary benign or malignant tumours that cannot be placed in any of the categories described above.

VI. EPITHELIAL ABNORMALITIES

These are often encountered in the inflamed bladder and are often designated, erroneously, as " cystitis ". They may be found in various combinations.

A. *Papillary [polypoid]* " *cystitis* " (Fig. 43)

This is characterized by hyperplastic epithelium that covers thickened, tapering, finger-like projections of the lamina propria. The latter is typically oedematous, hyperemic, and infiltrated with inflammatory cells.

Probably the best examples of this lesion are seen in cases of perivesical sepsis, as for example with incipient vesicointestinal fistula.

B. *von Brunn's nests* (Fig. 44)

These are compact groups of transitional epithelial cells lying in the lamina propria with or without connexion to the surface epithelium.

C. " *Cystitis* " *cystica* (Fig. 45)

These are groups of transitional epithelial cells with central cavitation, sometimes gross enough to form cysts, lying in the lamina propria, with or without connexion to the surface epithelium.

D. *Glandular metaplasia [glandular* " *cystitis* "] (Fig. 46)

This is characterized by mucus containing columnar epithelial cells either on the surface or forming glands in the lamina propria.

E. " *Nephrogenic adenoma* " (Fig. 47)

A benign epithelial lesion in which cuboidal cells line tubular structures reminiscent of those seen in the kidney.

F. *Squamous metaplasia* (Fig. 48 and 49)

Transitional epithelium is here replaced by squamous cells with or without keratinization; there is usually hyperplasia of the epithelium.

VII. TUMOUR-LIKE LESIONS

A. *Follicular cystitis* (Fig. 50)

A lesion with considerable lymphoid cell infiltration of the lamina propria characteristically forming lymphoid follicles.

Such lesions must be distinguished from lymphomas.

B. *Malakoplakia* (Fig. 51 and 52)

In this lesion, the lamina propria contains large numbers of macrophages in which Michaelis-Gutmann bodies are found. They may resemble, but must be distinguished from, the granular cell tumour [myoblastoma].

C. *Amyloidosis* (Fig. 53)

Tumour-like lesions are more frequently seen in secondary than in primary amyloidosis.

D. *Fibrous [fibroepithelial] polyp* (Fig. 54)

This is a polypoid lesion containing abundant amounts of fibrous tissue and varying numbers of inflammatory cells. The epithelium is typically not hyperplastic. It is commonly observed in association with schistosomiasis.

E. *Endometriosis* (Fig. 55)

For the diagnosis of endometriosis it is essential to see endometrial stroma. The glands may be in proliferative or secretory phase and there may be evidence of old or recent haemorrhage.

F. *Hamartomas*

These mostly contain tubular or transitional epithelial lined cavities surrounded by fibromuscular tissue.

G. *Cysts* (Fig. 56)

Urachal cysts are typically in the dome and anterior wall, whereas cloacal cysts are confined to the posterior wall.

INDEX

All the preparations shown in the photomicrographs reproduced on the following pages were stained with haematoxylin-eosin.

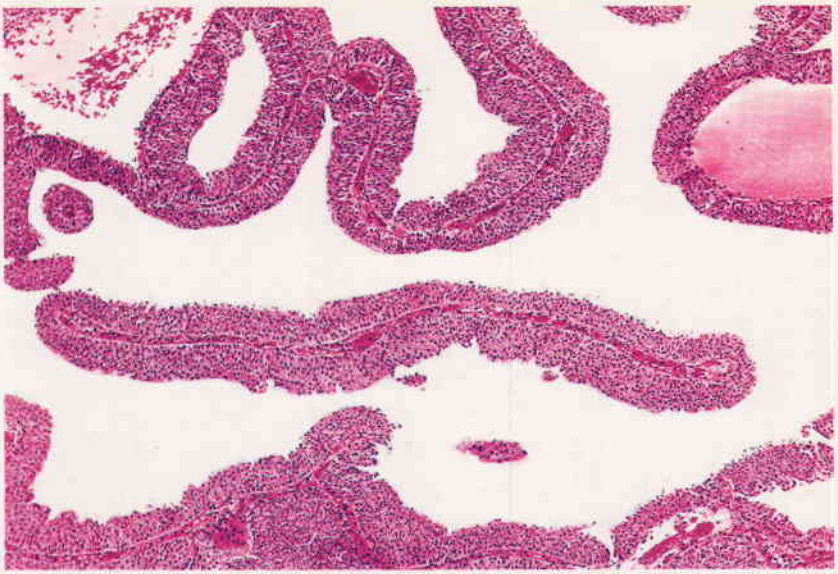


Fig. 1. Transitional cell papilloma

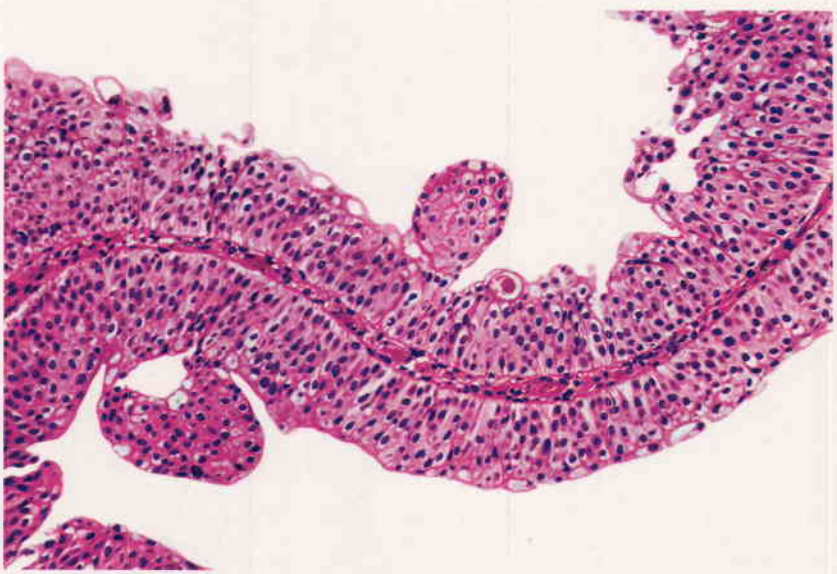


Fig. 2. Transitional cell papilloma

× 12

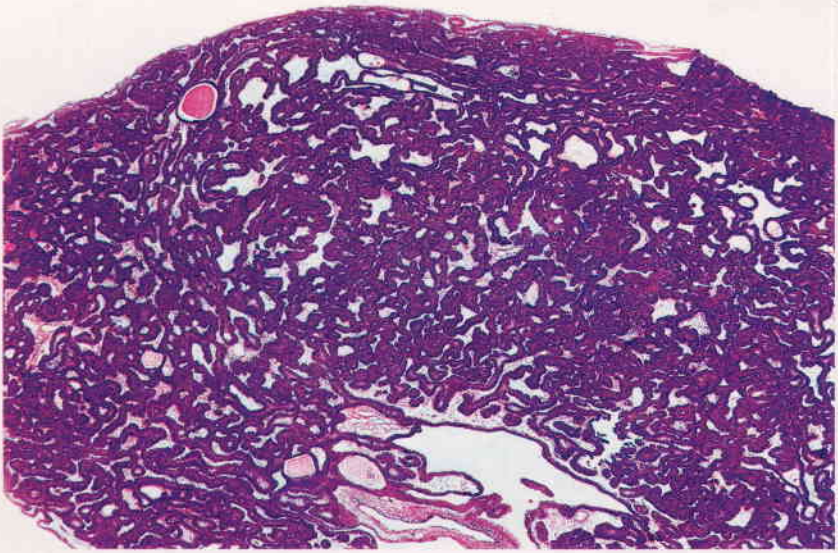


Fig. 3. Transitional cell papilloma, inverted type

× 195

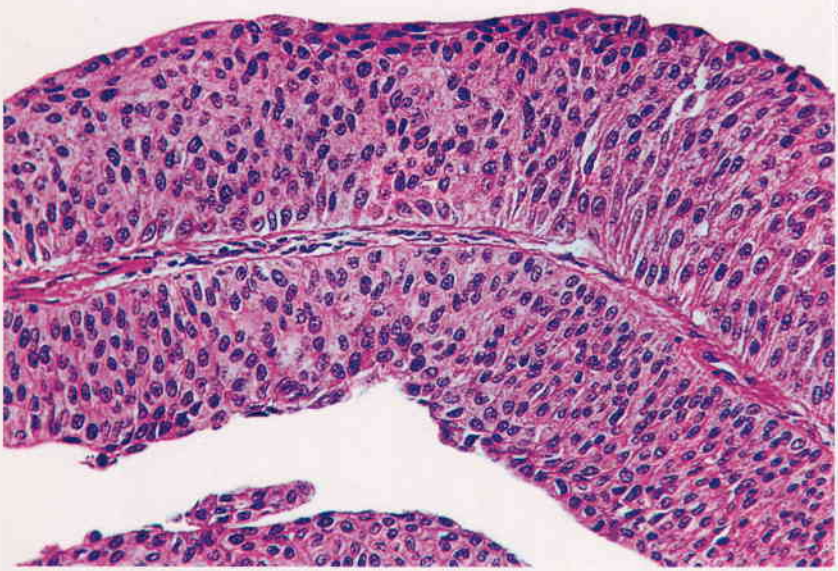
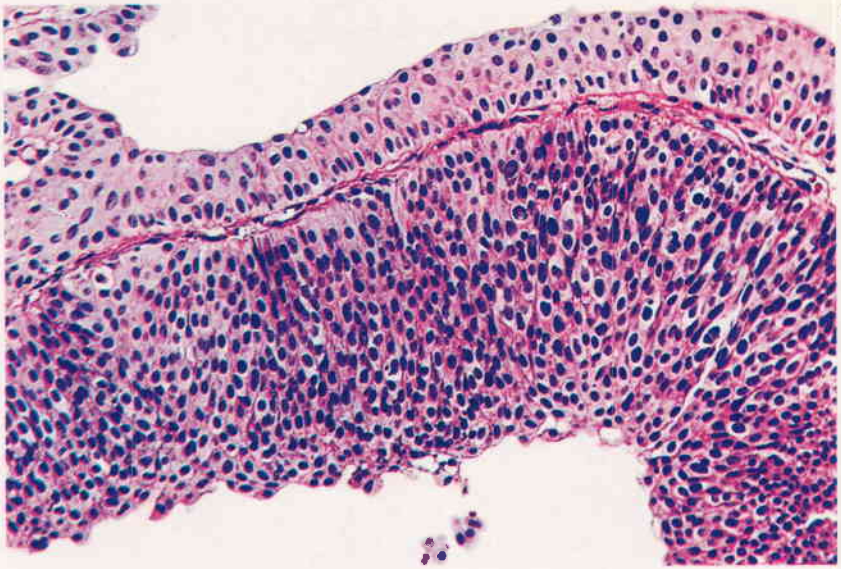
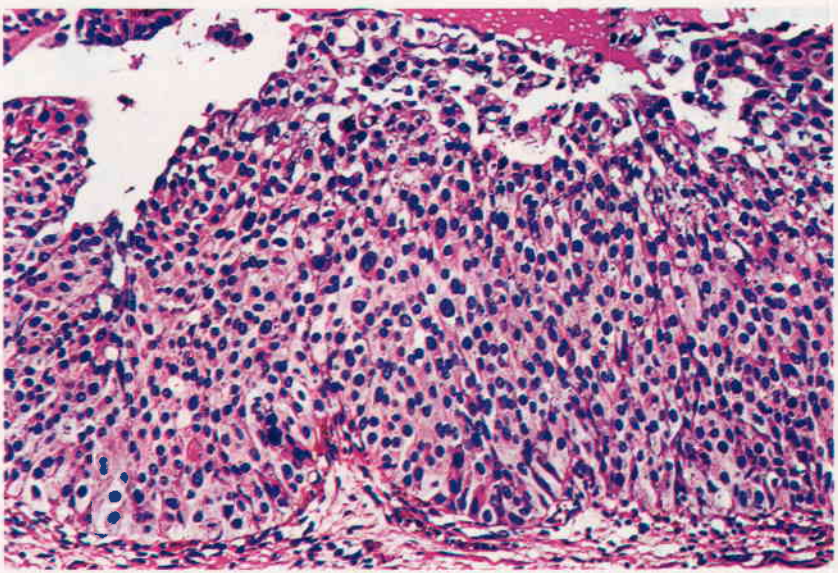


Fig. 4. Transitional cell carcinoma, grade 1



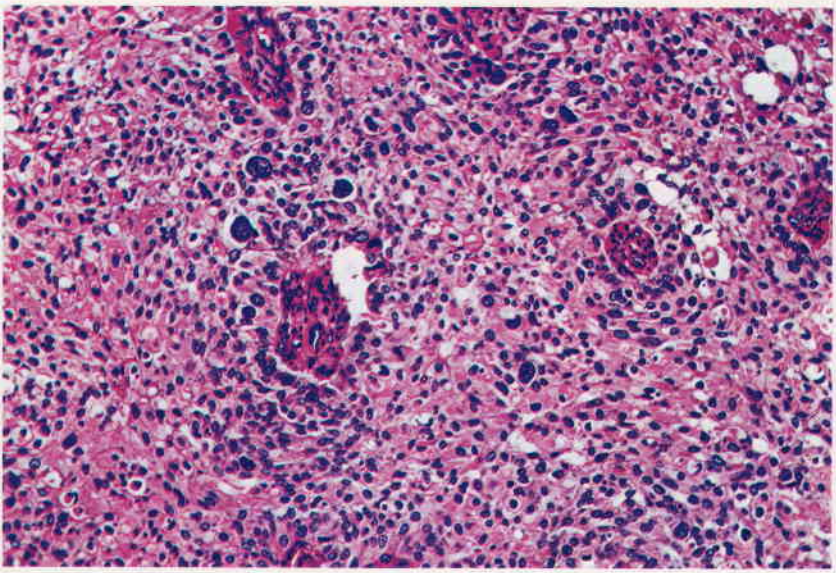
× 130

Fig. 5. Transitional cell carcinoma, grade 2
Lower grade of anaplasia in upper part of field



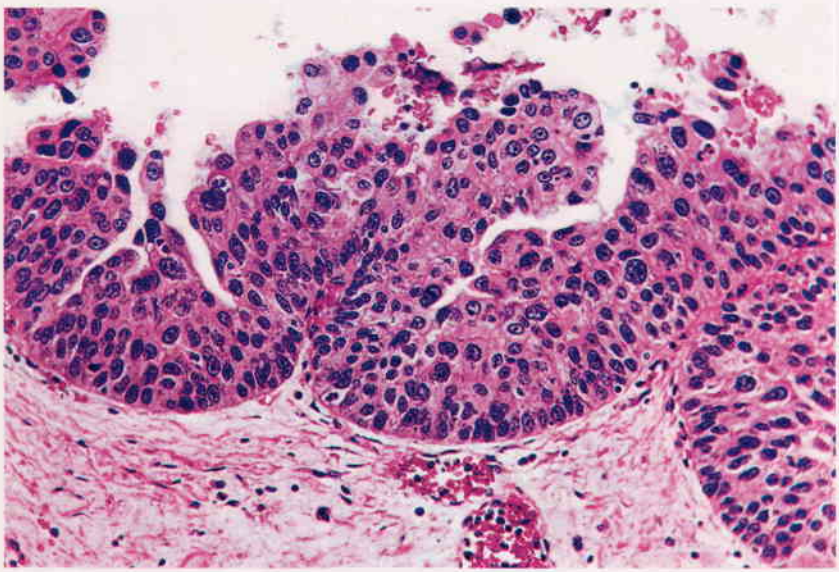
× 145

Fig. 6. Transitional cell carcinoma, grade 2



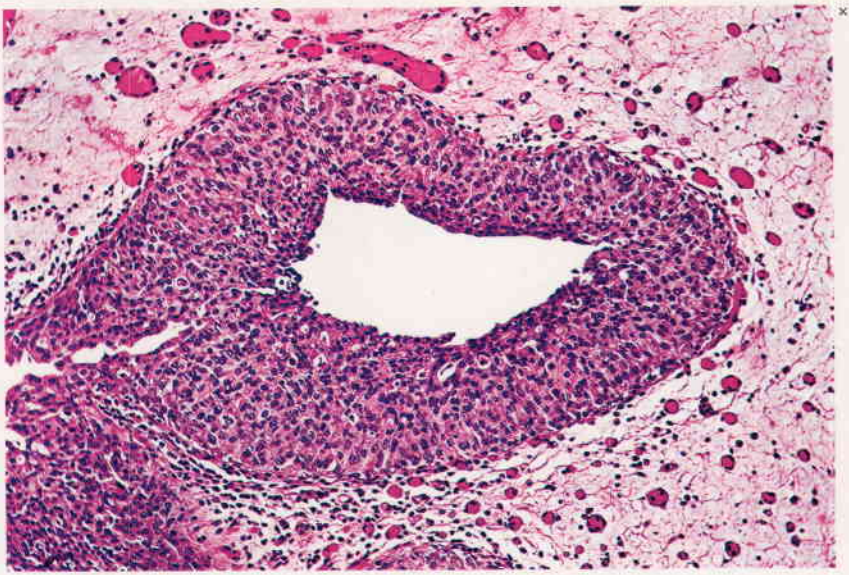
× 145

Fig. 7. Transitional cell carcinoma, grade 3



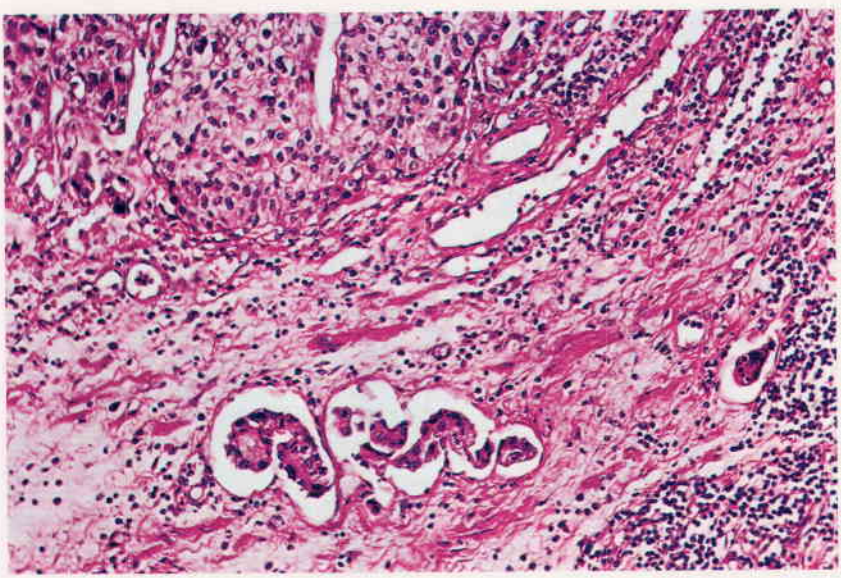
× 165

Fig. 8. Transitional cell carcinoma, non-papillary, non-infiltrating



× 115

Fig. 9. Transitional cell carcinoma in von Brunn's nest



× 130

10. Transitional cell carcinoma
Tumour in superficial lymphatics

× 6

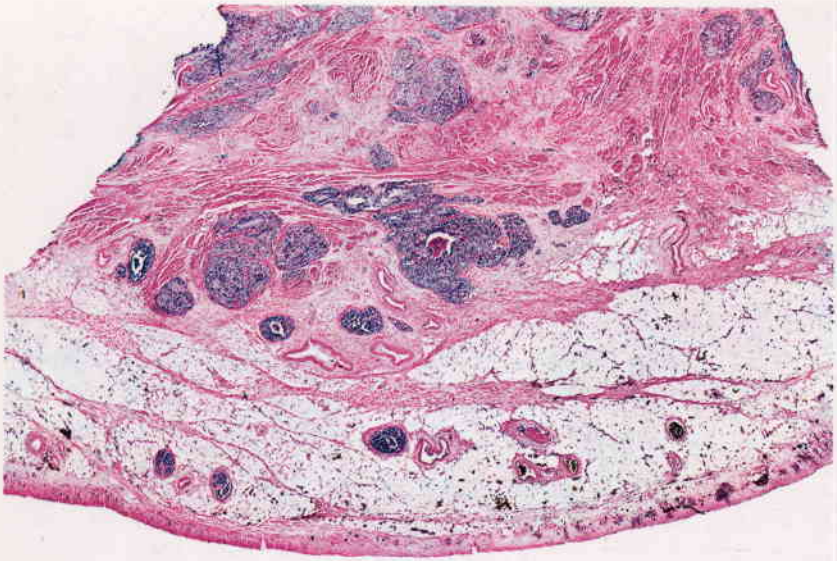


Fig. 11. Transitional cell carcinoma
Deep invasion of bladder wall

× 35

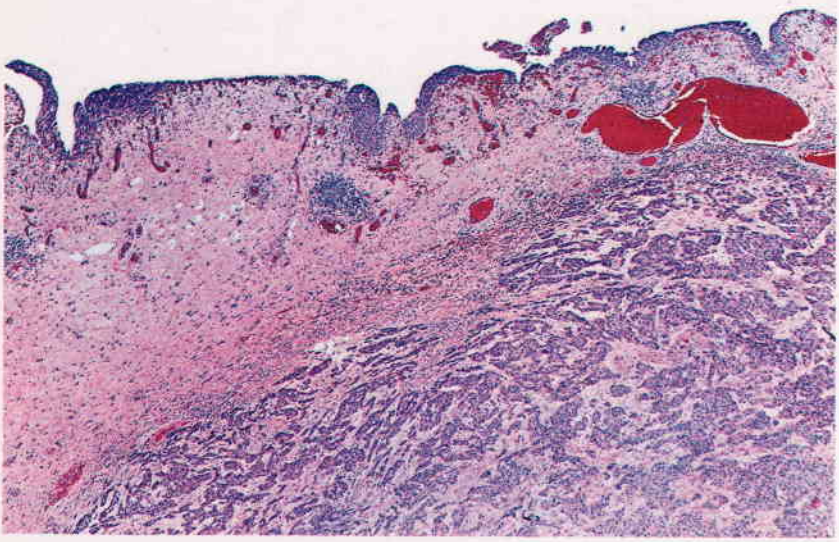
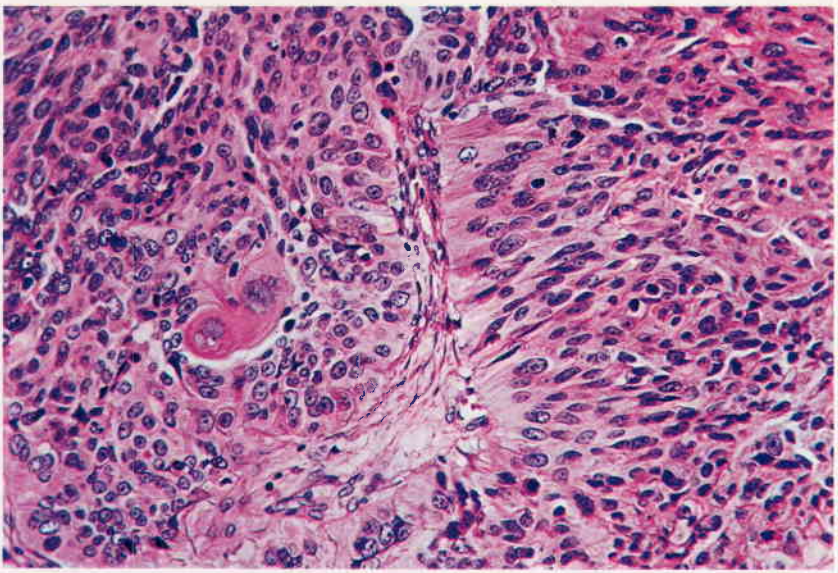
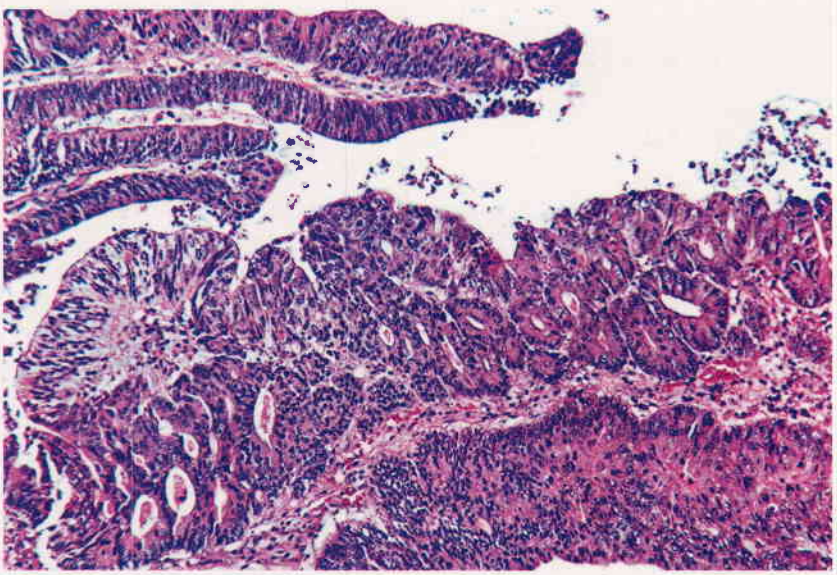


Fig. 12. Transitional cell carcinoma
Tumour undermines adjacent non-neoplastic mucosa



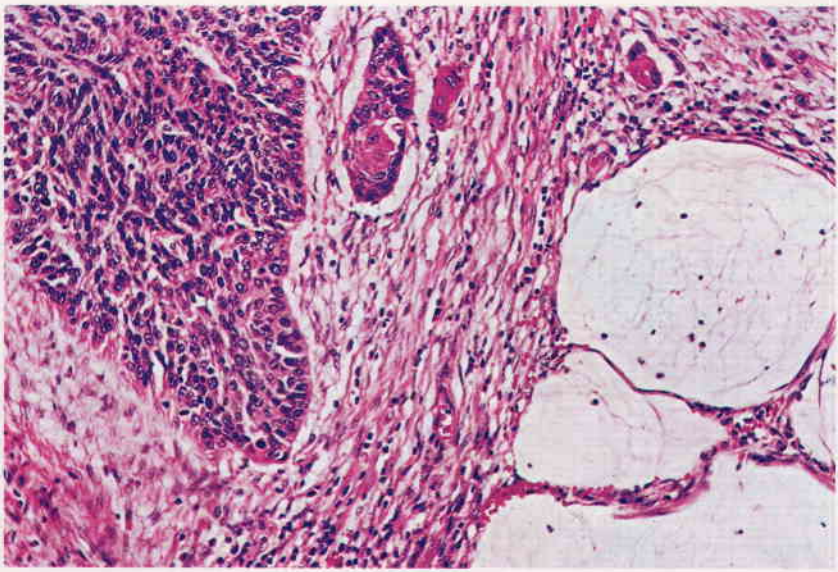
× 195

Fig. 13. Transitional cell carcinoma with squamous metaplasia



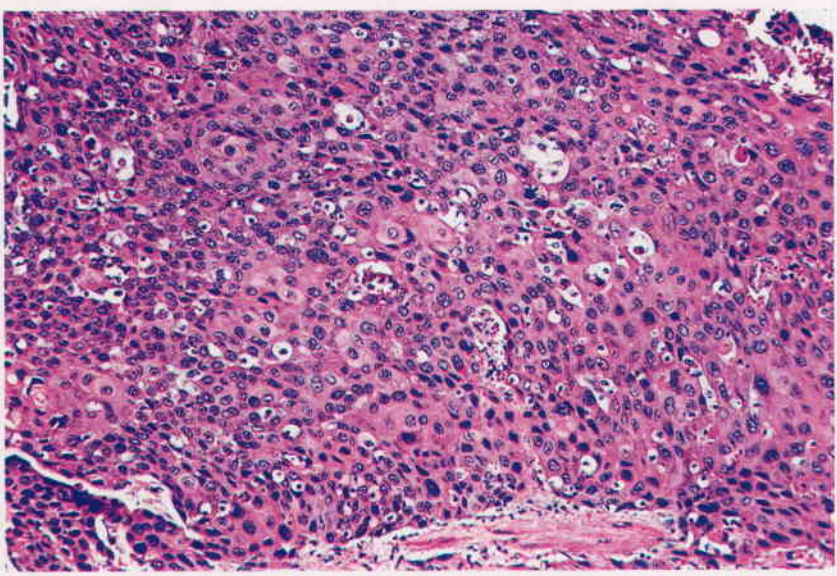
× 115

Fig. 14. Transitional cell carcinoma with glandular metaplasia



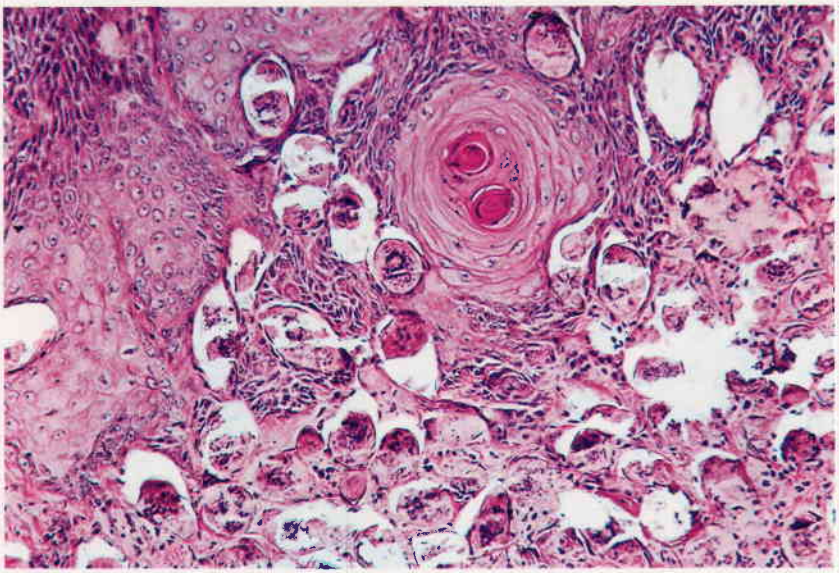
× 130

Fig. 15. Transitional cell carcinoma with squamous and glandular metaplasia
Epithelial lining obscured by pools of mucus



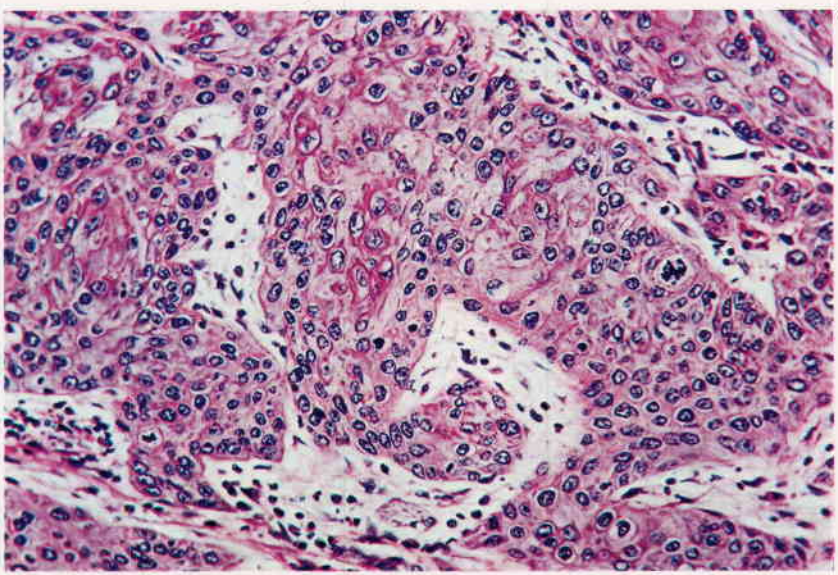
× 100

Fig. 16. Squamous cell carcinoma



× 130

Fig. 17. Squamous cell carcinoma with schistosomiasis



× 200

Fig. 18. Squamous cell carcinoma

× 6

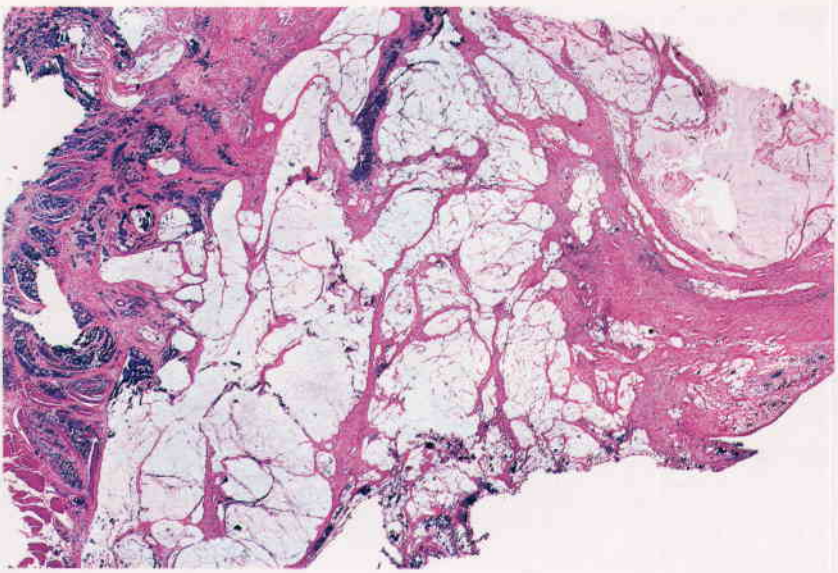


Fig. 19. Adenocarcinoma
Lakes of mucus extend through entire bladder wall

× 115

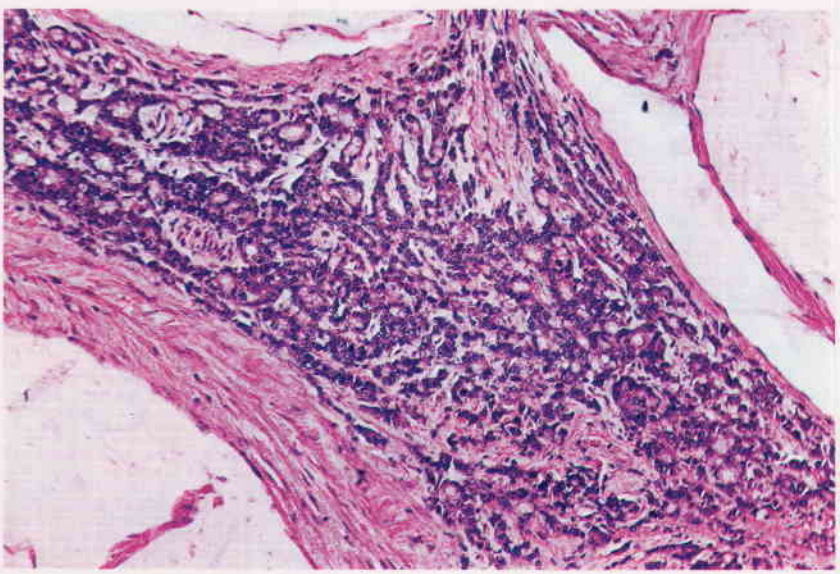
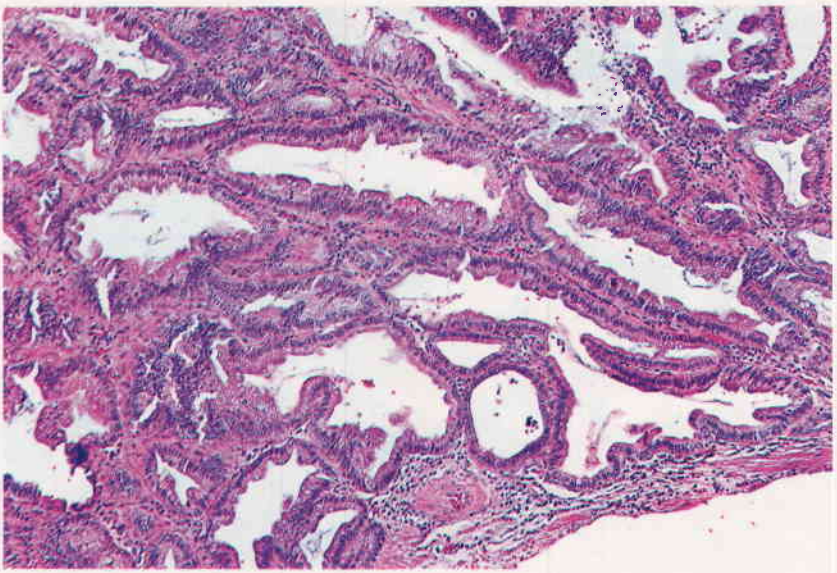
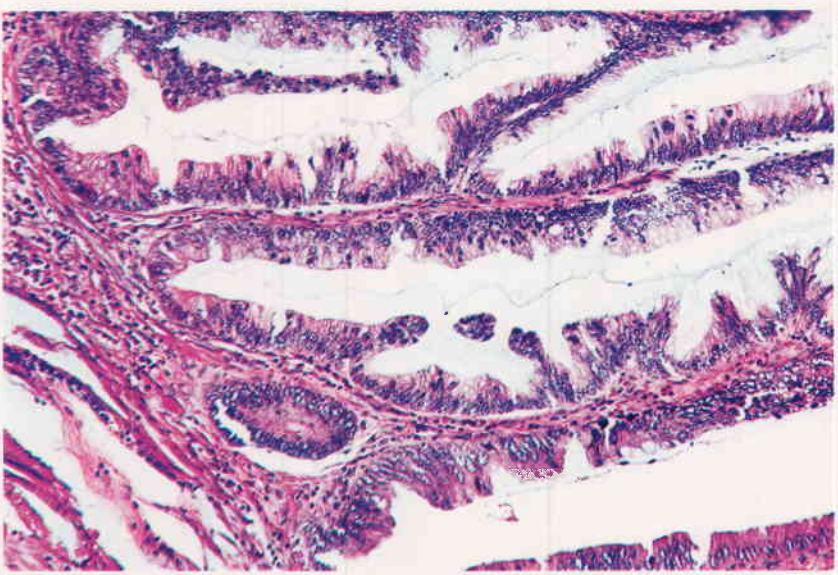


Fig. 20. Adenocarcinoma
Tumour surrounded by pools of mucus



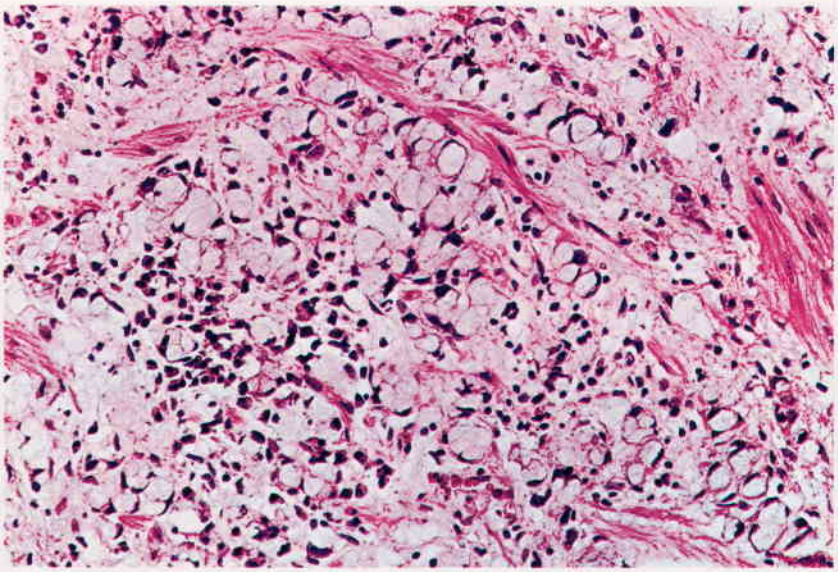
× 80

Fig. 21. Adenocarcinoma
Associated with vesical exstrophy



× 95

Fig. 22. Adenocarcinoma
Papillary pattern



× 350

Fig. 23. Adenocarcinoma
Signet-ring cells

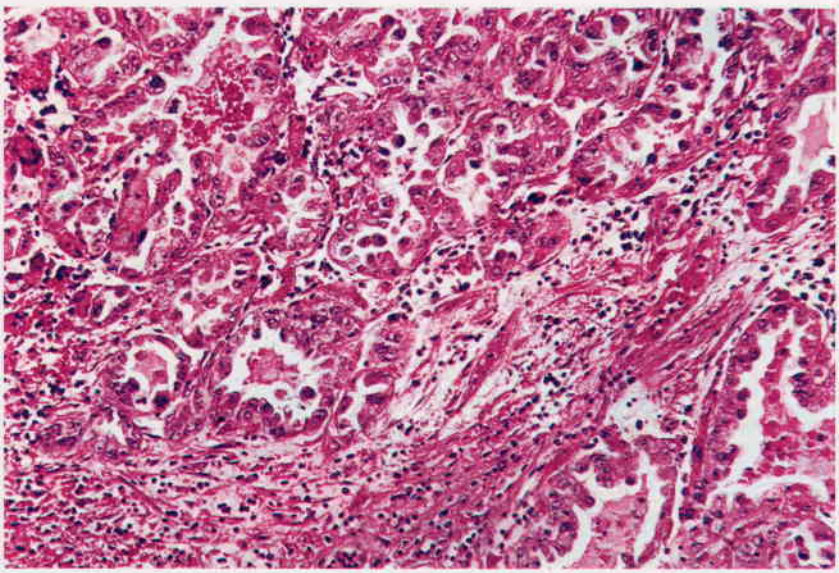


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Fig. 24. Adenocarcinoma, " mesonephric carcinoma "

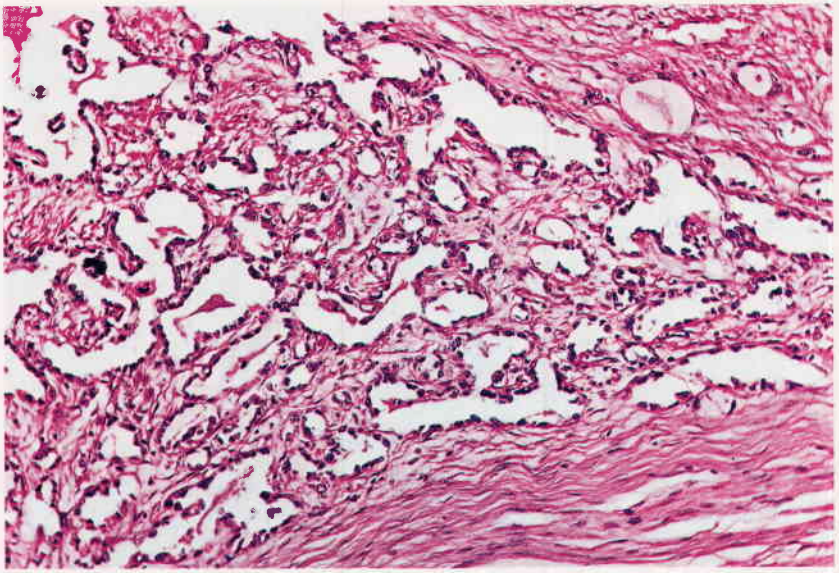

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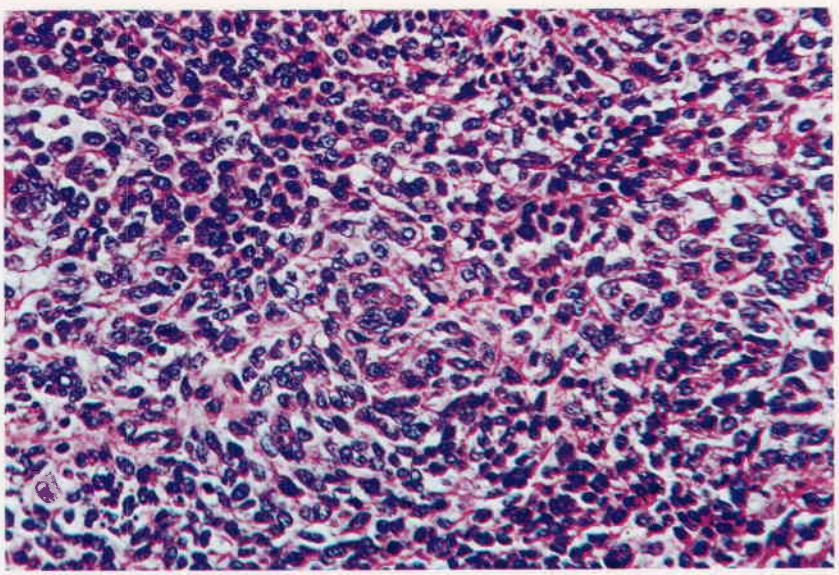
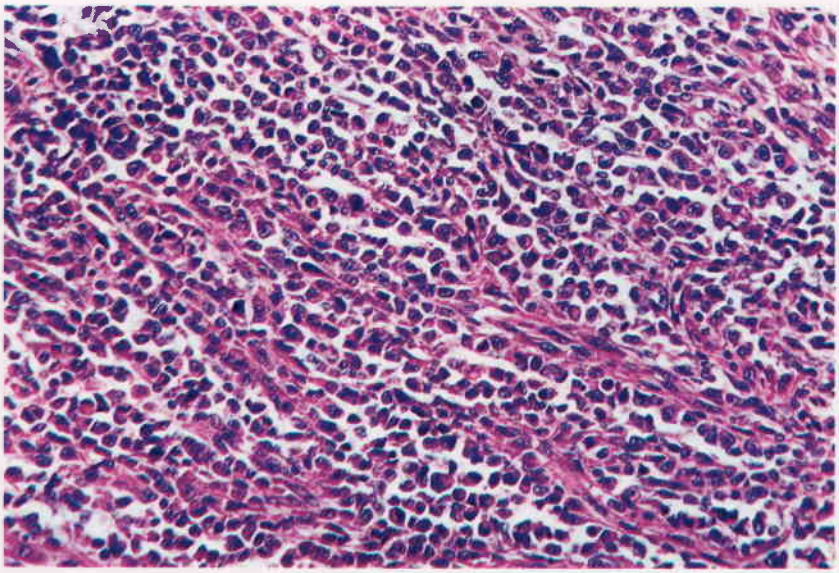
Fig. 25. Adenocarcinoma, " mesonephric carcinoma "



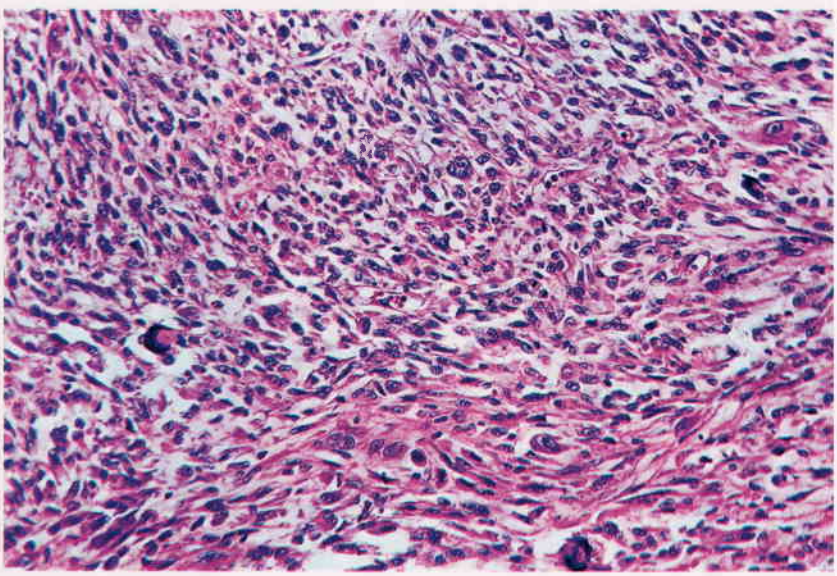
× 195

Fig. 26. Undifferentiated carcinoma



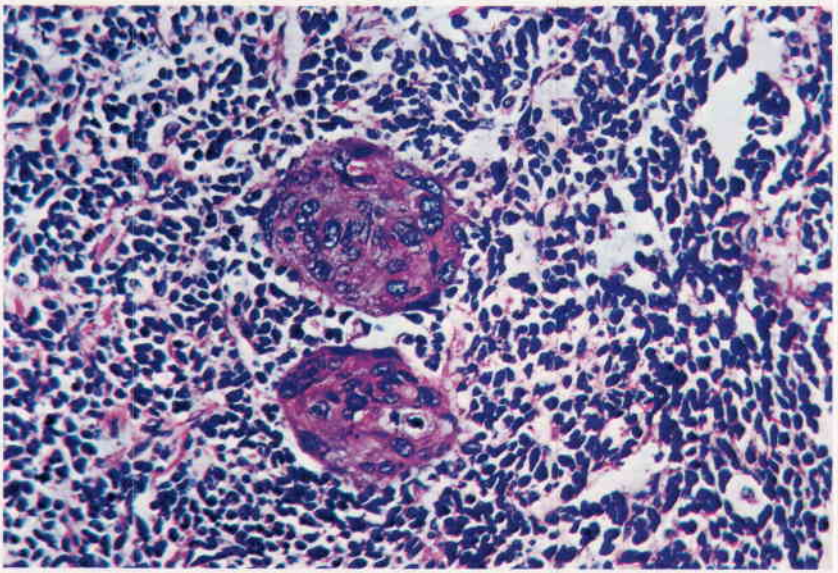
× 195

Fig. 27. Undifferentiated carcinoma



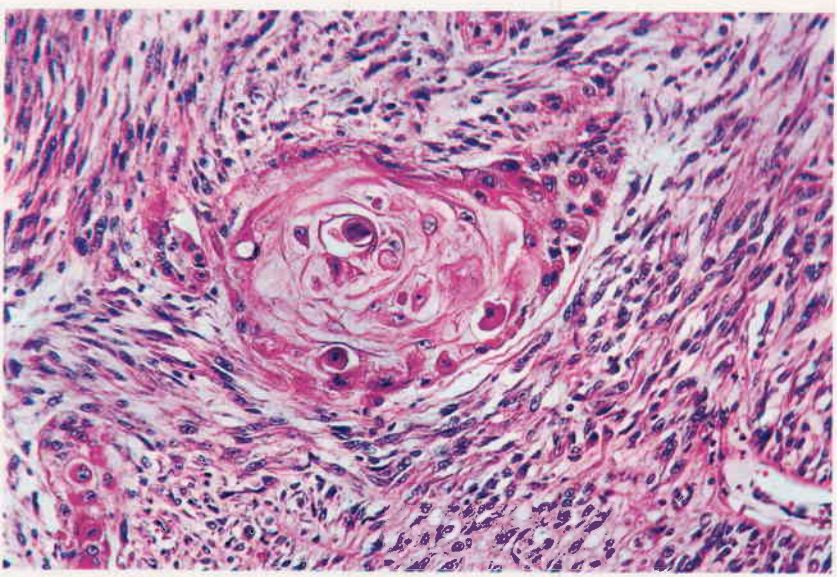
× 165

Fig. 28. Undifferentiated carcinoma
Spindle cells. From same tumour as Figure 27



× 220

Fig. 29. Undifferentiated carcinoma with squamous areas



× 165

Fig. 30. Undifferentiated (spindle) carcinoma with squamous areas

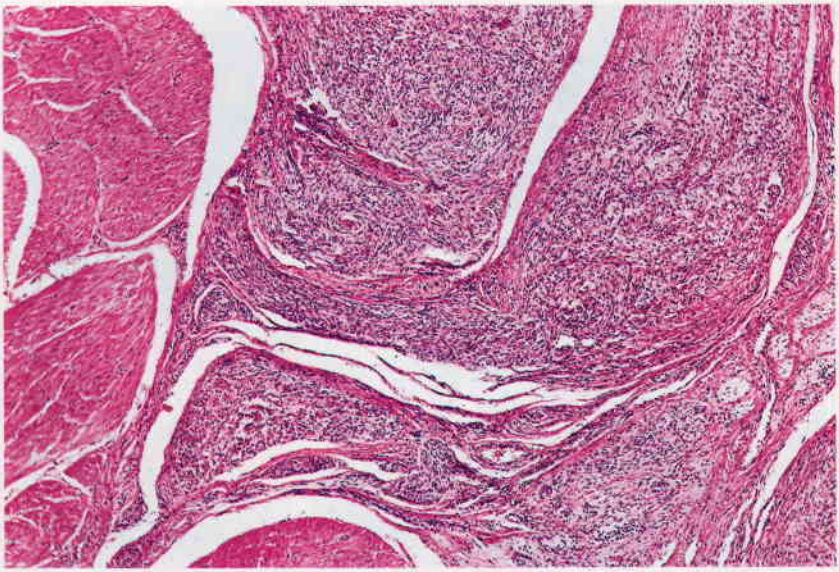


Fig. 31. Neurofibroma

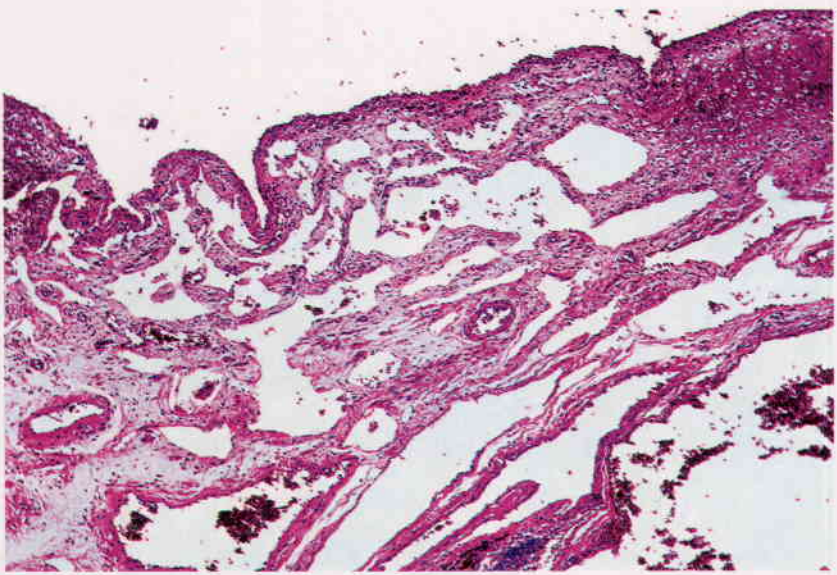


Fig. 32. Haemangioma

× 11

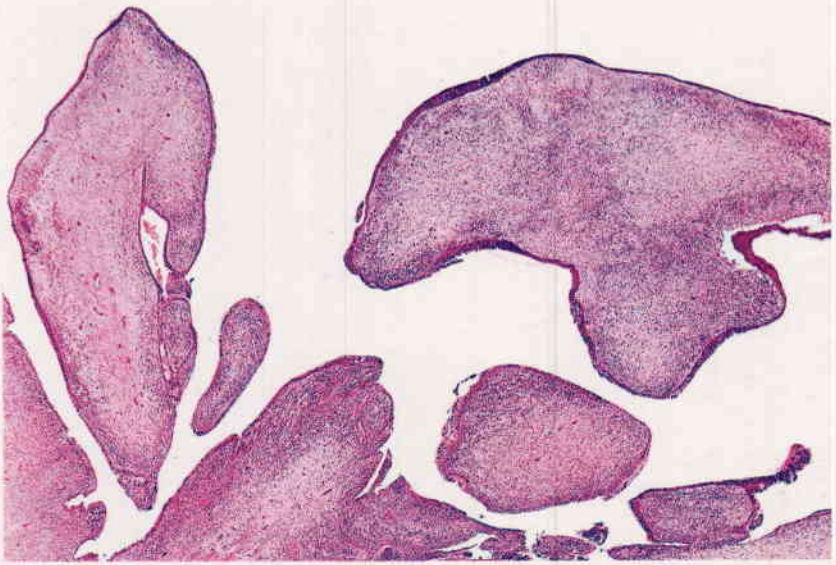


Fig. 33. Rhabdomyosarcoma

× 160

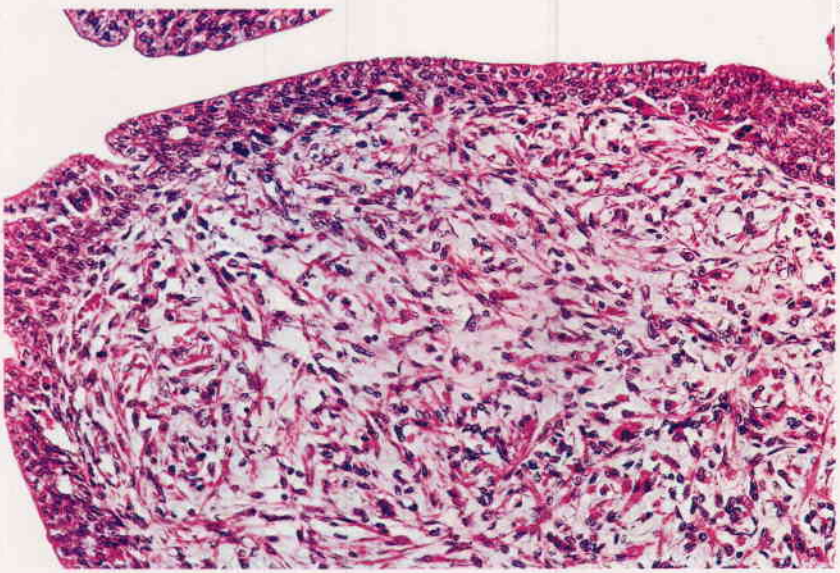


Fig. 34. Rhabdomyosarcoma

× 300

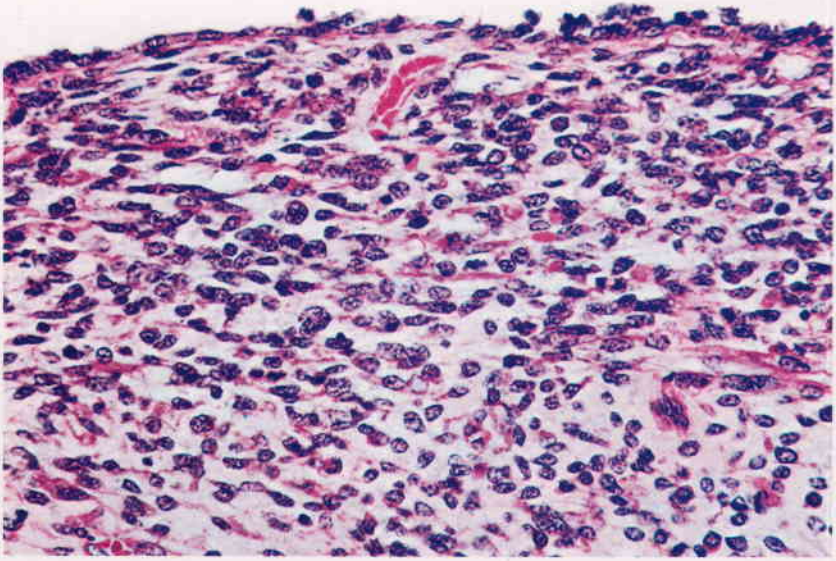


Fig. 35. Rhabdomyosarcoma

× 240

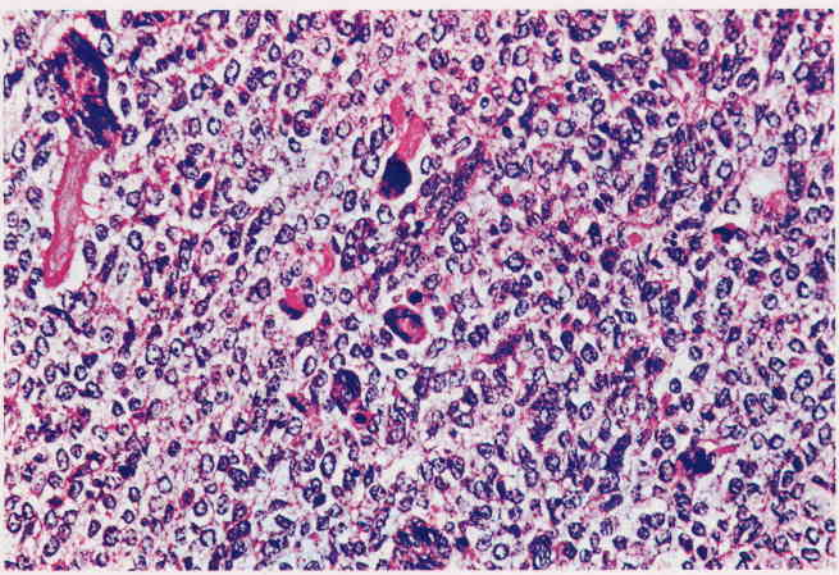
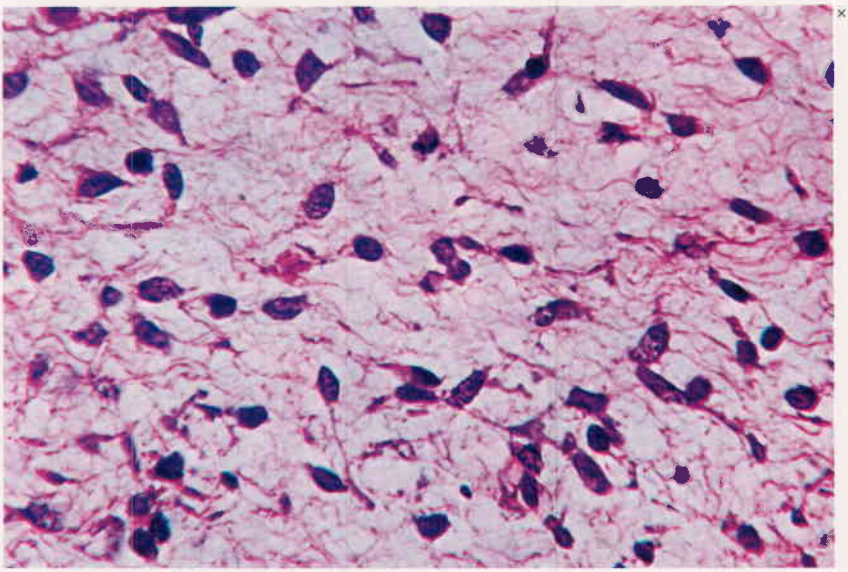
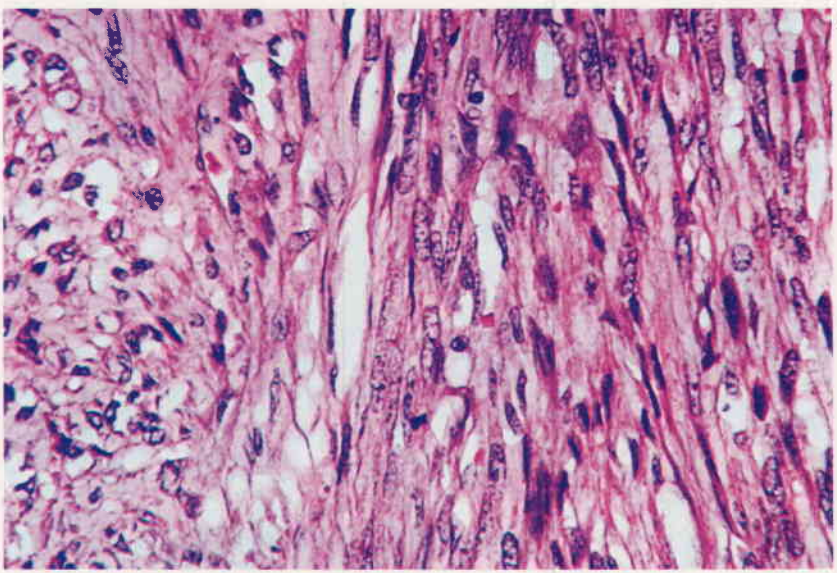


Fig. 36. Rhabdomyosarcoma



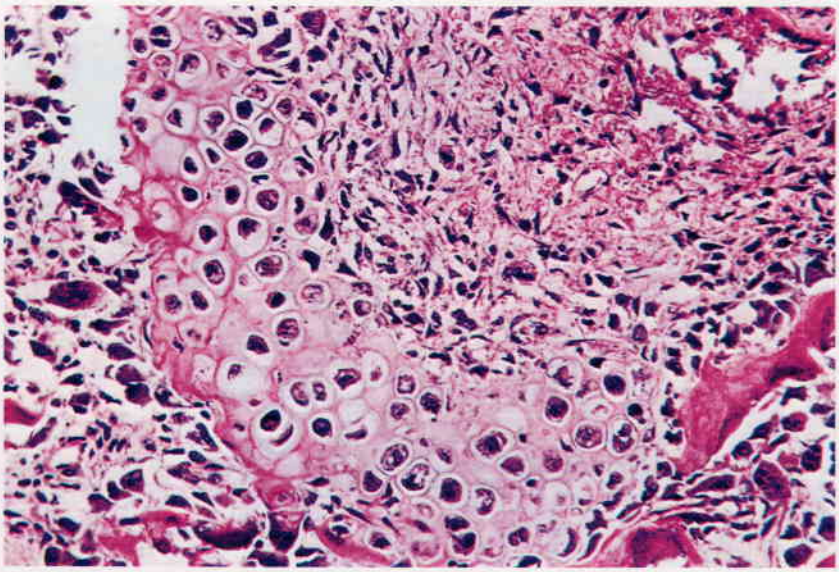
× 525

Fig. 37. Rhabdomyosarcoma



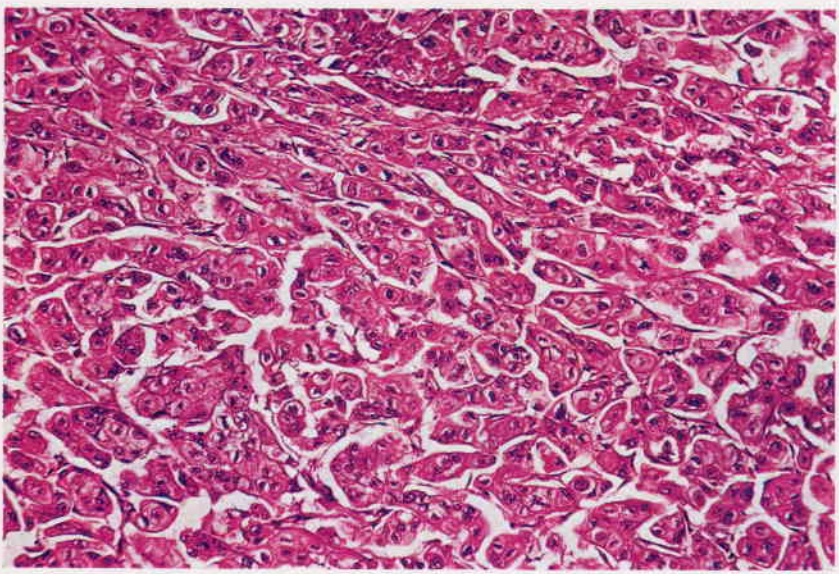
× 400

Fig. 38. Leiomyosarcoma



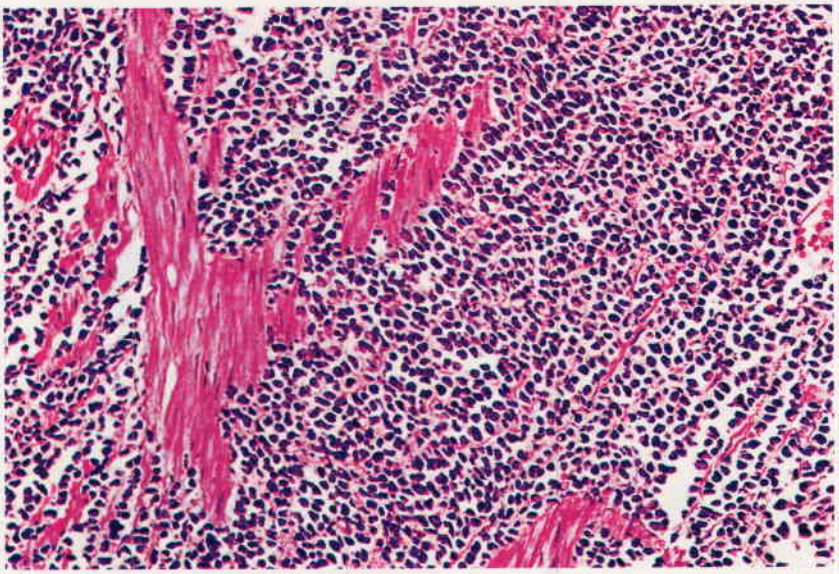
× 195

Fig. 39. Osteosarcoma
Cartilaginous area



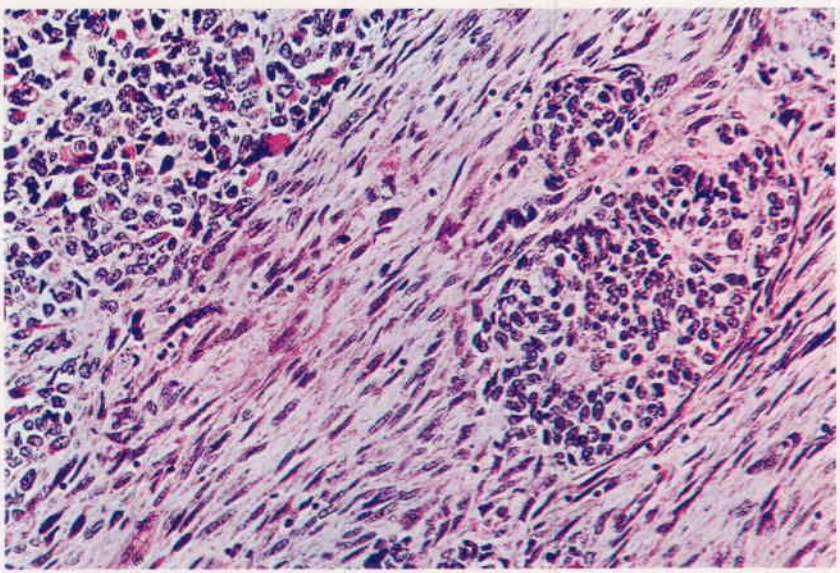
× 115

Fig. 40. Phaeochromocytoma



× 350

Fig. 41. Lymphosarcoma



× 210

Fig. 42. Carcinosarcoma
Nests of carcinoma surrounded by sarcoma. Focus of rhabdomyosarcoma at upper left

× 145

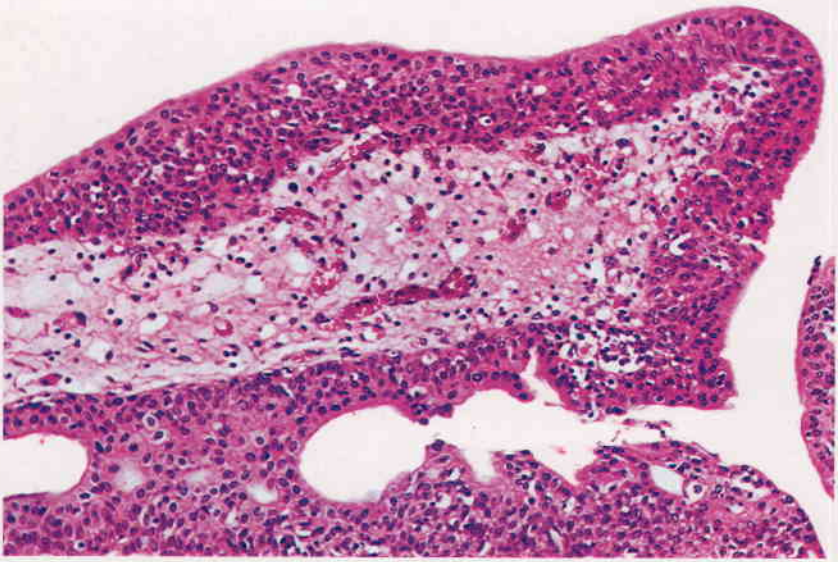


Fig. 43. Papillary " cystitis "

× 50

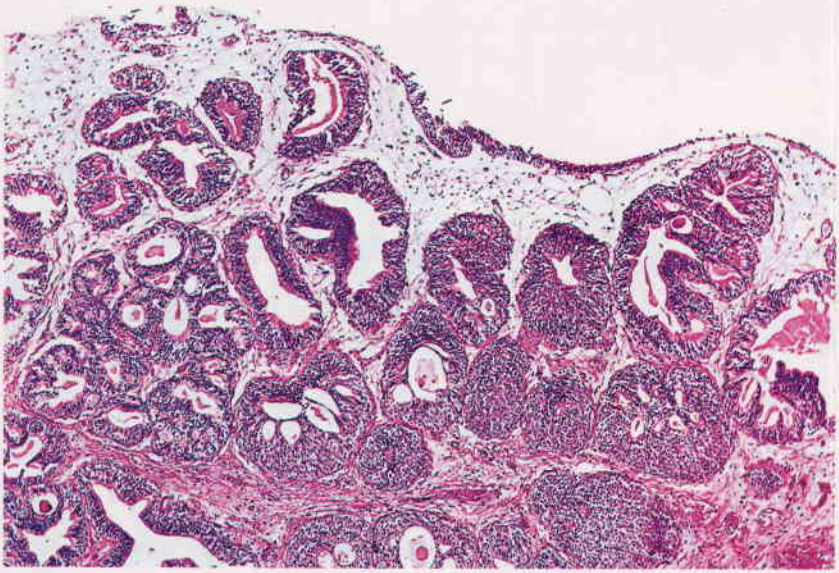
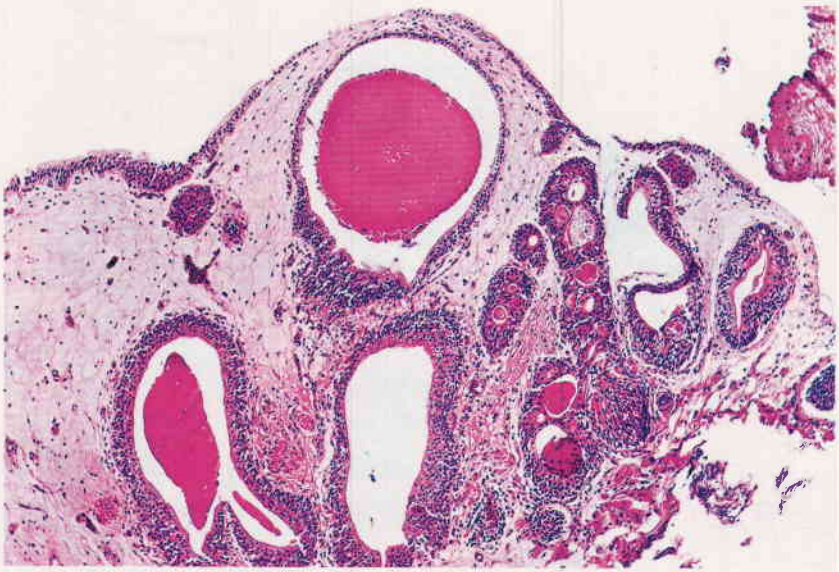
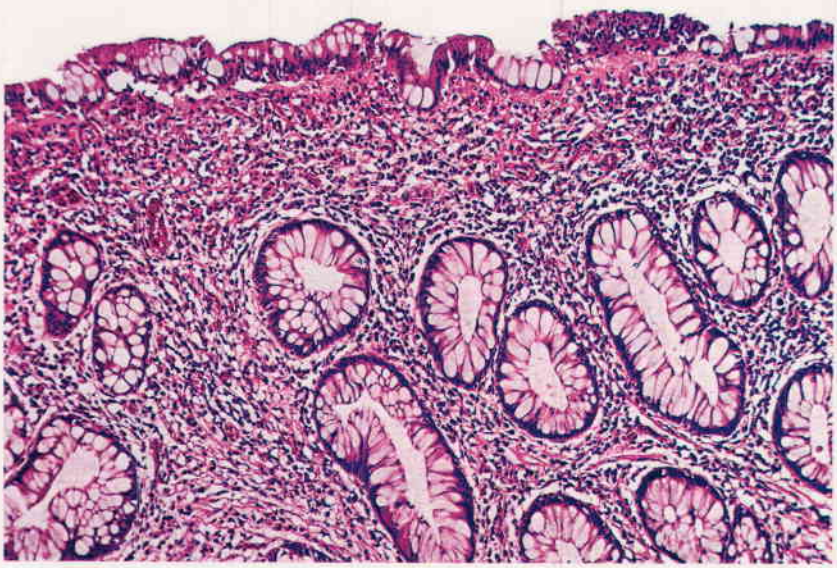


Fig. 44. von Brunn's nests



× 55

Fig. 45. "Cystitis" cystica



× 90

Fig. 46. Glandular metaplasia

× 100

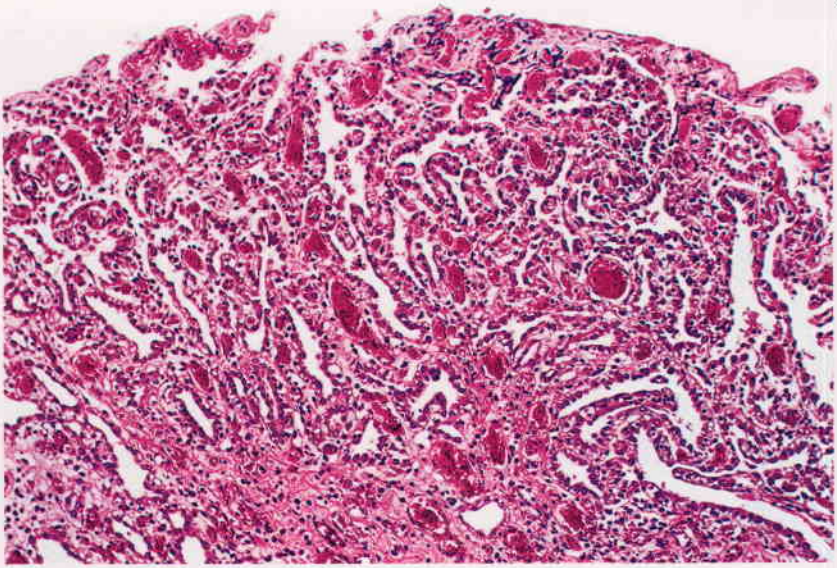


Fig. 47. " Nephrogenic adenoma "

× 145

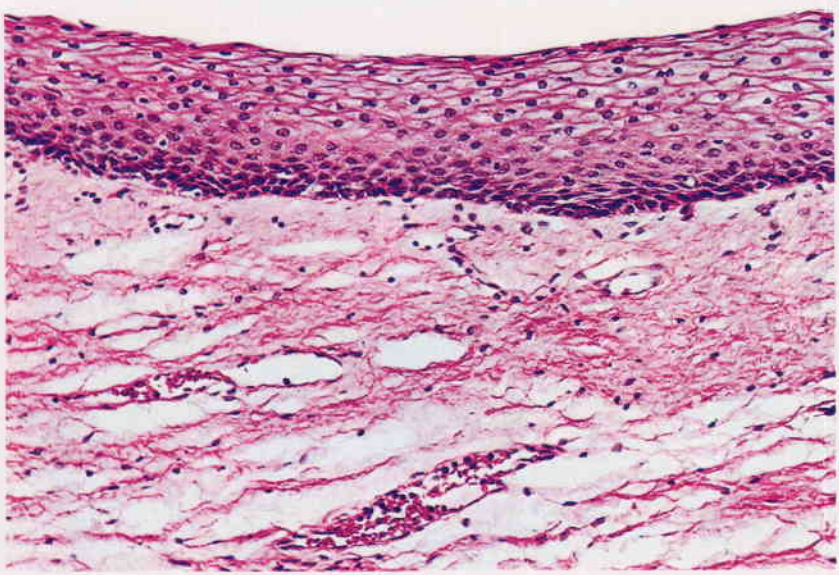


Fig. 48. Squamous metaplasia

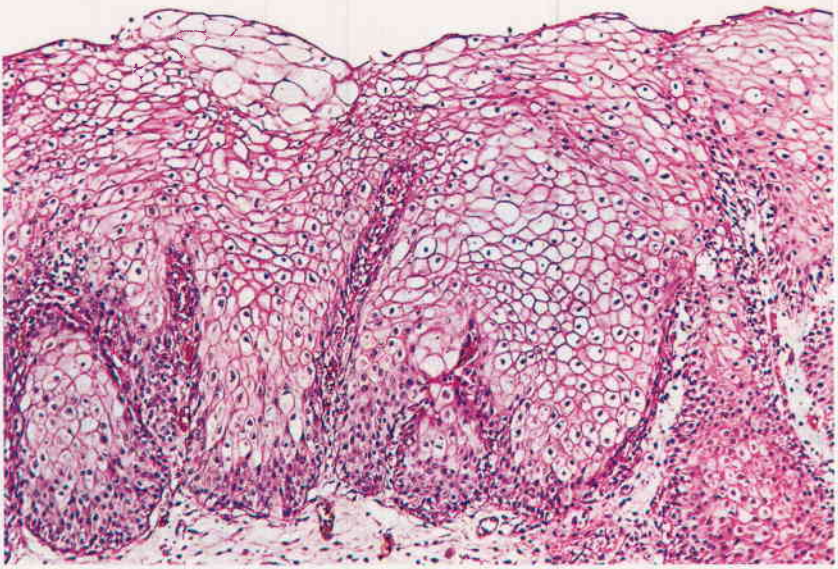


Fig. 49. Squamous metaplasia with hyperplasia

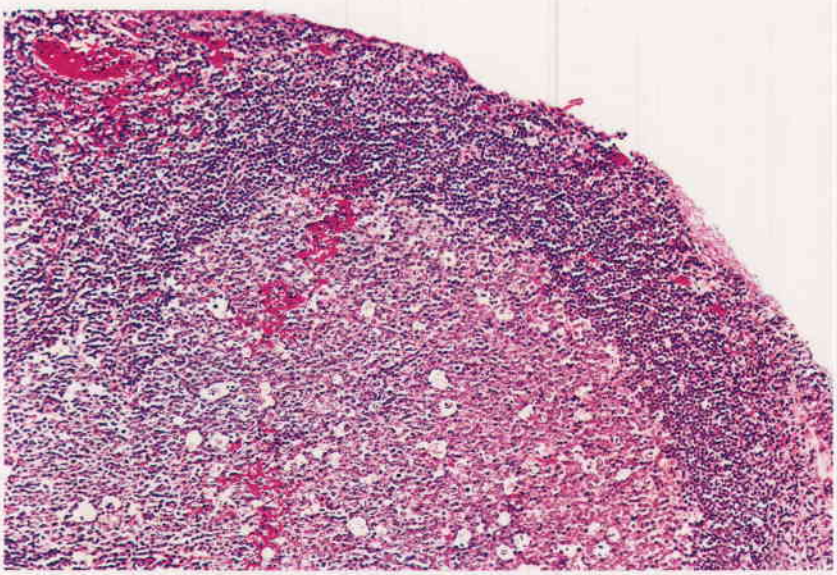


Fig. 50. Follicular cystitis

× 115

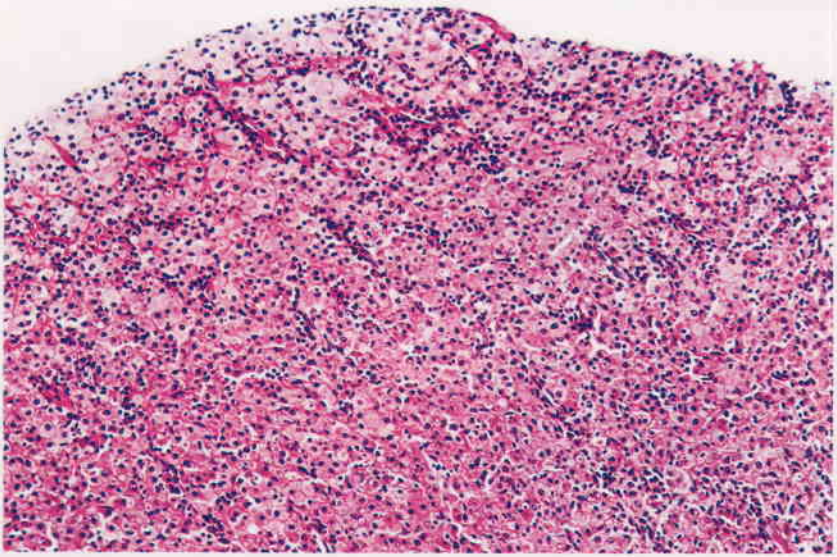


Fig. 51. Malakoplakia

× 525

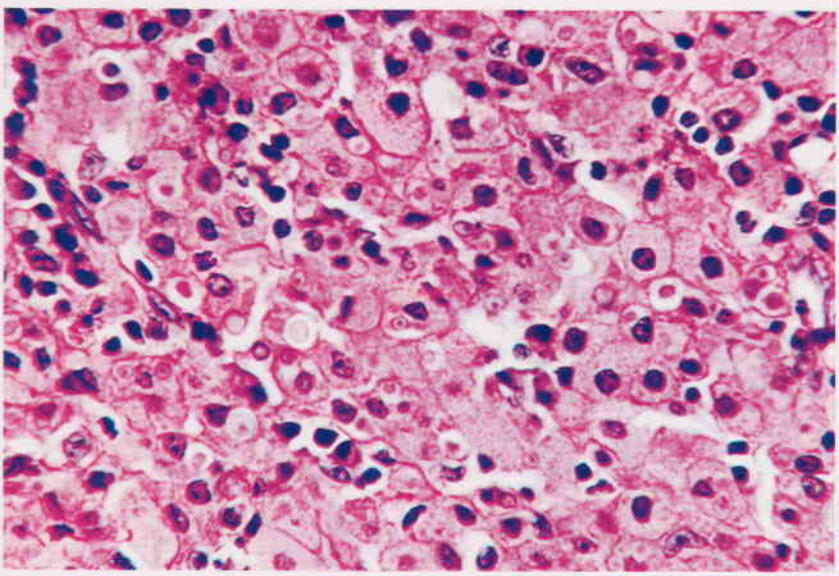
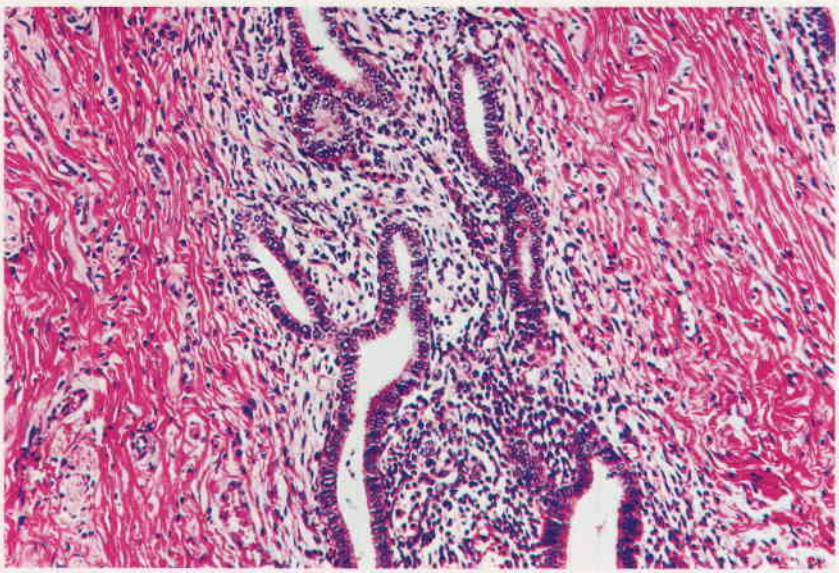
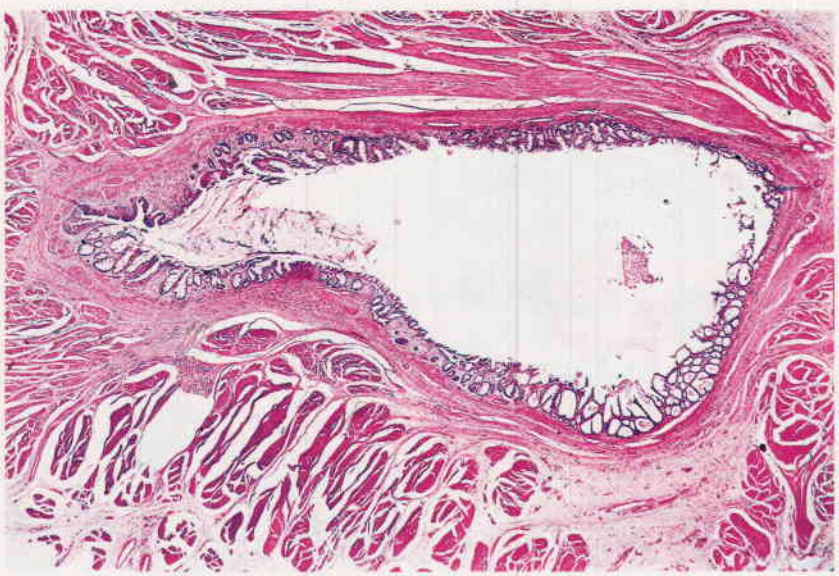


Fig. 52. Malakoplakia



× 130

Fig. 55. Endometriosis



× 9

Fig. 56. Urachal cyst

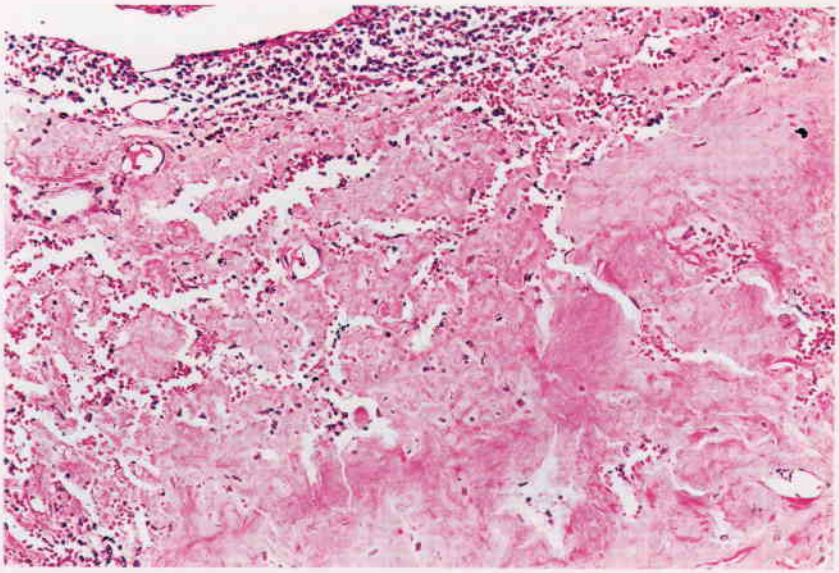


Fig. 53. Amyloidosis

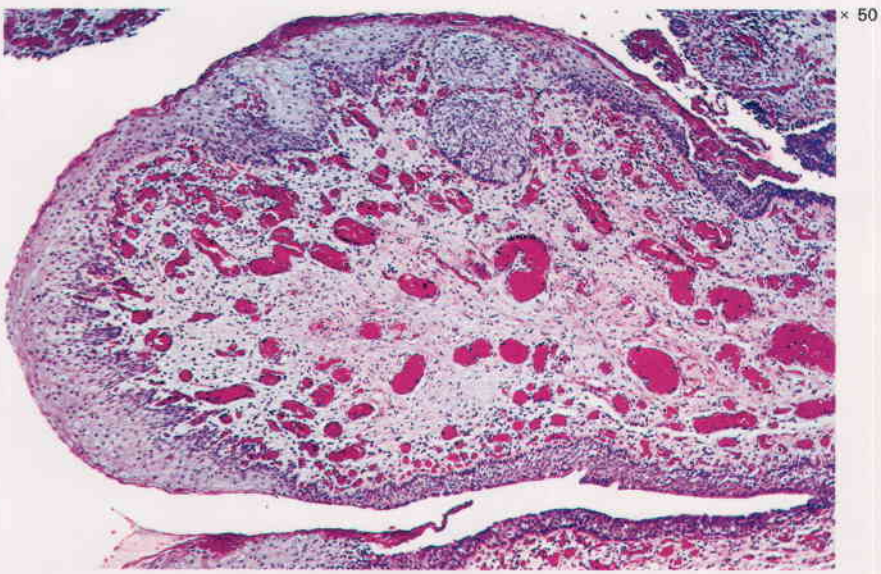


Fig. 54. Fibrous polyp
Squamous metaplasia present