Histological Typing of Endocrine Tumours
HISTOLOGICAL TYPING OF ENDOCRINE TUMOURS
INTERNATIONAL HISTOLOGICAL CLASSIFICATION OF TUMOURS
No. 23

HISTOLOGICAL TYPING OF ENDOCRINE TUMOURS

E. D. WILLIAMS
Head, WHO Collaborating Centre for the Histological Classification of Endocrine Tumours,
Department of Pathology, The Welsh National School of Medicine, Cardiff, Wales,
United Kingdom

in collaboration with

R. E. SIEBENMANN
Institute of Pathology,
Stadtspital Triemli,
Zurich, Switzerland

L. H. SOBIN
Pathologist,
World Health Organization,
Geneva, Switzerland

and pathologists in 13 countries

WORLD HEALTH ORGANIZATION
GENEVA
1980
LIST OF PARTICIPANTS

WHO Collaborating Centre for the Histological Classification of Endocrine Tumours, Department of Pathology, The Welsh National School of Medicine, Cardiff, Wales, United Kingdom

Head of Centre

Dr E. D. Williams

Participants

Dr J. Albores-Saavedra, Pathology Unit, Facultad de Medicina, Universidad Nacional, Hospital General, Mexico, D.F., Mexico
Dr O. K. Khmelnitsky, Chair of Pathological Anatomy, Postgraduate Medical Institute, Leningrad, USSR
Dr J. Kracht, University Institute of Pathology, Giessen, Federal Republic of Germany
Dr A. Mackay, Institute of Cancer Research in association with the Royal Marsden Hospital, Sutton, Surrey, England
Dr A. Pagès, Institut d’Anatomie pathologique, Centre médico-chirurgical Gui de Chauliac, Montpellier, France
Dr R. E. Siebenmann, Institute of Pathology, Stadtspital Triemli, Zurich, Switzerland
Dr L. H. Sobin, Cancer, World Health Organization, Geneva, Switzerland
Dr E. Solcia, Histopathological Diagnosis Centre, University of Pavia and Varese, Ospedale di Circolo, Varese, Italy
Dr A. L. Vickery, Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts, USA

Reviewers

Dr S. Falkmer, Institute of Pathology, University of Umeå, Umeå, Sweden
Dr W. Gepts, Laboratoire d’Anatomie pathologique, Hôpital universitaire Brugmann, Brussels, Belgium
Dr R. Raichev, Department of Pathology, Cancer Research Institute, Sofia, Bulgaria
Dr M. Ratzenhofer, Institute of Pathology, University of Graz, Graz, Austria
Dr J. Rosai, Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota, USA
Dr H. Suzuki, Laboratory of Pathology, Aichi Cancer Centre, Research Institute, Nagoya, Japan
ALREADY PUBLISHED IN THIS SERIES:

No. 1. Histological typing of lung tumours (1967)
No. 2. Histological typing of breast tumours (1968)
No. 3. Histological typing of soft tissue tumours (1969)
No. 4. Histological typing of oral and oropharyngeal tumours (1971)
No. 5. Histological typing of odontogenic tumours, jaw cysts, and allied lesions (1971)
No. 6. Histological typing of bone tumours (1972)
No. 7. Histological typing of salivary gland tumours (1972)
No. 8. Nomenclature of cytology of the female genital tract (1973)
No. 9. Histological typing of ovarian tumours (1973)
No. 10. Histological typing of urinary bladder tumours (1973)
No. 11. Histological typing of thyroid tumours (1974)
No. 13. Histological typing of female genital tract tumours (1975)
No. 15. Histological typing of intestinal tumours (1976)
No. 16. Histological typing of testis tumours (1977)
No. 17. Cytology of non-gynaecological sites (1977)
No. 18. Histological typing of gastric and oesophageal tumours (1977)
No. 19. Histological typing of upper respiratory tract tumours (1978)
No. 20. Histological typing of tumours of the liver, biliary tract and pancreas (1978)
No. 21. Histological typing of tumours of the central nervous system (1979)
No. 22. Histological typing of prostate tumours (1980)
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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, 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 resolution3 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 19574 and the following month a Study Group on Histological Classification of Cancer 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 the drafting of histological classifications and testing their validity. Briefly, the procedure is as follows:

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

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4 WHO Official Records, No 79, 1957, p 467 (resolution WHA10 18)
in the field in question. A 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 and the classification is amended to take account of criticisms.

In addition to preparing the publication and the photomicrographs for it, the centre produces up to 100 sets of microscope slides showing the major histological types for distribution to regional centres.

Since 1958, WHO has established 23 centres covering tumours of the lung; breast; soft tissues; oropharynx; bone; ovaries; salivary glands; thyroid; skin; male urogenital tract; jaws; female genital tract; 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 300 pathologists from over 50 countries. Most of these centres have completed their work, and their classifications have already been published (see page 6).

The World Health Organization is indebted to the many pathologists who have participated and are participating in this large undertaking. The pioneer work of many other international and national organizations in the field of histological classification of tumours has greatly facilitated the task undertaken by WHO. Particular gratitude is expressed to the National Cancer Institute, USA, which, through the National Research Council and the USA National Committee for the International Council of Societies of Pathology, is providing financial support to accelerate this work. 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 participants 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 ENDOCRINE TUMOURS

The WHO Collaborating Centre for the Histological Classification of Endocrine Tumours was established in 1972 at the Department of Pathology, The Welsh National School of Medicine, Cardiff, Wales, United Kingdom.

The Centre distributed histological sections from selected cases to the participants, a list of whom will be found on page 5, for typing according to a tentative classification drawn up at a WHO consultation in 1972. In all, over 200 cases were thus studied and were reviewed at meetings in 1974 and 1976 attended by the participants. The classification, its definitions and its nomenclature were amended at these meetings, in the light of this study. The classification and selected cases were reviewed by a second group of pathologists designated by WHO (see page 5). At the meeting in 1976, the present classification was adopted.

It will, of course, be appreciated that the classification reflects the present state of knowledge, and modifications are almost certain to be needed as experience accumulates. Although the present classification has been adopted by the members of the group, it necessarily represents a 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 welcomed. These should be sent to the World Health Organization, Geneva, Switzerland.

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 intentionally been kept to a minimum, and readers are referred to standard works on the subject for extensive bibliographies.
INTRODUCTION

This classification\(^1\) is based primarily on the microscopic characteristics of endocrine tumours and therefore is concerned with morphologically identifiable cell types and histological patterns as seen with conventional light microscopy. The secretory activity of endocrine tumours is not only of great clinical significance but also provides information relevant to the identification of the tumour cell type. These two approaches are complementary: microscopy provides evidence of the structural differentiation of the tumour, while the secretory activity, often resulting in a clinical syndrome, provides evidence of the functional differentiation of the tumour. For each endocrine tumour, the morphological classification should, if possible, be supplemented by information on the functional activity of the tumour.

Polypeptide hormone-producing tumours usually consist of one dominant cell type and are associated with the production of one major polypeptide hormone. However, the increasing use of immunolocalization and electron microscopy techniques has demonstrated the presence of more than one cell type in a significant proportion of tumours. There may also be variation either in the degree of differentiation of the cell or in the amount of hormone storage—as, for example, in the acidophil adenoma of the pituitary with acromegaly, where the cell type may vary from well-granulated acidophil to large non-staining chromophobe. In steroid hormone and biogenic amine-producing tumours, several related hormones are frequently produced by the tumour. For example, one adrenocortical tumour can produce several active hormones with differing effects, and also steroids without any known hormonal action.

Although in many cases the cell type of the tumour can be determined by a combination of special stains, immunohistochemical investigation and electron microscopy, a classification based on these methods could not at present be widely applied. The proposed classification is therefore essentially morphological and based largely on simple techniques.

The number of tumour types which are usually regarded as non-endocrine but which produce substances with a distant effect, and so could be termed endocrine tumours, is much greater than was once thought. Tumours which could be regarded as true endocrine tumours include the renin-secreting juxtaglomerular apparatus tumours, the amine-secreting pinealomas, and the gonadotrophin-secreting placental tumours. Other tumours which are difficult to classify may also, on occasion, produce hormones, for example, the catecholamine-secreting melanotic neuro-ectodermal tumour. In addition, there is now known to be a wide range of non-endocrine tumours

\(^1\) This classification covers tumours of the anterior pituitary, adrenal, parathyroid, endocrine pancreas, and the diffuse endocrine system. It also includes tumours of the paraganglia. Tumours of the thyroid and gonads have been dealt with in previous publications in this series.
associated with ectopic hormone production—for example, renal cell carcinoma producing parathyroid hormone. To explore all these possibilities would lead to too great an expansion of this volume and these tumours will not be further discussed here.

The histological assessment of the background activity of the gland of origin of the tumour, together with clinical studies of the level of hormone production and other relevant data such as suppression tests, may add information of considerable diagnostic, therapeutic and prognostic importance. For example, the apparent functional significance of a resected adrenal tumour in a case of Cushing's syndrome may be completely altered by the finding of hyperplastic cortex in the adjacent non-tumorous adrenal. Similarly, the interpretation of disturbing cellular abnormalities and mitotic activity in a thyroid tumour may be quite changed by the finding of the extreme activity suggestive of dyshormonogenesis in the surrounding thyroid tissue. It is therefore considered essential that whenever possible non-tumorous as well as tumorous endocrine tissue should be assessed.

It appears to be a common feature of endocrine glands that prolonged stimulation leads to neoplastic change, and autonomy of function may well accompany autonomy of growth. There may be a continuous gradient between diffuse hyperplasia, focal hyperplasia and adenoma, and in many cases it may be extremely difficult to draw a sharp line on morphological grounds between adenoma and carcinoma. Long-continued stimulation leads to the development within the hyperplastic endocrine gland of clones of cells which may grow more rapidly than the rest and form one or more localized rounded, ill-defined areas of focal hyperplasia, or "nodules." The cells of a nodule may retain their sensitivity to hormonal stimulation and suppression, although this may gradually be lost. The development of autonomy of growth and of function may coincide with the morphological features that distinguish an adenoma from a nodule, but the correlation is by no means exact.

A rather fanciful analogy is drawn with an old Scottish saying, "ane rook's a craw, twa craws is rooks," the implication being that the identification of similar birds—or tumours—may be helped by their normal patterns of occurrence—single or multiple. This suggestion that an adenoma is usually single, while nodules are usually multiple, is broadly true, but breaks down when adenomas develop on a background of hyperplasia with multiple nodule formation. The histological diagnosis in these cases may be very difficult, and perhaps not of great functional significance, as the hyperfunction may well continue or develop again after a latent period following resection of the adenoma.

This pattern of events is perhaps best documented in the parathyroid. In patients with long-standing hypocalcaemia, autonomy of parathyroid function may develop, leading to hypercalcaemia. In these cases the glands commonly show one or more nodules, and the term tertiary hyperparathyroidism has been used. A similar sequence of events may well occur in most, if not all, endocrines, for example the development of multiple nodules in the adrenal cortex in the adrenogenital syndrome. Nodules and adenomas also occur in the long-continued stimulation of the thyroid in dyshormono-
HISTOLOGICAL TYPING OF ENDOCRINE TUMOURS

genesis, and malignant as well as benign tumours have been described as occurring in the thyroid, pancreas, adrenal cortex and parathyroid in conditions of long-continued hyperplasia. Although a hyperplastic zona glomerulosa is described in many cases of adrenal adenoma with hyperaldosteronism, there is at present no proof of pre-existing secondary hyperaldosteronism.

Endocrine tumours may not only be multiple within the one gland, they may also involve several endocrines in one patient. Two consistent patterns of multiple endocrine neoplasia (MEN) occur, and are separately inherited. These tumours arise on a background hyperplasia which is usually both diffuse and nodular and are themselves often bilateral and multiple. In type I (MEN I), hyperplasia and tumour formation usually occur in the anterior pituitary, parathyroids and pancreatic islets, often with adrenal hyperplasia. A variety of other associated tumours have been described, including carcinoid tumours of the bronchus and thymus. The clinical syndromes which may occur include hypopituitarism, Cushing's syndrome, acromegaly, hyperparathyroidism, hyperinsulinism and Zollinger-Ellison syndrome. In type II (MEN II), medullary carcinoma of the thyroid and phaeochromocytoma occur together, sometimes with parathyroid involvement. Hypercalcitoninaemia, catecholamine-induced hypertension and hyperparathyroidism may occur; the Cushing's syndrome that has been described in these cases is usually attributed to ectopic production of ACTH by either medullary carcinoma or phaeochromocytoma. These tumours may also occur together with the syndrome of multiple mucosal neuromas.

The diagnosis of malignancy in endocrine tumours is often much more difficult than in other tissues. This is true for a variety of reasons. First, tumours of most endocrines commonly show a gradation of malignancy, many of the carcinomas being of very low grade malignancy. Secondly, the classical diagnostic criterion of vascular invasion may be difficult to apply to endocrine glands. Normal endocrine glands are richly vascular, with their cells lying close to vascular endothelium. In benign endocrine tumours this vascularity is maintained, and tumour cells may spread subendothelialiy, giving the false impression of vascular invasion. Thirdly, the criterion of nuclear pleomorphism is of little value; indeed, in many endocrine tumours nuclear pleomorphism is a feature of benign rather than of malignant tumours. In the diagnosis of malignancy, mitotic activity may be of value although its significance varies from endocrine to endocrine and may be particularly dependent on the degree of stimulation present. Vascular invasion is always of value if thrombus formation is associated with non-endothelialized tumour within a muscular-walled vessel. While capsular invasion is often difficult to interpret, invasion of surrounding fat and other tissues can be diagnostic. Adequate sampling of the tissues is of course essential. Other than accepting that the diagnosis of malignancy is commonly difficult in endocrines, it is dangerous to generalize, as the best criteria of malignancy may vary from gland to gland. Obviously, while the presence of metastasis establishes the presence of malignancy, the absence of metastasis does not establish that a tumour is benign. In keeping with the low-grade nature of the malignancy in many endocrine carcinomas, metastases may on
occasion not be apparent for many years after the recognition of the primary carcinoma.

One of the most important features of endocrine tumours is, of course, their ability to cause clinical syndromes due to hormone production. While the use of immunolocalization techniques,\(^1\) electron microscopy\(^2\) and biochemical studies in the complete diagnosis of endocrine tumours is commended, it was not felt that these are sufficiently widely available to enable them to be used as the sole basis of a classification designed to be of value to the non-specialist pathologist. It is recognized that the use of these techniques may improve the accuracy of diagnosis and provide information of clinical value. It must, however, be remembered that granule or hormone content of a cell may not correlate with its functional state; a cell may be storing a hormone and not releasing it, or it may be releasing a hormone and not storing it. Electron microscopy has shown that pituitary tumours classified as chromophobe may be made up of cells which are metabolically active and contain small numbers of secretory granules which may not be visible by light microscopy.

Because of the clinical importance of the function of the tumour and because with tumours which on examination with haematoxylin-eosin staining may be similar, the likelihood of malignancy differs according to the hormone produced, it was felt necessary to introduce a functional classification to supplement the morphological classification. The functional classification should be used only to refer to a clinical state caused by the tumour. It should not be used for clinical states that may precede and play a part in tumour formation (e.g., hypothyroidism with eventual mucoid cell adenoma of the pituitary) or clinical states related to tumours other than the one under discussion. In many centres this clinical assessment will, of course, be supplemented by biochemical evidence; however, it is not suggested that the biochemical evidence alone should be used to classify function. Many endocrine tumours may make small amounts of a number of different hormones, precursors or fragments which do not cause evident clinical abnormality. The hormone content of the tumour in these cases may help to identify the cell type of the tumour. It is also suggested that ectopic hormone production which produces a clinically evident syndrome should be noted; this too may provide information of value in assessing a tumour.

In this classification the term *tumour* is used synonymously with *neoplasm*; the phrase *tumour-like* is applied to lesions which clinically or morphologically resemble neoplasms but do not behave biologically in a neoplastic manner. They are included in this classification because of their importance in differential diagnosis and because of the unclear borderline between neoplasms and certain non-neoplastic lesions. Time-honoured terms have generally been retained. Synonyms are listed only if they have been widely used or if they are considered to be helpful for the understanding of the lesion. In such cases, the preferred term is given first, followed by the synonym in brackets.

\(^1\) See Appendix. B, page 65.

\(^2\) See Appendix. C, page 66
In summary, this classification is descriptive rather than histogenetic and is based primarily on morphology as seen with the light microscope using conventional staining techniques. Because of the importance of the function of endocrine tumours, it is felt that the complete classification of an endocrine tumour requires the use of a supplementary functional classification. Where possible, morphology has been correlated with function.

The histological classifications which appear on the following pages contain the appropriate morphology code numbers of the International Classification of Diseases for Oncology (ICD-O)\(^1\) for tumours, and of the Systematized Nomenclature of Medicine (SNOMED)\(^2\) for tumour-like lesions.

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\(^1\) World Health Organization *International classification of diseases for oncology (ICD-O)*. Geneva, 1976

\(^2\) College of American Pathologists *Systematized nomenclature of medicine (SNOMED)*. Chicago, Illinois, 1976
HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE ANTERIOR PITUITARY [ADENOHYPOPHYSIS]

I. GLANDULAR EPITHELIAL TUMOURS

A. BENIGN

1. Adenoma
   a. Acidophil
   b. Mucoid cell ["basophil"]
   c. Chromophobe
   d. Oncocytic
   e. Others

B. MALIGNANT

1. Carcinoma [adenocarcinoma]
   a. Chromophobe
   b. Others

II. MESENCHYMAL TUMOURS

III. MISCELLANEOUS TUMOURS

A. CRANIOPHARYNGIOMA

IV. SECONDARY TUMOURS

V. UNCLASSIFIED TUMOURS

VI. TUMOUR-LIKE LESIONS

A. CYSTS

1. Glandular

2. Squamous

B. HETEROTOPIAS

C. ECTOPIC ANTERIOR PITUITARY TISSUE

D. HYPERPLASIAS

E. OTHERS

* Numbers are from the morphology codes of ICD-O and SNOMED. See introduction, page 17
  * Code specific type. See ICD-O
  "0 for benign; /3 for malignant. /1 for borderline malignancy or uncertain whether benign or malignant
  33410 is Epidermoid cyst
DEFINITIONS
AND EXPLANATORY NOTES

I. GLANDULAR EPITHELIAL TUMOURS

A. Benign

1. Adenoma

This tumour may be encapsulated; its expansion leads to destruction of local structures without invasion. The cells may be arranged in sheets, columns or nests and may show a marked orientation around connective tissue trabeculae. The tumours may be subclassified on the basis of the cell types they contain; this correlates with the functional capacity of the tumour, but cannot be achieved by a study of haematoxylin and eosin-stained sections alone. Each of the cell categories identified in the PAS-orange G technique—mucoid, acidophil, and chromophobe—can be further subdivided by immunolocalization and electron microscopy techniques. These methods provide valuable information when applied to tumours. However, they are not readily available to diagnostic histopathologists, and the classification presented here is based mainly on the use of the PAS-orange G technique (Fig. 1). With this technique the mucoid (PAS-positive) cells correspond to the basophils and some of the chromophobes of the older classification using trichrome stains. The PAS technique is recommended because its mechanism is understood, it is more reproducible, and it shows more specific cell types than the trichrome techniques. Endocrine effects are discussed for the individual tumours, but any pituitary tumour, with or without hormone secretion, may cause hypopituitarism by compression of the residual anterior lobe. Stalk compression may also lead to hypopituitarism and to excess prolactin production.

Table 1 illustrates the value of special techniques and shows the correlation between structure and function in pituitary adenomas. It represents a simplified version of a complex situation.

a. Acidophil adenoma (Fig. 2–5): A benign tumour of acidophil cells with or without a variable admixture of chromophobe cells.

While the acidophils usually predominate, in some tumours the majority of cells are large chromophobes, and the minority are acidophils, often poorly granulated.

The great majority of acidophil adenomas are associated with growth hormone production and the clinical syndrome of acromegaly or gigantism. Prolactin production may occur together with galactorrhoea; the tumours in

1 See Appendix. A 1. page 59)
these cases are usually composed largely of weakly acidophil or apparently chromophobe cells.

Acidophil adenomas should not be confused with oncocytic adenomas (see I.A.1.d, below).

b. **Mucoid cell ["basophil"]\(^2\) adenoma** (Fig. 6–9): A benign tumour of mucoid (PAS-positive) cells with or without a variable admixture of chromophobe cells.

Cushing’s syndrome with bilateral adrenal cortical hyperplasia may be associated with mucoid cell adenoma. Following adrenalectomy in Cushing’s syndrome, rapidly growing mucoid cell adenomas, which may reach a large size, have been described and are commonly associated with cutaneous hyperpigmentation. Crooke’s hyaline change (Fig. 10) is rarely found in the mucoid cell adenomas associated with Cushing’s syndrome, although it is a constant finding in the accompanying non-tumorous anterior pituitary tissue. It is, of course, frequently seen in the pituitary after corticosteroid therapy. Mucoid cell adenomas are rarely associated with hyperthyroidism due to TSH production. They may also occur as a response to long-continued hypothyroidism. Excess gonadotrophin production has also been described; most of these rare tumours have arisen in primary hypogonadism.

c. **Chromophobe adenoma** (Fig. 11–13): A tumour consisting only of chromophobe cells; no neoplastic acidophil or mucoid cells are present.

Many chromophobe tumours are composed of medium to large cells which often can be shown by electron microscopy and other techniques to be actively hormone-producing. They may be associated with acromegaly, Cushing’s syndrome, thyrotoxicosis or galactorrhoea, and may follow prolonged hypothyroidism or hypogonadism. Some tumours consist of small cells with relatively little cytoplasm and small oval nuclei. They do not appear to produce hormones; their commonest presenting hormonal effect is, of course, hypopituitarism.

d. **Oncocytic adenoma** (Fig. 14–15): A tumour consisting entirely or
This pituitary tumour is moderately strongly eosinophilic with H & E, weakly acidophilic with orange G, and stains poorly with trichrome techniques. The diagnosis is difficult to make with certainty by routine light microscopy but can be confirmed by finding the typical closely packed mitochondria occupying most of the tumour cell cytoplasm on electron microscopy or semi-thin sections. While most of the tumours could be regarded as modified chromophobe adenomas, they are eosinophilic on light microscopy and should be classified separately.

The tumour is not associated with clinical syndromes other than those due to compression of the pituitary gland or stalk.

Oncocytes may occur in other types of pituitary adenoma.

e. Others

B. MALIGNANT

1. Carcinoma [adenocarcinoma]: A malignant tumour of anterior pituitary cells.

This rare tumour is locally invasive, may spread intracranially, and very rarely distant metastases have been described. Where possible, the diagnosis should be based on evidence of invasion or metastasis. Cytologically, these tumours usually show mitotic activity, but may show less pleomorphism than adenomas. Chromophobe carcinomas are relatively much more frequent than other carcinomas. Apart from hypopituitarism, the commonest, if not the only, endocrine effect is Cushing's syndrome.

a. Chromophobe carcinoma (Fig. 16)

b. Other carcinomas

II. MESENCHYMAL TUMOURS

These are classified and defined elsewhere.1

III. MISCELLANEOUS TUMOURS

A. Craniopharyngioma (Fig. 17): A tumour of the vestigial remnants of the craniopharyngeal duct (Rathke's pouch).

This is a cystic and solid tumour with a distinctive histological picture. It is characterized by broad communicating cords of stratified epithelium, separated by a loose connective tissue matrix, and by cysts lined by similar epithelium usually showing keratinization. Some cysts may derive from stromal degeneration. The layer of epithelial cells adjacent to the stroma is characteristically columnar and of basal cell type.

These tumours are usually both intra- and suprasellar in site; the cysts

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frequently contain cholesterol-rich fluid. While virtually never associated with frank malignancy, they cause considerable tissue destruction by compression of adjacent structures. They may produce hypopituitarism by compression of the hypothalamus, stalk or anterior pituitary. The histological picture described above has frequently been compared with that of ameloblastoma. Focal calcification may occur, both grossly and microscopically; it is often seen in areas of heavily keratinized epithelial cells. Secondary bone formation has also been described.

IV. SECONDARY TUMOURS

Microscopic metastases occur not infrequently, particularly with carcinoma of the breast and bronchus. Rarely, either through involvement of the stalk and portal vessels or of the pituitary fossa, diabetes insipidus or hypofunction of the anterior lobe may result. Compression or direct invasion of the pituitary from adjacent bony metastases may also occur.

V. UNCLASSIFIED TUMOURS

This includes tumours where no specific diagnosis is possible on the material available.

VI. TUMOUR-LIKE LESIONS

A. CYSTS

1. **Glandular** (Fig. 18)

Small colloid-filled cysts lined by cuboidal or columnar epithelium and lying between the anterior and posterior lobe occur so frequently as to be regarded as a normal finding. Rarely they may be so large that they cause hypopituitarism. Occasionally they lie within or above the anterior lobe.

2. **Squamous**

Microscopic foci of squamous cell nests (Fig. 19), sometimes with keratinization, are normal findings in the region of the pituitary stalk, and sometimes lie between the anterior and posterior lobes. These are usually easily separable from the rare, commonly suprasellar, squamous-lined, keratin-filled cysts, epidermoid cysts (Fig. 20).

In a few instances hair follicles and sebaceous glands may occur. In these cases the use of the term dermoid cyst is justified. These cysts can usually be distinguished from craniopharyngiomas by their lack of the ameloblastoma-like pattern.

B. HETEROTOPIAS

These include the occasional finding of a few salivary gland acini near the posterior lobe.
C. Ectopic anterior pituitary tissue

Fragments of ectopic anterior pituitary tissue have rarely been found in the sphenoid bone, but a small ovoid nodule of pituitary tissue is regularly found beneath the pharyngeal mucosa ("pharyngeal pituitary"). It may contain acidophils, mucoid cells and chromophobes, and their hormones, but is not normally under hypothalamic control. It is mentioned here as it may rarely be the source of tumours and because it should not be mistaken for a metastasis from a pituitary tumour.

D. Hyperplasias

Diffuse or nodular hyperplasias may occur. Acidophil hyperplasia has rarely been described as the cause of acromegaly, and mucoid cell hyperplasia without adenoma formation occurs not infrequently in cases of pituitary-dependent Cushing’s syndrome.

E. Others

A number of granulomatous lesions affect the pituitary, some of these behaving in a tumour-like fashion. Eosinophilic granuloma, when it occurs, not uncommonly involves the pituitary region, particularly the leptomeninges, clinoid processes and posterior lobe. The anterior lobe may rarely be involved. Most granulomatous conditions involve the posterior lobe more than the anterior pituitary, except for the rare "giant cell granuloma", etiology unknown, which may so extensively involve the anterior lobe as to cause hypopituitarism. Focal lymphoid infiltration and destruction of the anterior pituitary may occur (hypophysitis), giving rise to a histological pattern resembling Hashimoto's thyroiditis. It should not be confused with involvement of the pituitary by malignant lymphoma or leukaemia.
TUMOURS OF THE ANTERIOR PITUITARY—FUNCTIONAL CLASSIFICATION

I. FUNCTIONAL DISTURBANCE

A. HYPOFUNCTION

B. HYPERFUNCTION

1. Acromegaly and/or gigantism
2. Cushing’s syndrome
3. Galactorrhoea
4. Hyperthyroidism
5. Others

C. ECTOPIC HORMONE PRODUCTION

II. NO FUNCTIONAL DISTURBANCE

III. FUNCTIONAL STATE UNDETERMINED
HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE ADRENAL CORTEX

I. EPITHELIAL TUMOURS

A. BENIGN
   1. Adenoma
      a. Clear cell [spongiocytic]
      b. Compact cell
      c. Glomerulosa cell
      d. Mixed cell

B. MALIGNANT
   1. Carcinoma [adenocarcinoma]

II. EPITHELIAL TUMOUR-LIKE LESIONS

A. NODULAR HYPERPLASIA
   1. Single nodule
   2. Multiple nodular hyperplasia

B. CAPSULAR EXTRUSION

C. ACCESSORY ADRENAL CORTEX

D. OTHERS

III. MESENCHYMAL TUMOURS AND TUMOUR-LIKE LESIONS

A. BENIGN
   1. Myelolipoma
   2. Lipoma
   3. Cysts
   4. Others

B. MALIGNANT

IV. SECONDARY TUMOURS

V. UNCLASSIFIED TUMOURS

--- /6

8000/-

--- 26 ---

\(^a\) Code specific type. See ICD-O.
\(^b\) See footnote \(^b\), page 19
DEFINITIONS AND EXPLANATORY NOTES

I. EPITHELIAL TUMOURS

A. BENIGN

1. Adenoma: A benign, well-demarcated tumour of adrenocortical cells, consisting of cords and nests of cells resembling any type occurring in the normal cortex but lacking the normal structural patterns found in the different cortical zones.

The cells of an adenoma can therefore resemble glomerulosa cells, the lipid-laden cells of the outer cortex, or the lipid-poor cells of the inner cortex. The lipid-rich cell of the outer cortex is referred to as a clear cell or a spongiocytic cell because of its vacuolated appearance in paraffin sections. The lipid-poor cell of the inner cortex is referred to as a compact cell because of its non-vacuolated eosinophilic cytoplasm which often also contains lipofuscin. Adenomas usually consist of a mixture of these cell types. They are classified according to the predominant cell when there are minor admixtures.

An adenoma usually compresses the surrounding tissue, sometimes with the formation of a fibrous capsule. If these morphological signs of an expansile autonomous growth are inconspicuous, the distinction from a nodule may become extremely difficult or even impossible.

Adenomas of any type may show marked anisocytosis and nuclear pleomorphism, but this should not be interpreted as evidence of malignancy. Mitoses are only very rarely seen.

Lipomatous degeneration, sometimes associated with lymphocytic infiltration, may occur. There may also be more or less extensive myelolipomatous change in the adenoma. Both may be so extensive that the epithelial component is largely replaced by fat or bone marrow tissue (see myelolipoma, page 30).

Macroscopically, adenomas are round or ovoid, sharply defined, and grey, red, yellow, brown or black on the cut surface, depending on the component cell type and the amount of cellular pigmentation.

While a large number of adenomas have no known function, they may be associated with a variety of clinical syndromes. In those adenomas causing Cushing's syndrome, there is suppression of the adjacent and contralateral adrenal cortex (Fig. 36), which lose their compact cells and become composed of a thin layer of clear cells, sometimes with an apparently hyperplastic zona

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1 For convenience, mesenchymal and metastatic tumours that may occur in either adrenal cortex or medulla are dealt with under adrenal cortex.
glomerulosa. Similar changes may be found with some adenomas unassociated with clinical Cushing’s syndrome, when the adenoma is producing just enough glucocorticoids to replace the normal hormonal secretions. In those adenomas causing virilization or feminization, there are no discernible changes in the non-neoplastic adrenal cortex unless the tumour is also producing glucocorticoids. In Conn’s syndrome the non-neoplastic zona glomerulosa often appears hyperplastic (Fig. 26); the reason for this is unknown. Multiple adenomas may occur, especially in Conn’s syndrome but also in Cushing’s syndrome, and adenomas may arise on the background of a pre-existing nodular hyperplasia.

A rare but important cause of Cushing’s syndrome in childhood has been described under the term micronodular cortical adenomatosis (Fig. 42–43). In this condition multiple small adenomas occur with an inactive intervening cortex.

While Cushing’s syndrome occurs most commonly with the mixed type of adrenocortical adenoma, virilization is most common with a compact cell adenoma, often with prominent lipofuscin. Adenomas are a very rare cause of feminization, a syndrome almost invariably caused by carcinomas. Conn’s syndrome is most commonly caused by the clear-cell adenoma, but may also be due to adenomas of mixed or glomerulosa cell type. A transitional form from glomerulosa cell to spongiocytic cell, the so-called hybrid cell type, has also been described in mixed cell adenomas causing Conn’s syndrome.

a. Clear cell [spongiocytic] adenoma (Fig. 22–25): An adenoma consisting entirely or almost entirely of heavily lipid-laden cells. The nuclei are frequently small and dark and lie at the periphery of the cells. The distension of cells by lipid vacuoles may progress to disruption of the cell membrane and fusion of the cytoplasmic lipid vacuoles.

b. Compact cell adenoma (Fig. 27–30): An adenoma consisting entirely or almost entirely of cells with eosinophilic granular, non-vacuolated, i.e., compact, cytoplasm.

A variant of compact cell adenoma with cells having large amounts of lipofuscin in their cytoplasm has been referred to as black adenoma (Fig. 29). Its striking jet-black macroscopic appearance resembles that of a melanoma.

c. Glomerulosa cell adenoma: A very rare adenoma consisting entirely or almost entirely of cells whose nuclear cytoplasmic ratio is high, with a cytoplasmic volume intermediate between that of the compact and clear cell. The cell arrangement is commonly alveolar or trabecular. This tumour is associated with Conn’s syndrome.

d. Mixed cell adenoma (Fig. 31): An adenoma containing a significant proportion of more than one cell type.

The majority of adrenal adenomas are of this variety, including most of the apparently non-functional tumours commonly found at autopsy. The mixed cell tumours with Conn’s syndrome often include areas of glomerular
cell type and areas composed of cells intermediate between clear cells and glomerular cells (so-called hybrid cells).

B. MALIGNANT

1. Carcinoma [adenocarcinoma] (Fig. 32–35): A malignant tumour of adrenocortical cells.

All cell types described under adenoma can be found in carcinomas. The tumour may show a very wide variety of histological patterns.

The tumour is usually much larger than its benign counterpart and is characterized by capsular and vascular invasion. Invasive growth into the surrounding tissue and spread by both lymphatics and blood-vessels occurs. Tumour necrosis is more common in adrenocortical carcinomas than adenomas. Cellular pleomorphism and nuclear atypism may occur but are not reliable criteria of malignancy. The presence of mitotic activity, however, particularly atypical mitoses, is a useful indication of malignancy.

Functionally, cortical carcinomas most frequently produce mixed hyperadrenocorticism. However, carcinomas with pure virilization, Cush- ing’s syndrome or aldosteronism have been described. Feminizing cortical tumours are usually malignant. Adrenocortical carcinomas associated with Conn’s syndrome may show a mixture of cell types, or may be composed entirely of glomerulosa cells, sometimes arranged in a broad trabecular pattern with dilated sinusoids.

II. EPITHELIAL TUMOUR-LIKE LESIONS

A. NODULAR HYPERPLASIA: One or more incompletely demarcated tumour-like accumulations of benign adrenocortical cells.

The morphological distinction between nodules and adenomas may be difficult and even arbitrary, and multiple nodular hyperplasia has been referred to as “adenomatous” hyperplasia. The cells may be arranged in a similar fashion to the surrounding cortex or may form broader trabeculae or cell nests with a less regular arrangement. In contrast to the adenoma, the nodule is commonly continuous with the adjacent cortical tissue. Nodules may be composed of clear or of compact cells or a mixture. They may occasionally be heavily pigmented.

1. Single nodule (Fig. 37–38)

Single adrenocortical nodules are not uncommon findings, although close inspection of the residual cortex shows that they are frequently accompanied by minute hyperplastic foci.

2. Multiple nodular hyperplasia (Fig. 39–41)

Nodules are frequently multiple and sometimes form a much larger cell mass than the non-nodular cortex. In this form of nodular hyperplasia,
particularly in the primary nodular hyperplasia associated with Cushing's syndrome, there is often hyperplasia of the intervening cortex. This condition should be distinguished from micronodular cortical adenomatosis (Fig. 42-43, and see above, I.A.1). Nodular hyperplasia which is not exclusively confined to the zona glomerulosa has also been described in Conn's syndrome. Long-standing congenital adrenal hyperplasia may also lead to multiple nodular hyperplasia.

B. CAPSULAR EXTRUSION (Fig. 44)
Penetration of groups of cortical cells through the capsule occasionally forms rounded masses. This occurs frequently in hyperplastic glands.

C. ACCESSORY ADRENAL CORTEX (Fig. 45)
Small, discrete islands of well-demarcated adrenocortical tissue showing the structural characteristics and zonation of the normal cortex are often found in the periadrenal connective tissue and beneath the renal capsule. They are also found in many other sites, particularly the lower retroperitoneum, the broad ligament, mesovarium and epididymis. While these accessory cortical nodules are relatively common in the gonadal region in children they are less frequently seen in adults. They do not appear to occur within the gonads. These nodules may undergo both hyperplasia and neoplasia, giving rise to true adrenocortical tumours. Functioning tumours have been described in several extra-adrenal sites.

D. OTHERS
Marked nuclear pleomorphism of cells of the foetal zone is an occasional finding in stillbirths, and is known as "cytomegaly". It is mentioned here to call attention to it and to point out that it is related neither to neoplasia nor to cytomegalovirus. It is of unknown etiology.

III. MESENCHYMAL TUMOURS AND TUMOUR-LIKE LESIONS

A. BENIGN

1. Myelolipoma (Fig. 46-48): A solitary, sharply defined and sometimes encapsulated mass of fat cells with a variable amount of intermingled haemopoietic tissue.

Depending on the amount of haemopoietic tissue, the gross colour of the lesion varies from dark red to yellow.

The lesion may represent a cortical adenoma which has undergone total or subtotal myelolipomatous transformation. Residual adenomatous tissue

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1 See also EnZinger, F. M., Lattes, R. & Torloni, H. Histological typing of soft tissue tumours. Geneva, World Health Organization, 1969 (International Histological Classification of Tumours, No 3)
may be found at the periphery. A similar change may occur in non-neoplastic adrenal cortex.

2. Lipoma
3. Cysts

Cysts occasionally occur in the adrenal, often with a fibrous wall and associated with evidence of haemorrhage. These are unrelated to cystoid or tubular degeneration, the descriptive terms applied to the change that occurs in the outer fasciculata after severe stimulation.

4. Others

Rarely haemangiomas and capillary or cystic lymphangiomas occur. Their structure does not differ from similar tumours in other sites. Mention must be made of the pseudo-tumourous formation of bone tissue occurring as metaplasia in areas of calcified scar tissue. This is mostly found in the inner cortical zones and is most probably a sequel to perinatal haemorrhage.

B. MALIGNANT MESENCHYMAI TUMOURS

Very rarely primary malignant lymphomas and angiosarcomas have been described in the adrenal cortex.

IV. SECONDARY TUMOURS (Fig. 49)

These are frequently found in the adrenal. If they are small, metastatic tumour may be restricted to the cortex. More frequently the metastatic tumour has destroyed both cortical and medullary tissue. Some metastases may cause considerable enlargement of the gland. Quite frequently, apparently total or subtotal destruction of the cortical tissue is found at autopsy without evidence of hypocorticism. Addison's disease, however, has been described with metastatic tumours, especially from the lung.

A wide variety of tumours metastasize to the adrenal. Malignant melanoma is of note because it may also rarely occur as a primary tumour (see Adrenal medulla, IV, p 41). Direct invasion from renal, pancreatic and retroperitoneal neoplasms may occur.

V. UNCLASSIFIED TUMOURS
TUMOURS OF THE ADRENAL CORTEX
FUNCTIONAL CLASSIFICATION

I. FUNCTIONAL DISTURBANCE

A. HYPOFUNCTION

B. HYPERFUNCTION
   1. Cushing's syndrome
   2. Conn's syndrome
   3. Virilization
   4. Feminization
   5. Others

C. ECTOPIC HORMONE PRODUCTION

II. NO FUNCTIONAL DISTURBANCE

III. FUNCTIONAL STATE UNDETERMINED
HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE ADRENAL MEDULLA AND EXTRA-ADRENAL PARAGANGLIONIC STRUCTURES INCLUDING CHEMORECEPTOR ORGANS

I. NEUROENDOCRINE TUMOURS [PARAGANGLIOMAS]

A. BENIGN

1. Phaeochromocytoma 8700/0
2. Sympathetic paraganglioma 8681/0
3. Parasympathetic paraganglioma 8682/0
   [chemodectoma] 8693/0
   a. Carotid body tumour 8692/0
   b. Aortic body tumour 8691/0
   c. Vagus body tumour
   d. Tympano-jugular body [glomus jugulare] tumour 8690/0
   e. Others
4. Paraganglioma, not further classified 8680/0

B. MALIGNANT

1. Malignant phaeochromocytoma 8700/3
2. Malignant sympathetic paraganglioma 8681/3
3. Malignant parasympathetic paraganglioma 8682/3
   [malignant chemodectoma] 8693/3
4. Malignant paraganglioma, not further classified 8680/3

II. NEURAL TUMOURS

A. BENIGN

1. Neurofibroma 9540/0
2. Ganglioneuroma 9490/0

*No specific code available, 8682/0 can be used.
B. MALIGNANT

1. Ganglioneuroblastoma 9490/3
2. Neuroblastoma 9500/3

III. MIXED NEUROENDOCRINE-NEURAL TUMOURS

A. BENIGN

B. MALIGNANT

IV. MISCELLANEOUS

V. SECONDARY TUMOURS 44--/6e

VI. UNCLASSIFIED TUMOURS 8000/-d

VII. TUMOUR-LIKE LESIONS

\* Code specific components
\* Code specific type
\* See footnote b, page 19
DEFINITIONS AND EXPLANATORY NOTES

These sites are grouped together because they have related differentiated endocrine tumours: all arise from neuroendocrine cells and show similarities in their histological appearances and functions. In addition, several of the sites share common neural tumours. These neuroendocrine tumours have in the past been reported under three main headings: (1) phaeochromocytomas, tumours of the adrenal medulla and its immediate vicinity, typically chromaffin and associated with considerable catecholamine production and hypertension; (2) the paragangliomas, an ill-defined group of tumours resembling phaeochromocytomas but often non-chromaffin, rather infrequently associated with hypertension and arising in extra-adrenal sites; and (3) chemodectomas, the tumours of the carotid body and allied structures, some of which have been shown to be chemoreceptors. These have only very rarely been associated with the production of sufficient catecholamine to cause hypertension.

While these three broad groups should in general be retained, there is now evidence on which to suggest a more logical nomenclature. All the normal structures from which these tumours derive can be considered as paraganglia and broadly regarded as falling into three main categories. The first is the adrenal medulla, the second consists of small groups of neuroendocrine cells associated with the sympathetic chain, and the third is made up of small groups of similar cells, some of which have been shown to have a chemoreceptor function and which are known to have a parasympathetic innervation.

It is therefore considered that three categories of tumours should be distinguished: phaeochromocytomas, sympathetic paragangliomas, and parasympathetic paragangliomas.

The sympathetic paragangliomas broadly correspond to the aortico-sympathetic paragangliomas of the *Atlas of Tumour Pathology*\(^1\) and the parasympathetic paragangliomas broadly correspond to the branchiomeric and intravagal paragangliomas. The sympathetic paragangliomas are sometimes chromaffin, usually produce noradrenalin, and may be associated with hypertension; although less frequently than phaeochromocytomas. The parasympathetic paragangliomas are in general non-chromaffin, produce small amounts of biogenic amines, including catecholamines and 5-OH tryptamine (5-HT), and very rarely cause hypertension. Although it may not be possible to identify any one individual tumour with certainty from its histology without knowledge of its site of origin, there are differences between the

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\(^1\) **GLENNER, G. G. & GRIMLEY, P. H.** *Atlas of tumour pathology, tumours of the extra-adrenal paraganglion system.* Washington, DC, Armed Forces Institute of Pathology, 1974
groups. The cells of phaeochromocytomas and sympathetic paragangliomas tend to lie in islands and cords separated by prominent regular connective tissue trabeculae. The cells themselves are often fusiform with a granular cytoplasm and may show peripheral palisading. Giant nuclei are sometimes a prominent feature. The cells of the parasympathetic paragangliomas sometimes form rounded, well-defined clusters (zellballen) but lack the fusiform shape and may appear to have a haphazard arrangement, although the peripheral cells are sometimes arranged circumferentially. Sustentacular cells can sometimes be identified, and the granules on electron microscopy tend to be regular. Some of these points are shown in Table 2, which is an attempt to simplify and point out the broad differences that exist between these groups. Not all these features may, of course, exist in any one tumour.

I. NEUROENDOCRINE TUMOURS [PARAGANGLIOMAS]

A. BENIGN

1. Phaeochromocytoma (Fig. 50–52)

The tumour cells are pleomorphic, most often polygonal or fusiform, and may closely resemble normal adrenal medullary cells. They lie in sheets, cords or small nests, separated by regular connective tissue trabeculae. They may often appear ill-defined, and sometimes show peripheral palisading.

Table 2. Features of adrenal phaeochromocytomas, sympathetic paragangliomas and parasympathetic paragangliomas.

<table>
<thead>
<tr>
<th></th>
<th>Adrenal phaeochromocytomas</th>
<th>Sympathetic paragangliomas</th>
<th>Parasympathetic paragangliomas</th>
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<tr>
<td><strong>Morphology</strong></td>
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<tr>
<td>Zellballen</td>
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<td>Fusiform cells</td>
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<td>Pleomorphic secretory granules</td>
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<td>Uniform secretory granules</td>
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<td>Noradrenaline</td>
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<td>Dopamine</td>
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<td>5-Hydroxytryptamine</td>
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<td><strong>Clinical associations</strong></td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Neurofibromatosis</td>
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<td>Multiple endocrine neoplasia, type II</td>
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<tr>
<td>Ectopic ACTH production</td>
<td>+</td>
<td>±</td>
<td>–</td>
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</table>

- Never present or negative
+ Occasionally present or weakly positive
++ Usually present or moderately positive
+++ Frequently present or strongly positive
++++ Almost invariably present or very strongly positive
* By electron microscopy
The abundant cytoplasm includes chromaffin granules. The identification of chromaffin cells is only possible after primary fixation of the tumour tissue by one of the accepted methods used to demonstrate chromaffinity. Some phaeochromocytomas do not give a positive chromaffin reaction even after adequate fixation. Hyaline, PAS-positive droplets may occur in the tumour cells as in normal medullary tissue. Brown fat is often observed in or near the capsule. Capsular penetration alone is not evidence for malignancy; neither are subendothelial insinuations of tumour cells, which can be mistaken for true vascular invasion.

The tumour, on the cut surface, is grey, red, or brown, frequently cystic and haemorrhagic, and less often necrotic.

Whereas the small tumours are poorly defined, the larger ones are usually encapsulated, and the adrenal cortex may be stretched over the tumour capsule or even form a pseudo-capsule.

This tumour is usually unilateral and is occasionally associated with extra-adrenal paragangliomas. It may be bilateral, especially in association with neurofibromatosis, Hippel-Lindau's disease or medullary carcinoma of the thyroid, and then is commonly familial.

Functionally many of these tumours may be associated with both noradrenalin and adrenalin secretion and production of paroxysmal or continuous hypertension. Small amounts of 5-HT have been found in some of the phaeochromocytomas associated with medullary carcinoma of the thyroid, but this amine is not otherwise a usual finding in phaeochromocytomas.

It might be logical to restrict the term phaeochromocytoma to tumours of the adrenal medulla. However, the term is traditionally applied to tumours, histologically very similar to those of the adrenal medulla, that arise in the periadrenal area and in the urinary bladder. These tumours are usually strongly chromaffin and associated with hypertension, and are in most cases pure noradrenalin secretors. The absence of adrenalin may well be due to the absence of a steroid-rich blood supply.

2. Sympathetic paraganglioma (Fig. 53): A tumour of the sympathetic chain and its ganglia with a similar architecture and a similar cytology to phaeochromocytoma.

These tumours are often non-chromaffin, and are less often associated with excess catecholamine production and hypertension than phaeochromocytomas. When functional they usually produce noradrenalin alone.

Sympathetic paragangliomas of the urinary bladder are commonly referred to as phaeochromocytomas, as mentioned above.

3. Parasympathetic paraganglioma [chemodectoma] (Fig. 54–58)

The most common sites for these tumours are the carotid body, the tympano-jugular body (glomus jugulare) and the aortic body. Among other sites where these tumours occur are: lung, larynx, orbit, and ganglion nodosum of the vagus nerve. In the lung, as well as the very rare occurrence

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1 See Appendix, A.3, page 61
of single paragangliomas, multiple minute tumours with these histological patterns have been reported.

These tumours are well encapsulated, with the exception of those arising in the tympano-jugular body (glomus jugulare). In this site the tumour may be ill-defined, partly because of local destructive growth without other evidence of malignancy. This may, however, be difficult to assess as these tumours are often not accessible to radical excision and may be removed in small fragments.

Microscopically the normal architecture of parasympathetic paraganglia may be closely reproduced. Characteristic nests (zellballen) of epithelial or epithelioid chief cells are surrounded by thin stromal septa, consisting mostly of reticulin fibres and many capillaries; collagenous septa occur. In general, the tumours are highly vascular, particularly the glomus jugulare tumour, and contain large veins resembling those found in vascular glomus tumours. There may be stromal haemosiderin deposits.

The chief cells are uniform and large, with much finely granular cytoplasm and round or oval nuclei. The nuclei are occasionally pleomorphic, and hyperchromatic giant cells occur, without this being a sign of malignancy. As the cell boundaries are somewhat ill-defined, the impression of some multinucleated cells may be created. At the border of the nests the cells are frequently more elongated, giving the false impression of transition to the connective tissue cells. True sustentacular cells are only rarely seen. An artifact due to surgical handling can also produce elongated smaller and darker nuclei. Very few, if any, mitoses are found. The cells in the glomus jugulare tumours are usually smaller and somewhat more pleomorphic than in the other sites; this, however, may also be due to tissue handling.

In addition, the pattern may resemble an adenoma, with prominent nests or trabeculae of epithelial cells and inconspicuous vascular stroma, or an angioma, with prominent vascular stroma and more spindle cell epithelial components. Prominent lymphoid and plasma cell infiltrates occasionally occur. While these tumours not infrequently contain small amounts of catecholamines, they only very rarely secrete large amounts and give rise to hypertension.

Multiple and familial parasympathetic paragangliomas have been recorded. Carotid body tumours have been shown to be more frequent at high altitudes, and in addition have been described as occurring with papillary carcinoma of the thyroid.

4. Paraganglioma, not further classified

Rarely, paragangliomas cannot be assigned with certainty to any one of the above groups, often because an indeterminate histological picture is combined with an ill-defined site of origin.

B. MALIGNANT

1. Malignant phaeochromocytoma (Fig. 59)

These form about 10% of all phaeochromocytomas. There is often less pleomorphism than in the benign forms of these tumours. The presence of
necrosis and mitoses is helpful in making the diagnosis but is not constant. The diagnosis of malignancy is best based on the presence of true vascular invasion and, above all, metastases. Contralateral benign phaeochromocytomas or extra-adrenal paragangliomas should not be mistaken for metastases. Functionally malignant phaeochromocytomas may or may not be associated with constant or paroxysmal hypertension.

2. Malignant sympathetic paraganglioma (Fig. 60)

About 30% of sympathetic paragangliomas have been reported to be malignant, a considerably higher figure than for phaeochromocytomas. The microscopic features of these tumours are similar to those of malignant phaeochromocytomas.

3. Malignant parasympathetic paraganglioma [malignant chemodectoma] (Fig. 61)

The histological diagnosis of malignancy in these tumours may be very difficult, as is shown by the wide variation in the proportion of malignant cases reported in different series. The growth pattern of paragangliomas may lead to endothelialized groups of tumour cells lying within vascular spaces, and this must not be mistaken for true vascular invasion. No single histological feature other than metastasis is a reliable indication of malignancy. Clinically significant malignancy is uncommon.

4. Malignant paraganglioma, not further classified

II. NEURAL TUMOURS

A. BENIGN

1. Neurofibroma

This tumour does not differ structurally, when found in the adrenal medulla, from that described in other sites.

2. Ganglioneuroma: A benign tumour of mature ganglion cells and neurofibrils.

Microscopically, ganglion cells, sometimes multinucleate, are embedded in a loose fibrous stroma containing non-medullated nerve fibrils and sometimes areas of neurinomatous proliferation. The ganglion cells have very conspicuous large nuclei with prominent nucleoli and may show Nissl granules.

B. MALIGNANT

1. Ganglioneuroblastoma: A tumour composed of a mixture of neuroblasts and ganglion cells in various stages of differentiation.

Grossly, this tumour is richly vascular and may show haemorrhage and focal necrosis. An incomplete capsule may be present. Histologically, the ganglion cells are pleomorphic, of varying maturity and frequently multi-

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nucleate. There are often variable numbers of primitive cells similar to those found in neuroblastoma.

2. Neuroblastoma (Fig. 62–63): A highly malignant tumour of undifferentiated neuroblasts.

The classical primary site of this tumour is in the adrenal glands, but it may also occur as a primary tumour in the adjacent tissue and more rarely retroperitoneally, along the thoracic sympathetic ganglia, in the neck, as well as in other sites. It is incompletely encapsulated, forming multilobulated soft, friable and often haemorrhagic and necrotic tumours with a greyish-white cut surface. Microscopically, the small tumour cells lie in very scanty but richly vascularized stroma. There is a small amount of ill-defined cytoplasm and often the nuclei appear naked. The small chromatin-rich nuclei rarely show mitoses. Multinucleate forms are sometimes seen.

While the classical description of this tumour stresses the occurrence of rosettes in which the tumour cells lie in a radial arrangement around a central area of fibrillary matrix, it is more common to see an ill-defined acellular fibrillary area with a poorly oriented peripheral cellular layer.

Dense-core secretory granules may be seen in the tumour cells by electron microscopy and be an aid in diagnosis, particularly in distinguishing this tumour from Ewing's sarcoma.

Functionally, these tumours may be associated with hypertension or diarrhoea. When metastases are present the urinary excretion of 4-hydroxy-3-methoxymandelic acid (HMMA) is almost invariably increased.

This is characteristically a tumour of infancy and childhood, in contrast to the esthesioneuroblastoma, the related tumour of the nasal cavity, which is dealt with elsewhere.¹

Both ganglioneuroblastoma and neuroblastoma have been shown in some cases to mature towards ganglioneuroma.

III. MIXED NEUROENDOCRINE–NEURAL TUMOURS (Fig. 64–66)

While small numbers of ganglion cells and small amounts of ganglioneuromatous tissue are commonly found in benign phaeochromocytomas, some tumours may show extensive areas of both types of tissue and should be classified under the heading of mixed neuroendocrine-neural tumours. Occasional malignant tumours may be in part fully differentiated with areas showing the features of phaeochromocytoma or other paragangliomas, and other areas showing neural differentiation. These tumours can be associated with hypertension and may be of a high grade of malignancy.

ADRENAL MEDULLA AND PARAGANGLIA

IV. MISCELLANEOUS TUMOURS

Malignant melanoma has rarely been reported as a primary tumour of the adrenal medulla. Melanocytes have been described in this site. Care must be taken to separate a malignant melanoma of the adrenal medulla from a phaeochromocytoma with excessive lipofuscin pigmentation.

V. SECONDARY TUMOURS

VI. UNCLASSIFIED TUMOURS

VII. TUMOUR-LIKE LESIONS

Hyperplasia of the carotid body is known to occur at high altitudes and has been described in patients with chronic respiratory disease. Hyperplasia of the adrenal medulla is a very rare cause of hypertension. It has also been described in children belonging to families with inherited medullary carcinoma and phaeochromocytoma.

TUMOURS OF THE ADRENAL MEDULLA, EXTRA-ADRENAL PARAGANGLIONIC STRUCTURES AND CHEMORECEPTOR ORGANS—FUNCTIONAL CLASSIFICATION

I. FUNCTIONAL DISTURBANCE

A. HYPOFUNCTION

B. HYPERFUNCTION

1. Hypertension
2. Diarrhoea
3. Others

C. ECTOPIC HORMONE PRODUCTION

II. NO FUNCTIONAL DISTURBANCE

III. FUNCTIONAL STATE UNDETERMINED
HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE PARATHYROID GLANDS

I. EPITHELIAL TUMOURS

A. BENIGN
1. Adenoma
   a. Chief cell
   b. Water-clear cell
   c. Oxyphil cell
   d. Mixed cell

B. MALIGNANT
1. Carcinoma [adenocarcinoma]

II. MISCELLANEOUS TUMOURS

A. LIPOADENOMA
B. OTHERS

III. SECONDARY TUMOURS

IV. UNCLASSIFIED TUMOURS

V. TUMOUR-LIKE LESIONS

A. PRIMARY NODULAR [CHIEF CELL] HYPERPLASIA
B. PRIMARY WATER-CLEAR CELL HYPERPLASIA
C. OTHER HYPERPLASIAS
D. CYSTS

---/6a

8140/0
8321/0
8322/0
8290/0
8323/0
8140/3
8324/0

8000/ b

72030
72010
72000
33400

*a Code specific type.
*b See footnote b, page 19.
DEFINITIONS AND EXPLANATORY NOTES

I. EPITHELIAL TUMOURS

A. BENIGN

1. Adenoma (Fig. 67–73)

This tumour may show a wide variety of uniform or mixed patterns: solid sheets of cells, nests, trabeculae, tubular or follicular structures. A tumour composed entirely of follicles containing colloid-like material may be difficult to distinguish from thyroid. Here, the birefringent calcium oxalate crystals sometimes present in thyroid colloid may help in the differential diagnosis, as may the presence of glycogen or argyrophil granules in parathyroid cells. Large pleomorphic nuclei are not infrequently seen in parathyroid adenomas and should not be used as evidence of malignancy. Cysts may occur within parathyroid adenomas, either as a result of accumulation of secretions in epithelial-lined spaces or following degenerative changes. On occasion, the functioning adenomatous tissue may be embedded in the fibrous wall of a large cyst. Care must be taken not to confuse these cystic parathyroid adenomas with thyroid cysts.

The diagnosis of parathyroid adenoma in general requires the study of another gland as well as the tumorous gland. The second gland should show normal or suppressed parathyroid tissue with small glandular cells and excessive fat (Fig. 74). These same changes may be seen in a rim of normal tissue surrounding the tumour, but this is usually present in only a minority of cases—in part due to the problems of sampling.

These tumours may occasionally arise on a background of long-standing hyperplasia due to renal failure, steatorrhoea, osteomalacia, or primary hyperplasia. Parathyroid adenomas are commonly associated with hyperfunction, except for the oxyphil adenomas, many of which have been reported to be non-functional.

Amyloid may be found in parathyroid adenomas, usually as intrafollicular material. It may also occur in normal glands and in primary nodular hyperplasia.

While parathyroid adenomas usually occur at the classical positions of the normal glands, they may be found in a wide variety of sites, including intrathyroid, retro-esophageal, and mediastinal.

a. Chief cell adenoma (Fig. 68–71): An adenoma composed predominantly of cells with slightly granular, occasionally vacuolated cytoplasm. The cells are commonly 10–15 μm in diameter.

b. Water-clear cell adenoma (Fig. 72): A rare adenoma composed predominantly of cells with clear cytoplasm. This is regarded by some as a variant of chief cell adenoma.

c. Oxyphil cell adenoma (Fig. 73): An adenoma with a predominance of cells which are usually fairly large with abundant granular eosino-
philic cytoplasm, shown to contain numerous mitochondria on electron microscopy.

d. Mixed cell adenoma: An adenoma with more than a minor admixture of different cell types.

A considerable proportion of parathyroid tumours are of the mixed cell type.

B. MALIGNANT

I. Carcinoma [adenocarcinoma] (Fig. 75–78)

This tumour is rare but well documented. It is usually diagnosed by a combination of cytological changes, invasion of adjacent structures, and rarely metastasis. Microscopy may show a trabecular pattern, broad fibrous bands within the tumour, mitoses, vesicular nuclei and prominent nucleoli. The tumours are usually large and relatively slow growing, and if recurrence or metastasis occurs it is often long after the original resection. Reported cases have usually been associated with hyperparathyroidism; non-functional carcinomas may rarely occur. Parathyroid carcinoma has been recorded in familial hyperparathyroidism.

II. MISCELLANEOUS TUMOURS

A. Lipoadenoma (Fig. 79): A rare tumour, usually large, composed of an intimate admixture of mature fat and parathyroid cells.

Hyperparathyroidism has been reported with this tumour.

B. OTHERS

III. SECONDARY TUMOURS

Microscopic metastasis to one or more parathyroid glands is not uncommon, and hypoparathyroidism has been reported in rare instances to be due to metastatic carcinoma.

IV. UNCLASSIFIED TUMOURS

V. TUMOUR-LIKE LESIONS

A. Primary nodular [chief cell] hyperplasia (Fig. 80–83): Primary hyperplasia, usually of all parathyroids, characterized by the development of multiple nodules.

The nomenclature of this condition is difficult as it may be composed of oxyphil cells rather than chief cells and it may rarely not be nodular. While neither term is entirely satisfactory, on balance the term primary nodular hyperplasia is preferred as it separates this condition from the non-nodular hyperplasia of children, which is also regarded as a primary hyperplasia but is not known to be familial.

The enlarged glands show multiple nodules, often of varying patterns and sometimes of varying cell type. Although all glands are usually involved when the diagnosis is made, sequential involvement has been described. Moderate amounts of fat are sometimes found. As in adenomas, it is essential that more than one gland be studied in order to establish the diagnosis. Amyloid has occasionally been observed in primary nodular hyperplasia.

The lesion is frequently familial and frequently associated with nodular hyperplasia or adenomas of anterior pituitary and pancreatic islets (multiple
endocrine neoplasia, type I). A similar histological pattern in the parathyroids may be seen in association with medullary carcinoma of the thyroid and phaeochromocytoma (multiple endocrine neoplasia, type II). Primary nodular hyperplasia typically produces hyperparathyroidism.

B. PRIMARY WATER-CLEAR CELL HYPERPLASIA (Fig. 84): Diffuse hyperplasia of all parathyroids, the cells being particularly large and uniformly water-clear, with a characteristic ultrastructure.

In this rare condition all four glands are typically involved; the upper glands are often larger than the lower. The glands are pale brown and lobulated. Microscopically they show a typical pattern of very large water-clear cells which often form follicles or tubular structures, with small basal nuclei. Cystic degeneration may occur. The condition causes hyperparathyroidism but is not associated with other endocrine lesions.

C. OTHER HYPERPLASIAS (Fig. 85–90)
These less often cause confusion with adenomas than do primary nodular or primary water-clear cell hyperplasia. Diffuse hyperplasia with loss of fat cells and proliferation of chief cells is commonly seen in renal failure. This secondary hyperplasia is the typical response of the parathyroid glands to sustained stimulation and may also occur in steatorrhoea and osteomalacia. Long-continued stimulation of the parathyroids causing both hyperfunction and hyperplasia may eventually lead to the development of non-suppressible hyperfunction, usually accompanied by the development of either a single or multiple nodules (tertiary hyperparathyroidism), giving a histological picture that may be indistinguishable from either an adenoma or primary nodular hyperplasia. Small groups of hyperplastic oxyphil cells occur in old age but are not associated with any known functional disturbance.

In any attempt to reach an exact diagnosis in hyperparathyroidism associated with hyperplasia, the pathological observations must be interpreted together with the clinical data.

D. CYSTS
Microscopic cysts lined by columnar or cuboidal epithelium, often filled with colloid, are quite common in the normal parathyroid. Similar cysts or degenerative cystic changes may occur in parathyroid adenomas or hyperplasias; these should not be mistaken for simple cysts. Cysts up to one centimetre or more are occasionally found and have been noted in association with the upper parathyroids in cases of lingual thyroid.

TUMOURS OF THE PARATHYROID GLANDS—FUNCTIONAL CLASSIFICATION

I. FUNCTIONAL DISTURBANCE
A. HYPOFUNCTION
B. HYPERFUNCTION
C. ECTOPIC HORMONE PRODUCTION

II. NO FUNCTIONAL DISTURBANCE

III. FUNCTIONAL STATE UNDETERMINED
HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE DIFFUSE ENDOCRINE SYSTEM

I. CARCINOIDS

A. ENTEROCHROMAFFIN CELL [EC-CELL] CARCINOID
   ["CLASSICAL" CARCINOID, ARGENTAFFINOMA]

B. G-CELL TUMOUR [G-CELL CARCINOID]

C. OTHER CARCINOIDS

II. MUCOCARCINOID

III. MIXED CARCINOID-ADENOCARCINOMA

IV. TUMOUR-LIKE LESIONS
The concept of a diffuse endocrine system, put forward by Feyrter in a series of papers in the 1930s, has been further developed in the light of recent work on the gastrointestinal tract and its derivatives. It is now recognized that as well as enterochromaffin cells, a dozen or more other types of related specialized endocrine cells exist and are scattered through the mucosa of the gastrointestinal tract and other endodermal derivatives and in addition have been described in small numbers in other sites, sometimes in relation to intestinal metaplasia. Many of these cell types have been shown to produce a specific polypeptide hormone, and most are also able to metabolize amine precursors. This has led to the suggestion that some, if not all, of these cells, together with certain cell types known to be of neural crest origin—for example, thyroid C cells and carotid body chief cells—could be linked together under the term APUD (amine precursor uptake and decarboxylation) cell system. It is now apparent that with newer techniques such as electron microscopy, immunolocalization studies, and amine histochemistry, together with clinico-pathological correlation and biochemical studies, tumours derived from these cells can be further subdivided and related to the normal cell types.

The term carcinoid, earlier applied to the specific tumour of enterochromaffin cells of the small intestine, is now widely used in a less specific way for a variety of tumour types in a number of tissues. In this classification it is used to refer to tumours of the diffuse endocrine system, excluding tumours of the islets of the pancreas, medullary carcinoma of the thyroid and paragangliomas. The reported differences in carcinoids derived from the foregut, midgut or hindgut probably reflect the different distribution of endocrine cell types in the different parts of the gastrointestinal tract and associated structures. While some endocrine cell types are limited to one part of the gastrointestinal tract, others—for example, the enterochromaffin cell—may be widely distributed, as may the tumours associated with these cells. The only specific tumour type that can, with conventional techniques, be easily identified from among this varied group is the enterochromaffin cell carcinoid ("classical" carcinoid, argentaffinoma). The remaining tumours can be further subdivided on the basis of various silver and other granule staining techniques, but exact classification requires the use of the same specialized techniques as are needed to identify the normal cell types.

G-cell tumours which may be found in the stomach, duodenum and pancreas are of particular importance because of their relatively high degree of malignancy and their associated clinical syndrome. This tumour should be separately identified whenever possible and is therefore separately classified.

While all carcinoids should be regarded as malignant tumours on pathological grounds, it must also be recognized that their malignancy is
generally of a very low grade, and that their clinical behaviour may be entirely benign. This is particularly true of appendiceal carcinoids, and this point will be discussed further under the different location in which these tumours can be found. The likelihood of metastasis varies from site to site, partly due to the influence of the site on the early or late presentation of the tumour and partly on inherent variations in malignancy of tumours derived from different cell types. In addition, variations in nuclear pleomorphism and mitotic activity in tumours derived from one cell type may be reflected in variations in growth rate.

While all types of carcinoids may metastasize to both local lymph nodes and liver, the non-EC-cell carcinoids not infrequently show osteosclerotic bony metastases and may also show cutaneous metastases.

I. CARCINOIDS

A. ENTEROCHROMAFFIN CELL [EC-CELL] CARCINOID ["CLASSICAL" CARCINOID, ARGENTAFFINOMA] (Fig. 91–99)

This is the classical argentaffinoma found predominantly in the midgut, particularly the appendix, small intestine and caecum. It may be yellowish or grey on the cut surface before fixation, frequently becoming yellow after fixation in formalin. On light microscopy it shows a pattern of solid islands and nests of regular cells, with uniform nuclei and abundant eosinophilic granular cytoplasm. The peripheral layer of cells of each group tends to be oriented with the nuclei towards the centre of the group and the cytoplasm peripherally. The tumours are usually strongly positive with argentaffin\(^1\) techniques (provided that the fixative used contains formaldehyde or other aldehydes) and are usually also strongly argyrophil.\(^2\) Many of the cells are positive, particularly those in the peripheral layer. On electron microscopy the granules are usually large, pleomorphic and osmiophilic. The stroma is frequently hyalinized, occasionally calcified, and the vessels in and around the tumour may be thick-walled with elastosis and fibrohyaline intimal thickening. Fibrosis may occasionally extend widely through the mesentery and retroperitoneal tissues. When they originate near the intestinal surface they may show a muscular stroma and often have numerous central glandular lumina. They invade the muscular wall, often reaching the subserosa. Metastasis is uncommon, but in this group occurs most frequently with ileal tumours; lymph nodes and liver are the commonest sites.

Functionally these tumours are associated with the production of 5-HT and kallikrein. The patients may develop the carcinoid syndrome, with diarrhoea, flushing and later fibrotic endocardial thickening; the full syndrome is usually seen only if a large bulk of tumour is present.

Multiple carcinoids may be found throughout the intestine.

B. G-CELL TUMOUR [G-CELL CARCINOID] (Fig. 100–103)

Gastrin-producing cells (G cells) are scattered in the pyloric mucosa and, although less numerous, also in the duodenal mucosa. The majority of authors agree that they are not represented in the adult human pancreas.

\(^1\) Silver-positive with a technique that does not involve the use of an external reducer (see Appendix, A.5, page 63).

\(^2\) Silver-positive with a technique that uses an external reducing agent (see Appendix, A.4, page 62).
Despite this, G-cell tumours ("gastrinomas") occur more frequently in the pancreas, less frequently in the duodenum, and very rarely in the stomach. Most of the duodenal tumours occur in the first and second part of the duodenum; they are often small and may be very difficult to find macroscopically even when clinically active. They apparently originate from proliferation of G cells in the intestinal crypts and Brunner's glands and may extend deeply in the submucosa. Histologically, they are composed of rather uniform, medium-sized cells with relatively abundant, finely granular and faintly acidophilic cytoplasm. The cells are usually arranged in trabecular, ribbon, lobular or even pseudoglandular patterns. Besides these forms, G-cell tumours of the pancreas may also show basaloid or diffuse patterns and occasionally pleomorphic cells. A reliable distinction of G-cell tumours of the pancreas from some of the true islet cell tumours can only be achieved by immunohistochemical tests using antigastrin sera. Electron microscopy is less helpful; in many cases the cells are rather poorly differentiated and do not often show diagnostic features. The majority of pancreatic G-cell tumours are clinically malignant, due to local recurrence, with or without metastasis. Gastrin overproduction by tumour cells usually leads to a prominent life-threatening clinical syndrome (Zollinger-Ellison syndrome) with severe gastric hypersecretion and peptic ulcers. The same syndrome is also caused by duodenal G-cell tumours, which, however, seem to be less prone to recurrence and metastasis and may even represent occasional unexpected autopsy or surgical findings. Both pancreatic and duodenal G-cell tumours may occur as part of the syndrome of multiple endocrine neoplasia, type I. The tumours are not argentaffin but may be weakly argyrophil with the Grimelius technique.

C. OTHER CARCINOIDs

This group includes most tumours arising in foregut and hindgut derivatives, and a minority of midgut tumours, the majority of tumours in the midgut being EC carcinoids. Ideally, these tumours should be subdivided according to the major cell type found. However, identification of the cell type requires electron microscopy and immunolocalization studies and in addition it is likely that further cell types are yet to be identified. This classification therefore does not list the various subtypes as separate entities.

On light microscopy these tumours may show a lobular pattern with or without peripheral basal orientation of the cells. They may form rather thin ribbons or broader trabeculae (ribbon-like or trabecular pattern). Rarely they show a fascicular arrangement with fusiform cells; tubules and true rosettes may also occur and occasionally palisading of cells, which may give a neuroid appearance. A diffuse small cell pattern, with some similarities to oat-cell carcinoma, may occur. The cells are rarely as granular with hematoxylin and eosin as are the cells of the classical carcinoid tumour, and may even appear clear. The majority of tumours are negative with argentaffin techniques. Those that are positive usually contain only a few scattered positive cells. While the majority of tumours are positive with argyrophil techniques, often only a few cells are strongly positive while the rest are negative or weakly positive. These tumours may, at light microscope level, be indistinguishable from G-cell tumours and some islet cell tumours of the pancreas.
Carcinoids of the bronchus (Fig. 104–109)

These tumours may show the patterns described in the introduction, or a mixture of all types. The majority of cases show some argyrophilia. Bone formation may occur in the stroma of bronchial carcinoids. It is known that endocrine cells occur in the bronchial mucosa, and on electron microscopy most of these cells contain small, round secretory granules which resemble those found in many bronchial carcinoids. Multiple tumours may occur. When distant metastasis occurs, the carcinoid syndrome is not infrequent; occasionally the tumours may produce 5-hydroxytryptophan (5-HTP) rather than 5-hydroxytryptamine (5-HT). Bronchial carcinoids may produce ectopic ACTH. They have occurred in the syndrome of multiple endocrine neoplasia, type I.

Some bronchial carcinoids composed entirely of regular, small spindle cells must be distinguished from oat-cell carcinoma. Other bronchial carcinoids may be composed of large eosinophilic mitochondrion-rich cells.

The term atypical carcinoid of the bronchus has been applied to a tumour with greater pleomorphism and mitotic activity than usual, and a less organized structure. Its prognosis is considerably worse than that of the majority of cases of bronchial carcinoids.

The relationship which has been suggested between carcinoids and oat-cell carcinoma is debatable. A case can be made out for regarding the oat-cell carcinoma of the lung, which may contain endocrine secretory granules, secrete 5-HT, and lead to the carcinoid syndrome, as a very poorly differentiated endocrine tumour. However, these highly malignant carcinomas have not been shown to arise as a progression in malignancy of differentiated carcinoids and are not dealt with in detail here.

Carcinoids of the thymus (Fig. 110)

Endocrine cells have been described in the thymus in some species and a number of tumours previously regarded as pure epithelial thymomas are now considered to be carcinoid tumours both because of their histological appearance and because some have been shown to contain secretory granules. While they may repeat any of the histological patterns associated with carcinoid tumours, they tend to be less well differentiated and of a higher degree of malignancy. These tumours may also produce ectopic ACTH and can be associated with the syndrome of multiple endocrine neoplasia, type I. They may occur in the mediastinum adjacent to the thymus.

Carcinoids of the stomach (Fig. 111–112)

These tumours may also show a variety of patterns, and the classical carcinoid may also occur in this site. They may be multiple, sometimes with very many small tumours. Some gastric carcinoids may produce 5-HTP and histamine. These are usually strongly argyrophilic. When metastasis occurs, the carcinoid syndrome may be produced, the patient usually showing a geographic pattern of flush. Gastrin-producing tumours (G-cell tumours) are less common in the stomach than in the duodenum. Some carcinoid tumours of the stomach apparently produce neither gastrin nor histamine and may be of a different cell type. These tumours may on occasion produce ectopic ACTH.
Carcinoids of the pancreas (Fig. 113–114)

Both G-cell tumours and EC-cell carcinoids may occur in the pancreas. EC cells can be found in small numbers in pancreatic ducts and acinar tissue; EC-cell carcinoids in the pancreas are very rare tumours (see page 55).

Carcinoids of the duodenum (Fig. 115–117)

The majority of these rare tumours are G-cell tumours; a few are EC-cell carcinoids. Other carcinoids are extremely uncommon in the duodenum, and are usually incidental surgical or autopsy findings.

Carcinoids of the jejunum, ileum, Meckel’s diverticulum, appendix, caecum and right side of colon

The majority of endocrine tumours in these sites are EC-cell carcinoids.

Carcinoids of the rectum and left side of the colon (Fig. 118–120)

While EC-cell carcinoids occur in these sites, the commonest histological pattern is of delicate ribbons of tumour cells. The tumours are usually non-argentaffin and poorly argyrophilic. 5-Hydroxyindole production has occasionally been recorded and the carcinoid syndrome, although very rare, may occur. Watery diarrhoea has been described, but no specific polypeptide hormone production has so far been identified.

Carcinoids of the urogenital tract

Endocrine cells occur widely in the urogenital system and carcinoids have been described in a number of sites. Carcinoids of the cervix have recently been identified and are worthy of mention because they are relatively poorly differentiated. They are rare tumours and may contain amyloid. Carcinoids of the gonads are of interest; they may occur as part of a teratoma or as pure tumours. Carcinoids of the ovary, which are commonly of EC-cell type, have been recorded as causing the carcinoid syndrome without metastasis. Care must be taken to separate primary carcinoids of the ovary from metastatic carcinoids to the ovary, a relatively common occurrence in metastatic carcinoid tumours. A particular variant of carcinoid in the ovary, so-called “strumal carcinoid” is discussed elsewhere. Endocrine cells may occasionally be found in adenocarcinomas of various sites in the urogenital tract and are also found in a relatively high proportion of mucinous cystadenomas of the ovary.

Carcinoids of other sites (Fig. 121)

Carcinoid tumours have been described in a number of other sites, including the biliary tree, parotid, breast, skin, and oesophagus.

II. MUCOCARCINOID (Fig. 122–124)

A small number of tumours have been described which have the growth pattern of carcinoids and are largely composed of mucus-secreting epithelium forming ductal structures with a small number of endocrine cells. The epithelium may show a large number of goblet cells. These tumours could

be considered as very well differentiated adenocarcinomas with differentiation to both mucus-secreting epithelium and endocrine cells. However, the name mucocarcinoid is regarded as an acceptable descriptive term for this entity. It should not be applied to those otherwise unremarkable carcinomas which may show the presence of occasional endocrine cells. The tumours described under the term goblet-cell carcinoid and mucinous carcinoid can also be regarded as belonging to this category.

III. MIXED CARCINOID-ADENOCARCINOMA (Fig. 125–127)
A tumour showing in some areas a carcinoid pattern and in others an adenocarcinomatous pattern.

Although rare, these tumours can cause considerable diagnostic difficulty. While many carcinoid tumours contain a few mucus-producing glands, these tumours contain a large adenocarcinomatous component. They must be distinguished from the occasional occurrence of individual argentaffin and argyrophil cells in exocrine tumours of the gastrointestinal tract, both in primary tumours and metastases, and from mucocarcinoids (Fig. 128–130).

IV. TUMOUR-LIKE LESIONS

Hyperplasias of various endocrine cells in the gastrointestinal tract have been described, including the classical argentaffin cell and gastrin-producing (G) cells. These hyperplasias may be micronodular (microcarcinoidosis) and may progress to give rise to multiple tumours. Diffuse hyperplasia of the G cells has rarely been associated with excess gastrin production, hyperchlorhydria and peptic ulceration.

TUMOURS OF THE DIFFUSE ENDOCRINE SYSTEM—FUNCTIONAL CLASSIFICATION

I. FUNCTIONAL DISTURBANCE

A. HYPOFUNCTION

B. HYPERFUNCTION

1. Carcinoid syndrome
2. "Atypical" carcinoid syndrome
3. Zollinger-Ellison syndrome
4. Mixed forms
5. Others

C. ECTOPIC HORMONE PRODUCTION

II. NO FUNCTIONAL DISTURBANCE

III. FUNCTIONAL STATE UNDETERMINED
HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE ENDOCRINE PANCREAS

I. ISLET CELL TUMOURS
A. ADENOMA 8150/0
B. CARCINOMA 8150/3

II. TUMOURS OF THE DIFFUSE ENDOCRINE SYSTEM 8240/1a

III. POORLY DIFFERENTIATED ENDOCRINE CARCINOMAS 8150/3b

IV. TUMOUR-LIKE LESIONS
A. HYPERPLASIA 72000
B. ECTOPICT PANCREATIC ENDOCRINE TISSUE 26020

a 8240/1 is Carcinoid; G-cell tumour is 8153/1.
b No specific code available: 8150/3 is Islet cell carcinoma.
DEFINITIONS AND EXPLANATORY NOTES

It is now recognized that the endocrine component of the pancreas consists not only of the cells of the islets of Langerhans (Fig. 131–132), but also of endocrine cells, occurring singly or in small groups, scattered throughout the exocrine pancreas, and particularly in its ducts. Some of these duct cells are true enterochromaffin cells. All could be regarded as part of the diffuse endocrine system. The tumours that are presumed to arise from these islet cells cannot consistently be separated by light microscopy from tumours that arise from the duct endocrine cells or from tumours that arise from the diffuse endocrine system in the intestine. A considerable proportion of endocrine tumours arising in the pancreas are G-cell tumours, as are some of the carcinoids of the duodenum. These tumours are dealt with in the section on tumours of the diffuse endocrine system. The classification proposed is based primarily on structural features recognizable on simple routine stains. Further classification is possible for some but not all tumours by the use of simple histochemical techniques and is possible in many cases by the more sophisticated techniques of immunolocalization and electron microscopy.

I. ISLET CELL TUMOUR

A. Adenoma (Fig. 133–139): A benign tumour of epithelial cells arranged in trabeculae and solid nests, sometimes reproducing the structure of normal islets.

The individual tumour cells are often uniform, of small or medium size, with round to oval regular nuclei. There is a variable amount of connective tissue stroma, often collagenized, and in a minority of cases with amyloid. There can be calcification in the stroma, particularly when amyloid is present, and the collagen is frequently hyaline in nature. The tumours may be ill-defined, circumscribed or encapsulated. Because of the close relationship of the tumour cells to endothelium, and the frequency with which retraction spaces form around groups of tumour cells, care must be taken in identifying vascular invasion. Malignancy may be recognized by the presence of local invasion, pleomorphism, typical and atypical mitoses, and true vascular invasion. However, tumours which show none of these features may on occasion be associated with metastasis, and the metastases themselves are often composed of well-differentiated endocrine cells. Small amounts of ductal differentiation may occur in islet cell tumours; occasional tumours with more extensive duct formation have been referred to as islet-duct adenomas. Normal pancreatic ducts may also be enclosed by the tumour.

This tumour may be associated with the production of several clinical syndromes, including hyperglycaemia and hypoglycaemia. When immunolocalization techniques and electron microscopy are employed it is usually found that each tumour is composed of one dominant cell type, and on this
basis the tumours can be subdivided into *A-cell tumour* ("glucagonoma"), *B-cell tumour* ("insulinoma"), and other types. This distinction is of clinical importance, as is the separation of these tumours from G-cell tumours. The B-cell tumours are largely benign, while a majority of the G-cell tumours are clinically malignant. A pure gyriform pattern is suggestive of A-cell or B-cell rather than a G-cell tumour, and the G-cell tumours more often show areas with solid alveolar pattern reminiscent of a carcinoid. Unfortunately the distinction between these tumour subtypes cannot be made consistently on haematoxylin-eosin staining alone. While the aldehyde fuchsin technique\(^1\) is usually of value in the identification of B-cell tumours, a negative reaction does not exclude the diagnosis.

A-cell tumours presenting clinically with diabetes mellitus are often malignant and may be associated with bullous skin lesions and anaemia. Most of the small A-cell tumours which were incidental autopsy findings have been benign.

Islet cell tumours are not uncommonly multiple, and are then usually associated with the syndrome of multiple endocrine neoplasia, type I. When multiple they are commonly of a variety of tumour types. They may be associated with pancreatic or duodenal G-cell tumours.

**B. CARCINOMA** (Fig. 140-142): A low-grade malignant tumour of epithelial cells arranged in trabeculae and solid nests with recognizable islet cell differentiation.

The main diagnostic morphological features have been discussed under adenoma. Occasional ductular differentiation may be found. In contrast to the poorly differentiated endocrine carcinoma, this tumour is usually associated with the production of significant amounts of only one hormone. Ten per cent or more of all B-cell tumours are malignant.

**II. TUMOURS OF THE DIFFUSE ENDOCRINE SYSTEM**

These tumours show all the morphological and functional features of the tumour described in the gut. Most of them are G-cell tumours, which occur much more commonly in the pancreas than in the intestine.

Pancreatic tumours occurring in association with the Verner-Morrison or "pancreatic cholera" syndrome (watery diarrhoea, hypokalemia and achlorhydria syndrome) show trabecular, basaloid or pseudoglandular histologic patterns, which cannot be distinguished on haematoxylin-eosin staining from those shown by some G-cell tumours. Many of the reported cases have been clinically malignant. When appropriately tested, the majority of these tumours were found to produce vasoactive intestinal peptide (VIP), a secretin-like peptide hormone. Although VIP cells are widely represented in the normal intestine, proven VIP-producing tumours have not yet been found in the gut. Because of the present uncertainty of the exact nature of the cell of origin of this tumour, on morphological grounds it can be regarded simply as a non-EC-cell carcinoid. However, because of its dramatic clinical association, it could also be referred to as the Verner-Morrison tumour until the cell type of origin is clarified.

Rarely, EC-cell carcinoids occur in the pancreas.

Tumours of the endocrine pancreas thus largely fall into two broad

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\(^1\) See Appendix, A.2, page 60.
groups, the G-cell and Verner-Morrison tumours which are more malignant, carcinoid-like, and secrete hormones (gastrin and VIP) which predominantly occur in the gut; and A-cell and B-cell tumours, less malignant, often gyriform in pattern, which secrete hormones that are known to be exclusively or largely of pancreatic islet origin. These distinctions support the separation of the tumours of the endocrine pancreas into tumours of the diffuse endocrine system occurring in the pancreas and tumours of the islets of the pancreas. (See Diffuse endocrine system, page 47, and Carcinoids of the pancreas, page 51.)

III. POORLY DIFFERENTIATED ENDOCRINE CARCINOMAS
(Fig. 143–144)

Malignant tumours of epithelial cells with little structural evidence of endocrine differentiation but frequently showing evidence of functional endocrine differentiation.

These rare tumours may show two structural patterns, a small-cell malignant tumour resembling the oat-cell carcinoma of the lung, and a tumour made up of larger cells forming solid and ductular areas. These tumours are usually of a high grade of malignancy and are frequently associated with multiple hormone production, including ectopic hormone production.

IV. TUMOUR-LIKE LESIONS
A. HYPERPLASIA (Fig. 145–146)

Islet cell hyperplasia may involve an increase in the number of islets, in their size, or in both. Diffuse islet cell hyperplasia occurs in infants born to diabetic mothers, babies born with severe rhesus incompatibility, and in Beckwith’s syndrome. Hyperplasia may occur in severe long-standing chronic pancreatitis, and in the residual pancreas in cases of exocrine pancreatic tumours. In general, these conditions do not cause confusion with malignancy, except in chronic pancreatitis, where the concentration of islets, due to loss of exocrine tissue, together with true hyperplasia, may mimic an islet cell carcinoma. Islet cell hyperplasia is also a prominent feature of the pancreas in the syndrome of multiple endocrine neoplasia, type I, where all stages from simple hyperplasia to malignancy may be seen. The changes in the pancreas in these cases often illustrate very well the difficulty in drawing dividing lines between hyperplasia, nodule, adenoma and carcinoma.

Pure islet cell hyperplasia has been reported to be a cause of hyperinsulinism, particularly in children. In the Zollinger-Ellison syndrome, a diagnosis of islet cell hyperplasia alone should not be accepted without a careful search for an occult G-cell tumour in the pancreas, duodenum, or elsewhere in the gastrointestinal tract.

B. ECTOPIC PANCREATIC ENDOCRINE TISSUE

Endocrine cells, either scattered or forming islets, may be found in association with ectopic pancreatic exocrine tissue at its usual sites (stomach, duodenal wall and Meckel’s diverticulum). Occasionally, the only evidence of exocrine pancreas is ductular differentiation. Islet cell tumours may occur at these sites.
TUMOURS OF THE ENDOCRINE PANCREAS—
FUNCTIONAL CLASSIFICATION

I. FUNCTIONAL DISTURBANCE
A. HYPOFUNCTION

B. HYPERFUNCTION

1. Hyperglycaemia
2. Hypoglycaemia
3. Zollinger-Ellison syndrome
4. Verner-Morrison syndrome
5. Carcinoid syndrome
6. Mixed
7. Others

C. ECTOPIC HORMONE PRODUCTION

II. NO FUNCTIONAL DISTURBANCE

III. FUNCTIONAL STATE UNDETERMINED
As has been discussed in the text, the exact identification of an endocrine tumour is often dependent upon the use of a variety of specialized techniques. It has been considered appropriate to add to the text an appendix giving details of some of the more important techniques at present available. The techniques listed here are a small selection of many possible methods, and have been chosen either because they are relatively simple and widely applicable, or because they provide specific information that it may not be possible to obtain by other means.

A. Special stains and histochemical techniques
   1. Periodic acid Schiff (PAS)-orange G for anterior pituitary cells
   2. Aldehyde fuchsin for pancreatic islet and pituitary cells
   3. Chromaffin reaction and other techniques for catecholamines
   4. Argyrophil reaction
   5. Argentaffin reaction
   6. Azo-coupling reaction for 5-hydroxytryptamine

B. Immuno-localization techniques

C. Electron microscopy
A.1. Periodic acid Schiff (PAS)-orange G technique for differentiation of anterior pituitary cells

Fixation
Formaldehyde mixtures; formal-sublimate or Bouin’s fluid give better results than routine 10% formalin.

Staining
1. Deparaffinize and rehydrate tissue sections.
2. Oxidize in 5 g/l aqueous periodic acid solution for 5 minutes.
3. Treat with Schiff’s reagent\(^1\) for 15 minutes.
4. Wash in running water for 10 minutes.
5. Stain the nuclei if required in 5 g/l Celestin blue in 50 g/l iron alum for 30 seconds, and Meyer’s haemalum for 30 seconds or longer. Differentiate quickly in 1% acid alcohol and place in water.
6. Stain with 20 g/l orange G in 50 g/l phosphotungstic acid for 5–10 seconds.
7. Rinse in running water for 15 seconds.
8. Dehydrate and mount.

Result
Mucoid cells are stained red (PAS-positive) and acidophil cells orange while chromophobe cells are unstained. Different stages of decreasing mucoid granulation are well shown and it is to be noted that many of the large chromophobe cells of the conventional stains contain sparse PAS-positive granules.

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\(^1\) Schiff’s reagent (de Tomasi, 1936): Dissolve 1 g of basic fuchsin in 200 ml of boiling distilled water. Shake for 5 minutes and cool to exactly 50 °C. Filter and add to the filtrate 20 ml of 1 mol/l HCl. Cool to 25 °C and add 1 g of sodium (or potassium) metabisulphite (Na\(_2\)S\(_2\)O\(_5\)). Stand this solution in the dark for 14–24 hours. Add 2 g of activated charcoal and shake for 1 minute. Filter. Keep the filtrate in the dark at 0–4 °C. Allow to reach room temperature before use.
A.2. Aldehyde fuchsin for pancreatic islets and pituitary

_Fixation_

Bouin's fluid, glutaraldehyde, glutaraldehyde-formaldehyde or glutaraldehyde-picric acid. Routine formalin fixation is less good.

_Staining_

1. Deparaffinize and hydrate paraffin sections as usual.
2. Oxidize in freshly prepared acid permanganate solution (2.5 g of KMnO₄ and 2.5 ml of H₂SO₄ per litre) for 5 minutes.
3. Decolorize with 30 g/l aqueous solution of oxalic acid (about 1 minute).
4. Wash 5 minutes in running water.
5. Transfer to 70% ethanol.
6. Stain in the aldehyde fuchsin solution¹ for 2–5 minutes.
7. Wash in 70% ethanol.
8. Counterstain, if desired, with haematoxylin and orange G.
9. Dehydrate, clear and mount as usual.

_Result_

Granules of pancreatic B cells purple to violet; A cells stain yellow if orange G is used. Granules of pituitary TSH cells and sometimes also of MSH cells can be stained with aldehyde fuchsin using prolonged staining times.

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¹ Preparation of the aldehyde fuchsin solution. Dissolve 0.5 g of basic fuchsin in 100 ml of 60–70% ethanol; add 1 ml of concentrated HCl and 1 ml of paraaldehyde. At room temperature the mixture becomes a deep violet in 24–48 hours and is ready to use. Store at 0–5°C.
A.3. Techniques for detection of catecholamines

If formalin-fixed tissue only is available there are no specific staining methods for the precise identification of catecholamine granules. However, material may be post-fixed in osmium tetroxide for the identification of secretory granules by electron microscopy, although cytological preservation is poor.

If fresh tissue is available the most important technique is the demonstration of the chromaffin reaction. Although several methods are available, one of the most reliable is that recommended by Coupland (*The Natural History of the Chromaffin Cell*, London, Longmans, 1965). Thin slices of tissue are placed in the following fixative for 24 hours:

- formaldehyde solution, 400 g/l
- potassium dichromate solution, 50 g/l
- sodium acetate solution, 1 mol/l
- distilled water

It is important that the solution be buffered to the optimum pH of 5.8. Paraffin sections are best stained by haematoxylin alone, when catecholamine granules are brown, or by the Giemsa technique, when they are yellow-green. Both adrenalin and noradrenalin granules are stained.

If this procedure is not available, fixation with Orth's fixative is recommended.

Fixation in buffered glutaraldehyde (40 g/l) may be of value:

(a) for electron microscopic demonstration of secretory granules;
(b) for the demonstration of argentaffinity of noradrenalin- and dopamine-containing cells.

Fresh-frozen tissue or cryostat sections may be kept deep-frozen for the highly specific formalin-induced fluorescence (FIF) technique. Tissue may be stored in 0.01 mol/l HCl for the subsequent chemical extraction of catecholamine. Both these procedures are normally available only in specialized centres.
A.4. Grimelius' argyrophil reaction

Fixation
Optimal fixation is obtained with freshly-prepared Bouin's fluid with low concentrations of acetic acid (1-2%) for 24-48 hours.
Fixation with a 40 g/l solution of formaldehyde (a 1 in 10 dilution of formalin) for at least 24 hours, better up to 1 week, may also be used.

Impregnation
Immerse deparaffinized and rehydrated sections for 3 hours at 58-60 °C in the following solutions:
- silver nitrate solution, 10 g/l in distilled water: 4 ml
- acetate buffer, 0.2 mol/l, pH 5.6-5.8: 10 ml
- distilled water: 86 ml

Reduction
Sections are removed from the above solution, drained, and immersed for 1 to 1.5 minutes at 40-45 °C in the following mixture:
- hydroquinone: 1 g
- sodium sulfite: 5 g
- distilled water: 100 ml

Then the sections are rinsed in water, dehydrated, cleared and mounted.

Result
Argyrophil granules of most gut endocrine cells, and their tumours, pancreatic A cells, thyroid C cells, parathyroid chief cells, pituitary ACTH cells, adrenal medullary cells, paraganglia and chemoreceptor organs, as well as related tumours, are impregnated yellow-brown to black.
For a variety of reasons however only about 60% of "classical" carcinoids contain argyrophilic cells.

Note: In all these procedures use perfectly clean glassware (not plastic) and double-distilled water or deionized water.
A.5. **Masson-Hamperl's argentaffin reaction**  

**Fixation**

Formaldehyde solution, 40 g/l (a 1 in 10 dilution of formalin) for *at least 24 hours*.

1. Deparaffinized sections are carefully washed in several changes of distilled water.

2. Immerse for 15–30 minutes until light brown in the following solution at 60 °C in the dark:
   - To 100 g/l aqueous silver nitrate solution add strong ammonia solution drop by drop until the precipitate first formed redissolves. Then add 100 g/l silver nitrate solution drop by drop until a slight opalescence persists.
   - To every volume of this solution add 9 volumes of distilled water.

3. Wash in distilled water.

4. Immerse in 10 g/l aqueous sodium thiosulfate solution for 0.5 minute.

5. Counterstain if desired, with neutral red, safranin, haematoxylin or PAS–alcian blue.

6. Dehydrate, clear and mount.

**Result**

Argentaffin granules of enterochromaffin (EC) cells and their tumours show a black impregnation. The reaction may be positive only in some areas, frequently in a peripheral rim of the cell clusters. Positive results are also obtained with melanin and some lipofuscins.

Following glutaraldehyde fixation (40 g/l in 0.1 mol/l phosphate buffer, pH 7.3, 24 hours) granules storing primary catecholamines (noradrenaline, dopamine) in adrenal medulla, paraganglia and related tumours are also blackened.
A.6. Azo-coupling (diazonium) reaction for demonstration of 5-hydroxytryptamine

Fixation

40 g/l glutaraldehyde or 20 g/l glutaraldehyde + 20 g/l formaldehyde, in phosphate buffer, pH 7.3, for about 24 hours. Tissues fixed routinely in a 40 g/l solution of formaldehyde (a 1 in 10 dilution of formalin) for at least 24 hours may be used.

Staining

Deparaffinized and rehydrated sections are washed in several changes of distilled water and then stained 1-3 minutes in a solution of Fast Garnet GBC, Fast Red B, Fast Black K or other stable diazonium salt (1 mg/ml) in 0.1 mol/l barbital-acetate buffer pH 8.5. Alternatively 5 ml of a 1% solution of the diazotate is mixed with 2 ml of saturated lithium carbonate solution. The slides are washed in distilled water, counterstained, if desired, with haematoxylin or PAS–alcian blue, dehydrated and embedded as usual.

Result

5-hydroxytryptamine (after fixation in an aldehyde) in enterochromaffin (EC) cells and their tumours is stained orange red with Fast Garnet and Fast Red, and black with Fast Black.
B. Immunolocalization techniques

Although these techniques are usually only available in specialized centres, it is important to appreciate the general principles involved. The fixation required for immunolocalization varies with the antigen, and fixation is all-important. Routine formalin fixation in general gives poor results. Bouin, glutaraldehyde–picric acid or other specialized fixations may be needed, or freeze-drying with subsequent embedding.

Indirect immunolocalization techniques are usually employed; both fluorescent techniques and peroxidase labelling techniques have been used. Clearly the specificity of the antibody is of prime importance. Careful control studies are necessary to assess the importance of apparently positive results.
C. Electron microscopy

Electron microscopic examination is useful for the identification of secretory granules in cells of endocrine tumours. Whenever possible tissue for electron microscopy should be fixed in a special fixative as soon as possible after resection of the tumour—preferably within a few minutes. However, it may be possible to identify granules in tissue which was initially fixed in formalin or even in fresh autopsy material. Results of limited value have been achieved by electron microscopy of tissue after formalin fixation and paraffin embedding.

As with immunolocalization techniques, this investigation is likely to be carried out in a specialized centre. However, the initial fixation can be carried out in any laboratory, and the tissue sent to an electron microscopy laboratory after fixation. For this purpose the following fixative schedule is generally satisfactory.

Pieces of tissue no larger than 1 mm$^3$ should be placed in freshly prepared 60 g/l glutaraldehyde in 0.1 mol/l Sørensen's phosphate buffer, pH 7.2–7.4 (see below) at 4 °C. After 3 hours they should be transferred to buffer alone, where they should stay for at least 6 hours. During this time the buffer should be changed several times. The tissues should then be placed in buffered osmium tetroxide (50 ml of 0.1 mol/l Sørensen's phosphate buffer, 25 ml of distilled water, 1 g of osmium tetroxide) at 4 °C for 2–3 hours. Then transfer to 70% ethanol or acetone. After 2–3 changes in the first hour the tissue can remain in the fluid for several weeks prior to embedding.

The addition of 3 ml of calcium chloride to fixatives and buffers will help retain lipids and prevent artifacts, but is not essential.

Sørensen's phosphate buffer pH 7.2–7.4:

| Stock solution A | Na$\text{H}_2\text{PO}_4$, 0.2 mol/l |
| (to be stored in refrigerator) | (Na$\text{H}_2\text{PO}_4\cdot2\text{H}_2\text{O}$, 31.2 g/l) |
| Stock solution B | Na$_2$HPO$_4$, 0.2 mol/l |
| (to be stored in refrigerator) | (Na$_2$HPO$_4\cdot12\text{H}_2\text{O}$, 71.6 g/l) |

For 800 ml of 0.1 mol/l buffer at pH 7.3, take 92 ml of solution A + 308 ml of solution B + 400 ml of water.
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Unless otherwise stated, the preparations shown in the photomicrographs reproduced on the following pages were stained with haematoxylin-eosin.
Fig. 1 Normal anterior pituitary
Acidophils yellow, mucoid cells red-purple, chromophobes colourless. PAS—orange G. x 480

Fig. 2 Acidophil adenoma, pituitary
Uniformly well-granulated tumour cells. PAS—orange G. x 120
Fig. 3 Acidophil adenoma, pituitary
Well-granulated acidophils, some chromophobes. Edge of tumour. PAS—orange G. × 300

Fig 4 Acidophil adenoma, pituitary
Edges of tumour, same case as Fig. 3. Reticulin impregnation. × 120
Fig. 5 Acidophil adenoma, pituitary
Variable granulation. PAS—orange G. x 120

Acromegaly

Fig. 6 Mucoid cell adenoma, pituitary
PAS—orange G. x 20

Cushing's syndrome
Fig. 7 Mucoid cell adenoma, pituitary
Edge of tumour. PAS—orange G. × 120

Cushing's syndrome

Fig. 8 Mucoid cell adenoma, pituitary
Uniform moderate granularity. PAS—orange G. × 300

Cushing's syndrome
Fig. 9 Mucoid cell adenoma, pituitary

Poorly granulated tumour cells. Part of large, rapidly growing tumour. PAS—orange G. x 190

Cushing’s syndrome
Post-adrenalectomy

Fig. 10 Crooke cells, pituitary

Mucoid cells with abundant hyaline cytoplasm in non-neoplastic pituitary. Same case as Fig. 8. PAS—orange G. x 300

Cushing’s syndrome
Fig. 11 Chromophobe adenoma, pituitary
PAS—orange G. x 190

Infertility
Hyperprolactinaemia

Fig. 12 Chromophobe adenoma, pituitary
Large cell type. Edge of tumour, border of normal cells.
PAS—orange G. x 300
Fig. 13 Chromophobe adenoma, pituitary
Small cell type, with amyloid. Congo Red. x 120

Fig. 14 Oncocytic adenoma, pituitary
x 300
Fig. 15  Oncocytic adenoma, pituitary
Weak acidophilia. Same case as Fig. 14. PAS—orange G. 
× 330

Fig. 16  Chromophobe carcinoma, pituitary
Local invasion of hypothalamus × 50
Fig. 17  Craniopharyngioma, pituitary

Hypopituitarism

Fig. 18  Glandular cyst, pituitary

Edge of a colloid filled cyst. Mucoid cell "invasion" of posterior lobe with heterotopic tubular structures.
PAS—orange G. × 120
Fig. 19  Squamous cell nests, pituitary
Nests of squamous cells in pars tuberalis around pituitary stalk. $\times 50$

Fig. 20  Epidermoid cyst, pituitary
$\times 50$
Fig. 21  Normal adrenal cortex
  x 5

Fig. 22  Clear cell adenoma, adrenal cortex
  Edge with compressed but normally functioning cortex.  x 50
Fig. 23 Clear cell adenoma, adrenal cortex
Edge with compressed cortical cells. × 120

Fig. 24 Clear cell adenoma, adrenal cortex
× 75

Conn's syndrome
Fig. 25 Clear cell adenoma, adrenal cortex
Nuclear pleomorphism. × 120

Fig. 26 Hyperplastic zona glomerulosa
Same case as Fig. 24. × 30
Fig. 27 Compact cell adenoma, adrenal cortex
Trabecular pattern. × 120

Fig. 28 compact cell adenoma, adrenal cortex
Lipofuscin in tumour cells. × 190
Fig. 29 Black adenoma, adrenal cortex
Cushing's syndrome

Fig. 30 Compact cell adenoma, adrenal cortex
Lipofuscin in tumour cells. Normal cortex. From a black adenoma. × 50
Fig. 31  Mixed cell adenoma, adrenal cortex
Cushing's syndrome
× 120

Fig. 32  Carcinoma, adrenal cortex
Vascular invasion, focal necrosis. × 50
Cushing's syndrome
Fig. 33 Carcinoma, adrenal cortex
Liver metastasis, pleomorphism. x 120

Fig. 34 Carcinoma, adrenal cortex
Relatively uniform clear cells, mitotic activity. x 300
Fig. 35 Carcinoma, adrenal cortex
Uniform cells, mitosis. x 300

Cushing's syndrome

Fig. 36 Suppressed adrenal cortex
Normal medulla. Subendothelial benign cortical cells in central vein. Same case as Fig. 33. x 50

Cushing's syndrome
Fig. 37  Nodule, adrenal cortex
Small clear cell nodule in active cortex.  x 50

Fig. 38  Nodule, adrenal cortex
Ill-defined edge, slightly irregular but almost normal cell arrangement.  x 120
Fig. 39  Multiple nodular hyperplasia, adrenal cortex  
Cushing's syndrome

Multiple nodules, disorganized cortex.  × 50

Fig. 40  Multiple nodular hyperplasia, adrenal cortex  
Cushing's syndrome

Multiple nodules, disorganized cortex.  × 50
Fig. 41 Multiple nodular hyperplasia, adrenal cortex
Largely well demarcated clear cell nodule. × 120

Fig. 42 Micronodular cortical adenomatosis, adrenal cortex
Nodules at junction of narrow cortex and prominent medulla. Child. × 50

Cushing's syndrome
Fig. 43 Micronodular cortical adenomatosis, adrenal cortex
Nodule of large compact lipofuscin-containing cells. Child. PAS x 190

Cushing’s syndrome

Fig. 44 Capsular extrusion, adrenal cortex
x 50
**Fig. 45** Accessory adrenal cortex

Compact cells, normal but radial structure. × 50

**Fig. 46** Myelolipoma, adrenal cortex

Incidental autopsy finding. × 30
Fig. 47  Myelolipoma, adrenal cortex
Incidental autopsy finding. Residual compact cell adenoma at periphery. × 30

Fig. 48  Myelolipoma, adrenal cortex
Residual compact cells from adenoma. × 120
Fig. 49  Metastatic carcinoma, adrenal cortex
Oat-cell carcinoma. Active cortical cells. x 120

"Ectopic" Cushing's syndrome

Fig. 50  Phaeochromocytoma, adrenal medulla
Hypertension

x 120
Fig. 51 Phaeochromocytoma, adrenal medulla
Nucleomegaly. × 75

Hypertension

Fig. 52 Phaeochromocytoma, adrenal medulla
Same case as Fig. 51. Chromaffin reaction with Müller's solution. Neutral red. × 300

Hypertension
Fig. 53  Sympathetic paraganglioma, bladder  
\( \times 120 \)

Fig. 54  Parasympathetic paraganglioma, carotid body  
\( \times 120 \)
Fig. 55 Parasympathetic paraganglioma, carotid body
× 190

Fig. 56 Parasympathetic paraganglioma, carotid body
Fibrosis, vacuolation. × 120
Fig. 57 Parasympathetic paraganglioma, carotid body
Argyrophil cells. Grimelius. × 190

Fig. 58 Parasympathetic paraganglioma, glomus jugulare
Biopsy middle ear. × 120