



Best Practice No 172

Pituitary gland pathology

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This article reviews published evidence on the diagnosis and classification of pituitary gland tumours and the relevance of histological and genetic features to prognosis. Much of the literature is devoted to the histological, ultrastructural, and immunocytochemical classification of pituitary adenomas (extensively supported by multicentre studies), with little consensus on the identification of prognostic features in adenomas, particularly in relation to invasion. There is a lack of correspondence between clinical and pathological criteria to identify and classify invasion, and a need to reassess the nomenclature and diagnostic criteria for invasive adenomas and carcinomas. Recent cytogenetic, genetic, and molecular biological studies have identified no consistent abnormalities in relation to pituitary tumour progression, although many genes are likely to be involved. In light of these uncertainties, an approach to the diagnosis and classification of pituitary adenomas is suggested, based on robust criteria from earlier studies and incorporating provisional data that require reassessment in large prospective studies with an adequate clinicopathological database.

lesions that are encountered from within and around the pituitary gland, to assess current diagnostic pathological techniques, and to explore the expanding evidence base for the classification of pituitary adenomas and the clinical relevance of these approaches.

OVERVIEW OF PITUITARY REGION PATHOLOGY AND CLINICAL SYMPTOMATOLOGY

The pituitary gland can be affected by a wide range of lesions, which may arise either within the gland itself or its surrounding structures (table 1).^{2 5 7 12} These lesions all tend to present with clinical symptoms and signs that relate either to endocrine dysfunction of the pituitary gland, the local effects of an expanding mass in the region of the pituitary gland on adjacent structures (particularly the optic nerves and chiasm), or the non-specific effects of an expanding intracranial mass associated with raised intracranial pressure.^{2 4} The clinical symptoms are of course also dependent on the underlying nature of the lesion, its size and extension beyond the sella turcica, and the consequent effects on adjacent structures beyond this region.

“Larger lesions can produce signs and symptoms of raised intracranial pressure, of which headache is the most common manifestation”

Small lesions confined to the pituitary gland may be asymptomatic (see below for “silent” adenomas), or in the case of functioning adenomas will present with signs and symptoms of endocrine dysfunction (either excess or reduced production of one or several anterior pituitary hormones), particularly in younger patients.^{1 2 4} Clinical biochemistry laboratories in centres with an endocrine clinic are able to provide rapid and comprehensive assays for pituitary hormones and will also help with pituitary suppression or stimulation tests. Larger lesions with suprasellar

Intracranial lesions arising in the region of the pituitary gland are relatively common; the most frequent of these are pituitary adenomas, which account for 6–10% of all symptomatic intracranial tumours.^{1–3} However, the pituitary gland can be involved by a wide range of other pathological processes arising both within the gland itself and in the surrounding structures: the skull in the region of the sella turcica, dura mater, blood vessels, cranial nerves, and brain.^{4–6} Advances in neuroimaging have increased the sensitivity of detection of small lesions in the pituitary region,^{2 6–8} which are now readily accessible to neurosurgeons following recent developments in trans-sphenoidal surgery, including microsurgery and endoscopic resection of small intrasellar lesions.^{2 9–11} Consequently, pathologists now encounter an increasing number of lesions for diagnosis both within and around the pituitary gland, which comprise an ever widening spectrum of pathological processes.^{5 12} The aim of this article is to provide a brief review of the clinical features of

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Abbreviations: ACTH, adrenocorticotrophic hormone; CT, computerised tomography; FGF, fibroblast growth factor; GH, growth hormone; MEN-1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; PRL, prolactin; ptd-FGFR-4, pituitary tumour derived N terminally truncated isoform of fibroblast growth factor receptor-4; PTTG, pituitary tumour transforming gene; TSH, thyroid stimulating hormone

Table 1 Overview of pituitary region tumours

Tumours within the pituitary gland	
Adenoma	
Metastatic carcinoma	
Carcinoma	
Secondary lymphoma/leukaemia	
Craniopharyngioma	
Germ cell tumours (particularly germinoma)	
Granular cell tumour/spindle cell granular oncocyoma	
Gangliocytoma/ganglioglioma	
Pituicytoma	
Meningioma	
Lymphoma	
Non-neoplastic lesions involving the pituitary gland	
Nodular hyperplasia	
Epidermoid, dermoid, and Rathke cleft cysts	
Abscess	
Tuberculosis	
Sarcoidosis	
Histiocytosis (Langerhans and non-Langerhans)	
Lymphocytic hypophysitis	
Tumours arising from adjacent structures	
Optic chiasm/nerve: pilocytic astrocytoma, meningioma	
Cranial nerves: schwannoma	
Hypothalamus: gangliocytoma, pilocytic astrocytoma	
Sella turcica: meningioma, paraganglioma, chordoma/chondroma/chondrosarcoma	

extensions often present with visual field defects, such as bitemporal haemianopia caused by pressure on the optic chiasm, particularly the decussating fibres.^{2,3} Larger lesions can produce signs and symptoms of raised intracranial pressure, of which headache is the most common manifestation. Cranial nerve palsies may occasionally result from a large expanding sellar mass, and can vary from an isolated third nerve palsy to combined fourth, fifth, and sixth cranial nerve palsies if the cavernous sinus is invaded.⁵ An upward extension from an expanding sellar mass can cause distortion and compression of the pituitary stalk and/or hypothalamus, which in turn compromises the release of dopaminergic prolactin (PRL) inhibition, resulting in an increase in serum PRL (although usually not above 150 ng/ml).^{1,2} This may be the only endocrine abnormality in patients with large non-functioning adenomas. Distortion and invasion of the pituitary stalk may also compromise the portal blood supply to the anterior pituitary gland, resulting in infarction or haemorrhage, which can manifest clinically as pituitary apoplexy, with sudden visual loss, acute severe headache, meningism, and ophthalmoplegia.^{2,3} Large temporal lobe extensions from pituitary lesions may be associated with partial complex seizures. Although uncommon, infective and inflammatory lesions involving the pituitary gland may be associated with meningism, pyrexia, and neutrophilia or lymphocytosis according to the nature of the causative agent.^{3,5}

Plain skull *x* rays were for many years the basis of the anatomical diagnosis of a pituitary region mass lesion, and these are still helpful in the demonstration of enlargement of the sella turcica or erosion of the surrounding bone if the pituitary lesion is large.^{1,2} Computerised tomography (CT) scans are of more help in the demonstration of intrasellar lesions and can provide additional information on the nature of the lesion—for example, whether it is solid or cystic.² However, the results are partly dependent on the tumour size, because small intrasellar lesions can be missed even after the administration of intravenous contrast medium.^{2,8} CT scans are also helpful in delineating abnormalities in the bony structure of the sella turcica.² Magnetic resonance imaging (MRI) with Gadolinium enhancement has supplanted CT in the diagnosis of pituitary tumours in most centres. The main reason for this is the superior resolution of MRI, particularly for microadenomas, where

lesions as small as 2–3 mm can be routinely detected.⁸ Because the incidence of apparently clinically “silent” pituitary microadenomas has been estimated to be around 20% in the general population (rising to over 30% in the elderly), a continuing increase in the detection of these small lesions can be anticipated, although their clinical management is controversial.^{1–3} MRI is also useful for studies of macroadenomas and other large lesions, because it is better able to identify changes in the size of the gland, distortion of the pituitary stalk, elevation of the dura mater comprising the diaphragma sellae, and the position of the carotid arteries, the optic chiasm, and the cavernous sinus.^{7,8} The extent of the suprasellar and parasellar extensions is also more clearly visualised.

This brief summary of clinical and investigative features indicates that it is essential to obtain a full history for any patient who is undergoing surgery for resection of an intrasellar or parasellar mass, particularly if a pituitary adenoma is suspected. The clinical and radiological features should be supplemented with the results of biochemical investigations for pituitary hormones in the blood, because these can obviously provide much useful information concerning the probable nature of a pituitary region tumour before a pathology consultation request, particularly for intraoperative diagnosis. It is also essential to obtain details of medical treatment of the adenoma before surgery, because treatment can cause considerable changes in the morphological appearances of the tumour—for example, the changes seen in a prolactinoma after treatment with bromocryptine.^{1,4}

INTRAOPERATIVE DIAGNOSIS AND SPECIMEN HANDLING

Although many pituitary adenomas can be diagnosed after clinical, biochemical, and radiological investigations (and small intrasellar tumours producing PRL or growth hormone (GH) may be treated medically if there are no other indications for surgery²), neurosurgical management will often require intraoperative diagnosis to confirm the presence of a tumour in the resected tissue. This can help at the time of surgery to distinguish adenomatous from non-adenomatous pituitary tissue, and to ensure that for larger lesions extending beyond the sella turcica no other type of neoplasm is present for which further neurosurgical procedures may be required.⁵ Intraoperative diagnosis for pituitary adenomas is readily achievable on smear preparations alone, which can achieve a high degree of diagnostic accuracy.^{13–15} Smear preparations have several advantages in that they require the use of only small (1 mm³) portions of tissue, they can be prepared and stained rapidly using a variety of stains (of which the most common are toluidine blue and haematoxylin and eosin), and their preparation requires no specialised facilities or equipment other than access to a class 1 hood in which to handle the unfixed tissue.⁵ The preparation of smears from pituitary adenomas is relatively easy, because they usually have a soft consistency that readily allows a monolayer preparation to be made, which is ideal for cytological examination (fig 1).^{5,13} Smear preparations of pituitary adenomas allow a ready distinction from the non-adenomatous gland in terms of the nuclear pleomorphism and relatively uniform cytological characteristics seen in adenomas, and the identification of other pathological processes, such as inflammatory disorders or other forms of neoplasms, such as metastatic carcinoma or meningioma (fig 1). Certain specific cytological features may be identified in haematoxylin and eosin stained smear preparations that suggest a specific type of pituitary adenoma—for example, the paranuclear fibrous bodies in sparsely granulated growth hormone adenomas.

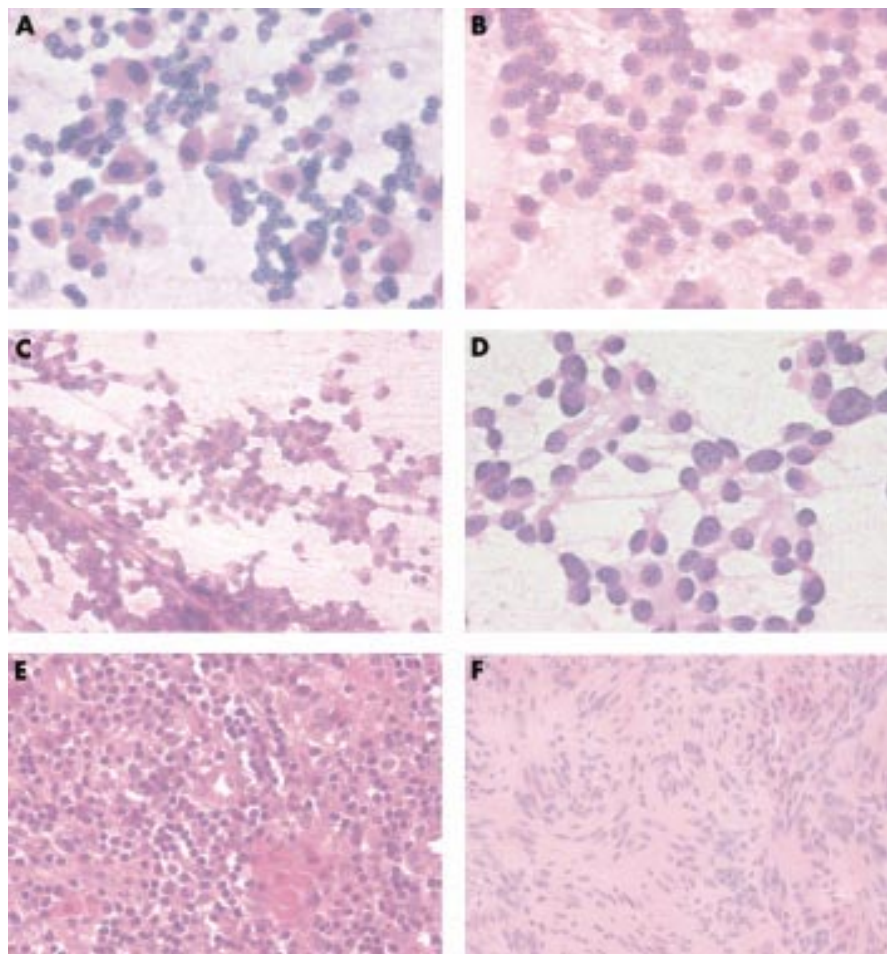


Figure 1 Examples of intraoperative diagnosis for pituitary region lesions. (A) Cytology of the normal anterior pituitary gland, with a mixed cell population exhibiting different tinctorial properties (smear preparation). (B) Gonadotroph adenoma, comprising a relatively uniform population of small cells with scanty pale staining cytoplasm (smear preparation). (C) Null cell adenoma, showing the close relation of the small tumour cells to capillary-like blood vessels. Some rosette-like structures are present (smear preparation). (D) Growth hormone adenoma, showing irregular tumour cells with greatly pleomorphic nuclei and a variable quantity of pale staining cytoplasm (smear preparation). (E) Lymphocytic hypophysitis. The anterior pituitary gland is invaded by large numbers of small lymphocytes (cryostat section). (F) Intracellular meningothelial meningioma, with several whorl-like structures and scanty blood vessels (cryostat section). All stained with haematoxylin and eosin.

“Intraoperative diagnosis for pituitary adenomas is readily achievable on smear preparations alone, which can achieve a high degree of diagnostic accuracy”

Smear preparations can be usefully supplemented by cryostat section diagnosis, particularly if the differential diagnosis includes other types of lesions such as schwannoma or craniopharyngioma, which may be tough in consistency and therefore difficult to smear.^{14 16} Rapid reticulin staining of a cryostat section may be useful in selected cases, particularly if there is doubt as to whether the tissue examined is normal anterior pituitary tissue or an adenoma, because adenomas lack the characteristic reticulin framework of normal anterior pituitary tissue.¹⁷ It has been suggested that the use of smear preparations for intraoperative diagnosis can achieve a higher degree of diagnostic accuracy than cryostat sections, but both approaches have their limitations in terms of assessment of adequacy of local resection.^{1 4 16} Furthermore, the use of tissue for cryostat sections can compromise the quality of the final histology obtained on the specimen, which can result in subsequent difficulties in histological interpretation and diagnosis. Therefore, cryostat sections for intraoperative diagnosis are best avoided in certain circumstances—for example, in specimens from patients with Cushing’s disease in whom no identifiable lesion is present on MRI scans. At the time of intraoperative diagnosis it is usually possible to store a piece of unfixed tumour tissue in a freezer, which can be used either for supplementary biochemical studies concerning hormone production, or for DNA or RNA extraction and analysis. It is also recommended that a small portion of tissue is placed into a fixative for electron microscopy, because ultrastructural examination is essential for the diagnosis of certain rare subtypes of pituitary adenoma.^{1 3 4}

PITUITARY ADENOMAS

These are by far the most common tumours arising in the pituitary gland and their pathology is extensively reviewed elsewhere.^{1 4 5 18 19} Rather than a repetitious listing of these well described lesions, this article will focus on the need to distinguish subtypes of pituitary adenomas that are of particular clinical relevance. The evidence base for the histological distinction of adenomas from nodular hyperplasia, invasive or atypical adenomas, and carcinomas will be reviewed. Table 2 summarises the clinicopathological features and relative incidence of pituitary adenomas. Pituitary adenomas occur across a wide age spectrum, from childhood and adolescence to old age.^{20–23} As noted above, it has been estimated from both clinical and postmortem studies that pituitary adenomas occur in around 20% of the normal population, but only a minority of these are symptomatic.^{1 3 24} Adenomas may rarely arise in ectopic pituitary tissue in the cranial cavity or bony sinuses,^{2 4 25} and have been described within an ovarian teratoma as an exceptional finding.²⁶ Multiple adenomas (including those of different cell types) have occasionally been reported, usually in patients with Cushing’s disease.^{27 28} Other apparently unrelated pathological processes occasionally coexist within a pituitary adenoma, including sarcoidosis,²⁹ toxoplasma infection,³⁰ and metastatic carcinoma.³¹

The classification of pituitary adenomas is based on a four step process,^{1 2 10 18 23} as follows:

- (1) Functional classification, to define these tumours in terms of their endocrine activity, noting that a large group of adenomas are clinically non-functional or endocrinologically inactive.^{1 2 19}
- (2) Anatomical and neuroradiological classification, based on tumour size and the degree of local invasion. The most widely

Table 2 Clinicopathological classification and incidence of pituitary adenomas (modified from Asa, 1998¹)

Functioning adenomas	Non-functioning adenomas
GH/PRL/TSH family	
(1) GH secretion (14%)	
Densely granulated GH adenoma	Silent somatotroph adenoma
Sparsely granulated GH adenoma	
Mammotroph adenoma	
(2) PRL secretion (29%)	
Densely granulated PRL adenoma	Silent lactotroph adenoma
Sparsely granulated PRL adenoma	
Acidophil stem cell adenoma	
(3) TSH secretion (1%)	
Thyrotroph adenoma	Silent thyrotroph adenoma
(β TSH and α subunit)	
ACTH family (13%)	
ACTH secretion	
Corticotroph adenoma	Silent corticotroph adenoma (types I and II)
Gonadotroph family (13%)	
β FSH/ β LH/ α subunit secretion	
Gonadotroph adenoma	Silent gonadotroph adenoma
Other adenomas (30%)	
Pleurihormonal adenomas	Null cell adenomas
Unclassified adenomas	Oncocytomas
	Silent subtype III adenoma

ACTH, adrenocorticotrophin; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinising hormone; PRL, prolactin; TSH, thyroid stimulating hormone.

Table 3 Neuroanatomical classification of pituitary adenomas (based on Hardy, 1969³²)

Grade	Size	Location	Bony changes
I	<10 mm	Intrapituitary	None
II	>10 mm	Intrasellar or suprasellar expansion, no invasion	Sellar expansion
III	Any	Intrasellar or suprasellar expansion, local invasion	Sellar erosion
IV	>10 mm	Suprasellar expansion, invasion of extrasellar structures	Bone invasion

used classification is based on that by Hardy, which places adenomas into four grades (table 3).^{1, 32} As part of this assessment, it is important to understand that local invasion in certain subtypes of pituitary adenomas is relatively common, although not necessarily indicative of malignant potential.^{33–35}

(3) Histological classification, firmly based on the immunocytochemical characterisation of the tumours in terms of hormone production, including the six major anterior pituitary hormones (adrenocorticotrophic hormone (ACTH), follicle stimulating hormone, GH, luteinising hormone, PRL, and thyroid stimulating hormone (TSH)) and the α subunit of glycoprotein hormones. Other antibodies can be used to identify certain subtypes of pituitary adenoma—for example, the use of antibodies to low molecular weight cytokeratins to label the fibrous bodies in sparsely granulated GH adenomas. Older classifications of adenomas based on tinctorial stains are obsolete and should be abandoned.

(4) Ultrastructural classification, which can confirm that non-functional lesions are of pituitary origin, and characterises the cytological differentiation of tumour cells in terms of anterior pituitary cell types.^{1, 3, 4} It also allows the recognition of specific diagnostic features, particularly in unusual rare pleurihormonal adenomas, such as acidophil stem cell adenomas,³⁶ oncocytomas,³⁷ and silent subtype 3 adenomas.³⁸

INVASIVE PITUITARY ADENOMAS

The apparent contradiction in nomenclature of an invasive benign tumour is not confined to pituitary adenomas alone, but this topic is of particular importance in view of the relation of the pituitary gland to crucial intracranial structures. Pituitary adenomas lack a true capsule, and their relation to the

surrounding normal anterior pituitary tissue can be difficult to assess, particularly in fragmented biopsy specimens.^{5, 18} More important than invasion of the surrounding gland is the propensity of adenomas to invade surrounding structures. Sampling of the dura mater of the diaphragma sellae found evidence of invasion in 66% of Hardy grade I tumours, which rose to over 90% for grade III tumours in one series.³⁹ In a more recent larger study,³⁵ dural invasion was found in 45% of all cases, with a higher frequency in patients undergoing repeated trans-sphenoidal surgery and for those patients with macroadenomas (> 40 mm). The identification of dural invasion indicates that an adenoma may be incompletely resected, and there was a significantly decreased survival rate in patients with invasive adenomas in this study.³⁵

“More important than invasion of the surrounding gland is the propensity of adenomas to invade surrounding structures”

Because dura mater sampling is not routinely performed in pituitary surgery, the identification of invasion generally depends on neuroradiological and neurosurgical assessment (see above). It is established that certain tumour types are more likely to be invasive, including macroadenomas, non-functioning adenomas (particularly silent ACTH adenomas and silent subtype 3 adenomas), and TSH adenomas.^{4, 38–40, 41} The identification of histological criteria related to invasiveness has not been the subject of a standardised prospective assessment, but there is general agreement that “brisk” mitotic activity is associated with aggressive

growth.^{4 42 43} Although early studies showed no relation between tumour ploidy and invasion, there is an association between macroscopic invasion and the proportion of cells in the S phase of the cell cycle.^{44 45} This relation has been confirmed in immunocytochemical assessment of cell proliferation indices using the Ki-67 and MIB-1 antibodies.^{46 47} A threshold Ki-67 labelling index of 3% distinguished aggressive tumours from non-invasive adenomas with 97% specificity, with positive and negative predictive values of 96% and 80%, respectively, in one series.⁴⁶ No consistent relation between tumour invasion and nucleolus organiser regions in adenoma cells has been identified.⁴⁸ Although immunoreactivity for p53 is absent in non-invasive adenomas, it is present in some, but not all, invasive adenomas and pituitary carcinomas (including metastatic deposits).^{42 49 50} It has also been suggested that immunoreactivity for other proteins, including hst, heat shock protein 27, and interleukin 6, may also be useful in the identification of invasive adenomas.^{51 52} Further assessments are required on larger prospective series to investigate these and other potential markers for invasive adenomas. Genetic events that may be associated with invasion in pituitary adenomas are summarised below.

PITUITARY CARCINOMAS

These extremely rare malignant tumours are identified on the basis of their capacity to metastasise via the cerebrospinal fluid pathway or to extracranial tissues.^{1 3 4} Brain invasion is not yet considered a criterion for malignancy, but it is likely that this possibility will be reassessed as neuroradiological techniques for the identification of brain invasion improve and that the practicality of brain sampling for the identification of invasion is reconsidered by neurosurgeons (as it has been for the identification of invasive meningiomas). Pituitary carcinomas are usually endocrinologically functional, with ACTH and PRL producing tumours being the most frequent.^{3 42 53 54} Carcinomas show a variable degree of nuclear atypia and cellular pleomorphism, but with significantly higher mitotic rates and cell proliferation indices than adenomas.^{43 46} Vascular endothelial proliferation and necrosis are uncommon features; immunoreactivity for p53 has been found in some metastatic deposits, but the primary tumours show a much lower incidence of immunoreactivity.^{42 49 50} As for invasive adenomas, it appears that there are no consistently expressed cellular markers of aggressive biological behaviour for pituitary carcinomas.

PITUITARY HYPERPLASIA

Physiological pituitary hyperplasia occurs in pregnancy and lactation, and primarily involves PRL cells.^{1 3} Non-neoplastic hyperplasia of individual pituitary cell types is an uncommon cause of excess hormone secretion. Two main patterns of pituitary cell hyperplasia may be encountered: diffuse and nodular; these may occur either singly or in combination. Diffuse hyperplasia does not greatly alter the acinar structure of the gland, and thus may be difficult to detect in a fragmented biopsy specimen, particularly because there is a considerable degree of variation in the distribution of cell types in the normal anterior pituitary gland.^{3 4} The most clinically important form of pituitary hyperplasia is nodular hyperplasia,^{18 55} which most often involves a single cell type and is more likely to be associated with clinical features as a result of excess endocrine activity, mimicking a functional adenoma. All cell types can be involved, but PRL hyperplasia is the most common form, and can occasionally result from longstanding pituitary stalk compression by a pre-existing adenoma or another adjacent mass lesion.^{3 4} Reticulin stains are helpful in the assessment of nodular hyperplasia, because the abnormally expanded acinar structures are not uniformly distributed throughout the gland and they may become confluent, resulting in disruption of the normal reticulin framework.^{18 55}

GENETIC STUDIES IN PITUITARY TUMOURS

There is much evidence to support the notion that pituitary tumours are clonal lesions caused by intrinsic pituitary cell defects, most which are based on X chromosome inactivation.^{4 56 57} In support of this concept, it is extremely unusual to find hyperplasia of the anterior pituitary gland surrounding an adenoma (which might be expected if the adenoma arose as the result of an external hormonal stimulus), although occasional examples have been described.⁵⁸ Multiple synchronous adenomas have been described in the pituitary gland, including tumours of different cell types, although they are extremely rare.^{27 28} A multiclonal origin has been proposed for these tumours, and there is increasing evidence to suggest that at least some sporadic tumours may also be multiclonal.^{57 59-61}

"Deletions in the region of 13q14 have been identified in pituitary adenomas, suggesting the presence of a tumour suppressor gene at this locus"

Genetic studies of pituitary adenomas have revealed that most of the mutations that have been identified in other malignancies are usually absent, and the molecular events leading to adenoma formation are still poorly understood.^{59 62-64} Although pituitary adenomas occur in multiple endocrine neoplasia type 1 (MEN-1),⁶⁵ loss of heterozygosity at the MEN-1 gene locus is uncommon in sporadic adenomas.^{62 64} Similarly, although pituitary GH adenomas occur as part of the Carney complex, one of the genes responsible, PRKARIA, does not appear to be involved in sporadic pituitary tumours.⁶⁶ Deletions in the region of 13q14 have been identified in pituitary adenomas, suggesting the presence of a tumour suppressor gene at this locus.^{63 64 67} It has also been suggested that amplification of the HRAS and CMYC genes and inactivation of the tumour suppressor genes RB1, TP53, and NM23 may represent mechanisms by which pituitary tumours progress, but there is as yet no evidence of their consistent involvement in pituitary adenoma invasion or in pituitary carcinomas.^{59 68-72} Certain cell specific genetic abnormalities have been identified—for example, up to 40% of GH adenomas have GSP mutations, resulting in activation of the Gs α subunit.^{59 60 73} Inactivation of p16 has been identified in up to 80% of adenomas (particularly in large tumours) in two recent studies, possibly as a result of CDKN2A methylation.^{74 75} A novel oncogene, pituitary tumour transforming gene (PTTG), is overexpressed in a wide range of pituitary adenomas and immunocytochemistry for PTTG protein is positive in most adenomas, but absent in normal pituitary cells.⁷⁶ The precise role of PTTG in oncogenesis is uncertain; PTTG may interact with fibroblast growth factor (FGF) to stimulate vascular growth, or it may activate p53 to cause apoptosis.^{76 77} A recent large study found an association between cyclin D1 genotype (CCND1) and tumour grade in sporadic pituitary adenomas,⁷⁸ but the clinical relevance of this finding remains uncertain until it is reproduced in other populations with these tumours. A novel pituitary tumour derived, N terminally truncated isoform of FGF receptor-4, ptd-FGFR4, has been identified recently.⁷⁹ ptd-FGFR4 is not expressed in normal pituitary tissue, and has a distinctive cytoplasmic residence. It is transforming both in vivo and in vitro, and targeted expression of ptd-FGFR4 in transgenic mice results in pituitary tumours that morphologically resemble PRL adenomas in humans, in the absence of PRL cell hyperplasia.⁷⁹

OTHER TUMOURS ARISING IN THE PITUITARY GLAND

Table 1 summarises the other tumours that arise in the pituitary gland.⁸⁰⁻⁸² Many of these, particularly the cystic lesions such as craniopharyngioma, meningiomas, and germ cell

tumours are extensively described in the literature and generally do not pose major diagnostic problems. Pituitary adenomas (regardless of cell type) are characterised by the expression of synaptophysin, neurone specific enolase, low molecular weight cytokeratins, and PTTG.⁷⁶⁻⁸³ However, tumours arising in the neurohypophysis are uncommon and can represent a source of diagnostic difficulty, which is particularly important in terms of implications for patient management.²⁻²³ The most common tumour arising in the neurohypophysis is the granular cell tumour, which is occasionally encountered as an incidental finding at necropsy.²⁴⁻⁸¹ These tumours resemble granular cell tumours arising in other parts of the body. Their histogenesis is uncertain; they occur in adults (usually in late middle age) and occasional examples have been reported in association with endocrine syndromes, including acromegaly.⁸¹⁻⁸⁴ Most are benign, but occasional cases exhibit local infiltration or recur after surgery.³⁷⁻⁸¹ Pituitary cytomas are extremely uncommon tumours of glial lineage, which occur in adults and are curable by total resection.⁸⁵⁻⁸⁶ These benign tumours are thought to be derived from neurohypophyseal pituitary cells, and are characterised by the expression of S-100 protein and vimentin, with variable positivity for glial fibrillary acidic protein. Although not associated with MEN-1, a case has been described that occurred in a patient with multiple endocrine tumours.⁸⁷

Other rare primary pituitary tumours include gangliogliomas and gangliocytomas,⁸⁸⁻⁸⁹ which can be associated with endocrine secretion.⁹⁰ It has been suggested that some of these lesions may represent examples of transdifferentiation, rather than a primary neuronal neoplasm of the neurohypophysis.⁹¹ Other even rarer tumours arising in the pituitary gland include lymphomas,⁹² astrocytomas (including pilocytic astrocytomas and pleomorphic xanthoastrocytomas),⁸²⁻⁹³⁻⁹⁴ ependymomas,⁹⁵ and the recent entities of spindle cell oncocyoma⁹⁶ and the rather poorly defined suprasellar monomorphous pilomyxoid neoplasm.⁹⁷ The pituitary gland may also be involved in a wide range of non-neoplastic cystic lesions⁴⁻⁸²⁻⁹⁸ and inflammatory infectious disorders,⁹⁹⁻¹⁰⁶ which may present with clinical features similar to those of a non-functioning adenoma; these lesions are summarised in table 1.

CONCLUSIONS

The pathologist has a key role to play in the multidisciplinary team dealing with patients with pituitary region tumours. An

Take home messages

- The pituitary gland can be affected by a wide range of disorders, which present with similar clinical features
- Intraoperative diagnosis using smear preparations or cryostat sections can make a major contribution to the surgical management of pituitary region tumours
- Immunocytochemistry and electron microscopy are essential for the diagnosis and classification of pituitary adenomas
- Certain pituitary adenoma subtypes are more likely to exhibit local invasion and aggressive growth
- There are no currently accepted genetic markers for predicting biological behaviour in pituitary gland tumours
- The pathologist has a key role in the multidisciplinary team dealing with patients with pituitary region tumours

accurate pathological diagnosis of these lesions can only be achieved if the pathologist is in close cooperation with clinicians dealing with the patient, so that full clinical details (including medical treatment, biochemical, and neuroradiological findings) are provided on the consultation request form; this is particularly important if an intraoperative diagnosis is requested. The adequate pathological assessment of pituitary adenomas requires extensive immunocytochemistry and, in some cases, electron microscopy. Based on available evidence, a diagnostic approach for pituitary adenomas is outlined in table 4, which includes prognostic indicators in addition to markers of cytodifferentiation. It is inevitable that this approach will require future modification as further data emerge on the genetic abnormalities associated with pituitary tumour pathogenesis. As this genetic data improves, it is anticipated that the relation between pituitary adenomas, invasive adenomas, and carcinomas will be clarified, allowing greater diagnostic accuracy and the provision of prognostically useful information.

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Table 4 Approach to the investigation and diagnosis of pituitary adenomas

<i>Intraoperative diagnosis</i>	
Smear preparation	Haematoxylin and eosin Toluidine blue
Cryostat section	Haematoxylin and eosin Rapid reticulin stain in selected cases
<i>Paraffin wax sections</i>	
Routine diagnosis	Haematoxylin and eosin Reticulin stain Immunocytochemistry for anterior pituitary hormones (GH, PRL, ACTH, β TSH, β FSH, β LH, α subunit) Synaptophysin, neurone specific enolase, low molecular weight cytokeratins, and PTTG* immunoreactivity
Prognostic markers	Mitotic figures (no threshold mitotic index) Ki-67 labelling index >3% p53*, hst*, hsp 27*, and IL-6* immunoreactivity
<i>Electron microscopy</i>	
	Granule size and localisation Specific features, such as fibrous bodies or misplaced exocytosis
<i>Genetic studies*</i>	
<i>PTTG upregulation</i>	
	LOH 11q13 HRAS, CMYC amplification CCND1 genotype RB1, TP53, CDKN2A, and NM23 inactivation

*Provisional data to be confirmed in future studies.

ACTH, adrenocorticotropic hormone; FSH, follicle stimulating hormone; hsp, heat shock protein; IL, interleukin; LH, luteinising hormone; PRL, prolactin; TSH, thyroid stimulating hormone.

REFERENCES

- Asa SL. *Tumors of the pituitary gland*. Atlas of tumor pathology, 3rd series, Fascicle 22. Washington: Armed Forces Institute of Pathology, 1998.
- Kaye AH, Laws ER, eds. *Brain tumors. An encyclopedic approach*. Edinburgh: Churchill Livingstone, 1995.
- Thapar K, Kovacs K. Neoplasms of the sellar region. In: Bigner DD, McLendon R, Bruner J, eds. *Russell and Rubinstein's pathology of tumors of the nervous system*, 6th ed. London: Arnold, 1998.
- Horvath E, Scheithauer BW, Kovacs K, et al. Hypothalamus and pituitary. In: Graham DI, Lantos PL, eds. *Greenfield's neuropathology*, 7th ed. London: Arnold, 2002.
- Ironsides JW, Moss TH, Louis DN, et al. *Diagnostic pathology of nervous system tumours*. Edinburgh: Churchill Livingstone, 2002.
- Freda PU, Post KD. Differential diagnosis of sellar masses. *Clin Endocrinol Metab North Am* 1999;**28**:81-117.
- Connor SEJ, Penny CC. MRI in the differential diagnosis of a sellar mass. *Clin Radiol* 2003;**58**:20-31.
- Naidich MJ, Russell EJ. Current approaches to imaging of the sellar region and pituitary. *Endocrinol Metab Clin North Am* 1999;**28**:45-80.
- Laws ER, Jr, Thapar K. Pituitary surgery. *Clin Endocrinol Metab North Am* 1999;**28**:119-32.
- Zhang X, Fei Z, Zhang J, et al. Management of non-functioning pituitary adenomas with suprasellar extensions by transsphenoidal microsurgery. *Surg Neurol* 1999;**52**:380-5.
- Hae-Dong J. Endoscopic transsphenoidal surgery. *J Neurooncol* 2001;**54**:187-95.
- McLendon RE, Bigner DD, Bigner SH, et al. *Pathology of tumors of the central nervous system. A guide to histologic diagnosis*. London: Arnold, 2000.
- Moss TH, Nicoll JAR, Ironsides JW. *Intra-operative diagnosis of CNS tumours*. London: Arnold, 1997.
- Smith AR, Elsheikh TM, Silverman JF. Intraoperative cytologic diagnosis of suprasellar and sellar cystic lesions. *Diagn Cytopathol* 1999;**20**:137-47.
- Ng HK. Smears in the diagnosis of pituitary adenomas. *Acta Cytol* 1998;**42**:614-18.
- Adelman LS, Post KD. Intra-operative frozen section diagnosis for pituitary adenomas. *Am J Surg Pathol* 1979;**3**:173-5.
- Velasco ME, Sindely SO, Roessmann U. Reticulum stain for frozen-section diagnosis of pituitary adenomas. Technical note. *J Neurosurg* 1977;**46**:548-50.
- Kovacs K, Horvath E, Vidal S. Classification of pituitary adenomas. *J Neurooncol* 2001;**54**:121-7.
- Kujas M. Pituitary adenomas. *Ann Pathol* 2001;**21**:237-43.
- Kunwar S, Charles B, Wilson B. Pediatric pituitary adenomas. *J Clin Endocrinol Metab* 1999;**84**:4385-9.
- Lakka-Papadodima E. Non-secreting pituitary tumors in adolescents—consequence in adulthood. *J Pediatr Endocrinol Metab* 2001;**14**:1217-26.
- Turner HE, Adams CB, Wass JA. Pituitary tumours in the elderly: a 20 year experience. *Eur J Endocrinol* 1999;**140**:383-9.
- Arafah BM, Nasrallah MP. Pituitary tumors: pathophysiology, clinical manifestations and management. *Endocr Relat Cancer* 2001;**8**:287-305.
- Tomita T, Gates E. Pituitary adenomas and granular cell tumors. Incidence, cell type and location of tumor in 100 pituitary glands at autopsy. *Am J Clin Pathol* 1999;**111**:817-25.
- Hosaka N, Kitajiri S, Hirami H, et al. Ectopic pituitary adenoma with malignant transformation. *Am J Surg Pathol* 2002;**26**:1078-82.
- Axiotis CA, Lippes HA, Merino MJ, et al. Corticotroph cell pituitary adenoma within an ovarian teratoma. A new cause of Cushing's syndrome. *Am J Surg Pathol* 1987;**11**:218-24.
- McKelvie PA, McNeill P. Double pituitary adenomas: a series of three patients. *Pathology* 2002;**34**:57-60.
- Meij BP, Lopes MB, Vance ML, et al. Double pituitary lesions in three patients with Cushing's disease. *Pituitary* 2000;**3**:159-68.
- Robin MR, Bruce JN, Khandji AG, et al. Sarcoidosis within a pituitary adenoma. *Pituitary* 2001;**4**:195-202.
- Zhang X, Li Q, Hu P, et al. Two case reports of pituitary adenoma associated with *Toxoplasma gondii* infection. *J Clin Pathol* 2002;**55**:965-6.
- Hanna FW, Williams OM, Davies JS, et al. Pituitary apoplexy following metastasis of bronchogenic adenocarcinoma to a prolactinoma. *Clin Endocrinol* 1999;**51**:377-81.
- Hardy J. Transsphenoidal microsurgery of the normal and pathological pituitary. *Clin Neurosurg* 1969;**16**:185-217.
- Oruckaptan HH, Senmevsim O, Ozcan OK, et al. Pituitary adenomas: results of 684 surgically treated patients and review of the literature. *Surg Neurol* 2000;**53**:211-19.
- Blevins LS, Jr, Verity DK, Allen G. Aggressive pituitary tumors. *Oncology (Huntingt)* 1998;**12**:1307-12, 1315-18.
- Meij BP, Lopes MB, Ellegala DB, et al. The long-term significance of microscopic dural invasion in 354 patients with pituitary adenomas treated with transsphenoidal surgery. *J Neurosurg* 2002;**96**:195-208.
- Asa SL, Kovacs K, Horvath E, et al. Hormone secretion in vitro by plurihormonal pituitary adenomas of acidophil stem cell line. *J Clin Endocrinol Metab* 1992;**75**:68-75.
- Giungaspero F, Cenacchi G. Oncocytic and granular cell neoplasms of the central nervous system and pituitary gland. *Semin Diagn Pathol* 1999;**16**:91-7.
- Horvath E, Kovacs K, Smyth HS, et al. A novel type of pituitary adenoma: morphological features and clinical correlations. *J Clin Endocrinol Metab* 1988;**66**:1111-18.
- Selman WR, Laws ER, Jr, Scheithauer BW, et al. The occurrence of dural invasion in pituitary adenomas. *J Neurosurg* 1986;**64**:402-7.
- Bradley KJ, Wass JAH, Turner HE. Non-functioning pituitary adenomas with positive immunoreactivity for ACTH behave more aggressively than ACTH immunonegative tumours but do not recur more frequently. *Clin Endocrinol* 2003;**58**:59-64.
- Scheithauer BW, Jaap AJ, Horvath E, et al. Clinically silent corticotroph tumors of the pituitary gland. *Neurosurgery* 2000;**47**:723-9.
- Gaffey TA, Scheithauer BW, Lloyd RV, et al. Corticotroph carcinoma of the pituitary: a clinicopathologic study. *J Neurosurg* 2002;**96**:352-60.
- Thapar K, Yamada Y, Scheithauer BW, et al. Assessment of mitotic activity in pituitary adenomas and carcinomas. *Endocr Pathol* 1996;**7**:215-21.
- Anniko M, Tribukait B, Wersall J. Significance of high percentages of S-phase cells in human pituitary tumours. *ORL J Otorhinolaryngol Relat Spec* 1983;**45**:177-86.
- Chatterjee S, May PL, Forster G, et al. Prediction of recurrence in pituitary tumours: a flow cytometric study using in vivo bromodeoxyuridine. *Br J Neurosurg* 1993;**7**:165-9.
- Thapar K, Kovacs K, Scheithauer BW, et al. Proliferative activity and invasiveness among pituitary adenomas and carcinomas: an analysis using the MIB-1 antibody. *Neurosurgery* 1996;**38**:99-106.
- Turner HE, Wass JA. Are markers of proliferation valuable in the histological assessment of pituitary tumours? *Pituitary* 1999;**1**:147-51.
- Hucumenoglu S, Kaya H, Kotiloglu E, et al. AgNOR values are not helpful in the differential diagnosis of pituitary adenomas. *Clin Neurol Neurosurg* 2002;**104**:293-9.
- Oliveira MC, Marroni CP, Pizarro CB, et al. Expression of p53 protein in pituitary adenomas. *Braz J Med Biol Res* 2002;**35**:561-5.
- Kumar K, Macaulay RJ, Kelly M, et al. Absent p53 immunohistochemical staining in a pituitary carcinoma. *Can J Neurol Sci* 2001;**28**:174-8.
- Gandour-Edwards R, Kapadia SB, Janecka IP, et al. Biologic markers of invasive pituitary adenomas involving the sphenoid sinus. *Mod Pathol* 1995;**8**:160-4.
- Shimon I, Hinton DR, Weiss MH, et al. Prolactinomas express human heparin-binding secretory transforming gene (hst) protein product: marker of tumour invasiveness. *Clin Endocrinol (Oxf)* 1998;**48**:23-9.
- Pichard C, Gerber S, Laloi M, et al. Pituitary carcinoma: report of an exceptional case and review of the literature. *J Endocrinol Invest* 2002;**25**:65-72.
- Popadic A, Witzmann A, Buchfelder M, et al. Malignant prolactinoma: case report and review of the literature. *Surg Neurol* 1999;**51**:47-54.
- Horvath E, Kovacs K, Scheithauer BW. Pituitary hyperplasia. *Pituitary* 1999;**1**:169-79.
- Suhardja AS, Kovacs KT, Rutka JT. Molecular pathogenesis of pituitary adenomas: a review. *Acta Neurochir (Wien)* 1999;**141**:729-36.
- Clayton RN, Farrell WE. Clonality of pituitary tumours: more complicated than initially envisaged? *Brain Pathol* 2001;**11**:313-27.
- Vidal S, Horvath E, Syro LV, et al. Prolactin-producing pituitary adenoma associated with prolactin cell hyperplasia. *Endocrinol Pathol* 2002;**13**:157-65.
- Asa SL, Ezzat S. The pathogenesis of pituitary tumours. *Nat Rev Cancer* 2002;**2**:836-49.
- Faglia G, Spada A. Genesis of pituitary adenomas: state of the art. *J Neurooncol* 2001;**54**:95-110.
- Buch H, El-Hadd T, Bicknell J, et al. Pituitary tumours are multiclonal from the outset: evidence from a case with dural metastases. *Clin Endocrinol (Oxf)* 2002;**56**:817-22.
- Boggild MD, Jenkinson S, Pistorello M, et al. Molecular genetic studies of sporadic pituitary tumors. *J Clin Endocrinol Metab* 1994;**78**:387-93.
- Farrell WE, Clayton RN. Molecular pathogenesis of pituitary tumors. *Front Neuroendocrinol* 2000;**21**:174-98.
- Lloyd RV. Molecular pathology of pituitary adenomas. *J Neurooncol* 2001;**54**:111-19.
- Komminoth P, Heitz PU, Kloppel G. Pathology of MEN-1: morphology, clinicopathologic correlations and tumour development. *J Int Med* 1998;**243**:455-64.
- Sandrini F, Kirschner LS, Bei T, et al. PRKAR1A, one of the Carney complex genes, and its locus (17q22-24) are rarely altered in pituitary tumours outside the Carney complex. *J Med Genet* 2002;**39**:e78.
- Alexander JM. Tumor suppressor loss in pituitary tumors. *Brain Pathol* 2001;**11**:342-55.
- Yu R, Melmed S. Oncogene activation in pituitary tumors. *Brain Pathol* 2001;**11**:328-41.
- Karga HJ, Alexander JM, Hedley-Whyte ET, et al. Ras mutations in human pituitary tumors. *J Clin Endocrinol Metab* 1992;**74**:914-19.
- Pei L, Melmed S, Scheithauer B, et al. H-ras mutations in human pituitary carcinoma metastases. *J Clin Endocrinol Metab* 1994;**78**:842-6.
- Nam D-H, Song S-Y, Park K, et al. Clinical significance of molecular genetic changes in invasive pituitary adenomas. *Exp Mol Med* 2001;**33**:111-16.
- Suhardja A, Kovacs K, Rutka J. Genetic basis of pituitary adenoma invasiveness: a review. *J Neurooncol* 2001;**52**:195-204.
- Spada A, Vallar L. G-protein oncogenes in acromegaly. *Horm Res* 1992;**38**:90-3.
- Ruebel KH, Jin L, Zhang S, et al. Inactivation of the p16 gene in human pituitary non-functioning tumors by hypermethylation is more common in null cell adenomas. *Endocr Pathol* 2001;**12**:281-9.
- Seeman N, Kuhn D, Wrocklage C, et al. CDKN2A/p16 inactivation is related to pituitary adenoma type and size. *J Pathol* 2001;**193**:491-7.

- 76 **Zhang X**, Horwitz GA, Heaney AP, *et al*. Pituitary tumor transforming gene (PTTG) expression in pituitary adenomas. *J Clin Endocrinol Metab* 1999;**84**:761–7.
- 77 **Hunter JA**, Skelly RH, Aylwin SJ, *et al*. The relationship between pituitary tumour transforming gene (PTTG) expression and in vitro hormone and vascular endothelial growth factor (VEGF) secretion from human pituitary adenomas. *Eur J Endocrinol* 2003;**148**:203–11.
- 78 **Simpson DJ**, Fryer AA, Grossman AB, *et al*. Cyclin D1 (CCND1) genotype is associated with tumour grade in sporadic pituitary adenomas. *Carcinogenesis* 2001;**22**:1801–7.
- 79 **Ezzat S**, Zheng L, Zhu X-F, *et al*. Targeted expression of a human pituitary-derived isoform of FGF receptor-4 recapitulates pituitary tumorigenesis. *J Clin Invest* 2002;**109**:69–78.
- 80 **Inoue T**, Matushima T, Fukui M, *et al*. Immunohistochemical study of intracranial cysts. *Neurosurgery* 1988;**23**:576–81.
- 81 **Kleihues P**, Cavenee WK, eds. *Tumours of the nervous system. Pathology and genetics. World Health Organisation classification of tumours*. Lyon: IARC, 2000.
- 82 **Kovacs K**, Horvath E. The differential diagnosis of lesions involving the sella turcica. *Endocr Pathol* 2001;**12**:389–95.
- 83 **Lloyd RV**, Scheithauer BW, Kovacs K, *et al*. The immunophenotype of pituitary adenomas. *Endocr Pathol* 1996;**7**:145–50.
- 84 **Losa M**, Saeger W, Mortini P, *et al*. Acromegaly associated with a granular cell tumor of the neurohypophysis: a clinical and histological study. Case report. *J Neurosurg* 2000;**93**:121–6.
- 85 **Brat DJ**, Scheithauer BW, Staugaitis SM, *et al*. Pituicytoma: a distinctive low-grade glioma of the neurohypophysis. *Am J Surg Pathol* 2000;**24**:362–8.
- 86 **Figarella-Branger D**, Dufour H, Fernandez C, *et al*. Pituicytomas, a mis-diagnosed benign tumor of the neurohypophysis: report of 3 cases. *Acta Neuropathol* 2002;**104**:313–19.
- 87 **Schultz AB**, Brat DJ, Oyesiku NM, *et al*. Intracellular pituicytoma in a patient with other endocrine neoplasms. *Arch Pathol Lab Med* 2001;**125**:527–30.
- 88 **Geddes J**, Jannsen GH, Robinson SF, *et al*. “Gangliocytomas” of the pituitary: a heterogeneous group of lesions with differing histogenesis. *Am J Surg Pathol* 2000;**24**:607–13.
- 89 **McCowen KC**, Glickman JN, Black PM, *et al*. Gangliocytoma masquerading as a prolactinoma. Case report. *J Neurosurg* 1999;**91**:490–5.
- 90 **Fehn M**, Lohmann F, Ludecke DK, *et al*. Ganglioglioma of the neurohypophysis with secretion of vasopressin. *Exp Clin Endocrinol Diabetes* 1998;**106**:425–30.
- 91 **Horvath E**, Kovacs K, Tran A, *et al*. Ganglion cells in the posterior pituitary: result of ectopia or transdifferentiation? *Acta Neuropathol* 2000;**100**:106–10.
- 92 **Giustina A**, Gola M, Doga M, *et al*. Clinical review 136. Primary lymphoma of the pituitary: an emerging clinical entity. *J Clin Endocrinol Metab* 2001;**86**:4567–75.
- 93 **Tacconi L**, Farah JO, Rossi ML, *et al*. Neurohypophyseal pilocytic astrocytoma invading the skull base. *Br J Neurosurg* 1999;**13**:614–17.
- 94 **Arita K**, Kurisu K, Tominaga A, *et al*. Intracellular pleomorphic xanthoastrocytoma: case report. *Neurosurgery* 2002;**51**:1079–82.
- 95 **Thomson S**, Chakrabarty A, Marks P. Ependymoma of the neurohypophysis. *Br J Neurosurg* 2001;**15**:277–8.
- 96 **Roncaroli F**, Scheithauer BW, Cenacchi G, *et al*. “Spindle cell oncocyoma” of the adenohypophysis: a tumor of folliculostellate cells? *Am J Surg Pathol* 2002;**26**:1048–55.
- 97 **Fuller CE**, Frankel B, Smith M, *et al*. Suprasellar monomorphous pilomyxoid neoplasm: an ultrastructural analysis. *Clin Neuropathol* 2001;**20**:256–62.
- 98 **Shin JL**, Asa SL, Woodhouse LJ, *et al*. Cystic lesions of the pituitary: clinicopathological features distinguishing craniopharyngioma, Rathke’s cleft cyst and arachnoid cyst. *J Clin Endocrinol Metab* 1999;**84**:3972–82.
- 99 **Vates GE**, Berger MS, Wilson CB. Diagnosis and management of pituitary abscess: a review of twenty-four cases. *J Neurosurg* 2001;**95**:233–41.
- 100 **Skandarajah A**, Hoe W, Gonzales M, *et al*. Lymphocytic hypophysitis mimicking pituitary macroadenoma. *J Clin Neurosci* 2002;**9**:586–9.
- 101 **Ouma JR**, Farrell VJR. Lymphocytic infundibulo-neurohypophysitis with hypothalamic and optic pathway involvement: report of a case and review of the literature. *Surg Neurol* 2002;**57**:49–53.
- 102 **Sharma MC**, Arora R, Mahapatra AK, *et al*. Intracellular tuberculoma—an enigmatic pituitary infection: a series of 18 cases. *Clin Neurol Neurosurg* 2000;**10**:72–7.
- 103 **Oweity T**, Scheithauer BW, Ching HS, *et al*. Multiple system Erdheim–Chester disease with massive hypothalamic–sellar involvement and hypopituitarism. *J Neurosurg* 2002;**96**:344–51.
- 104 **Mosca L**, Costanzi G, Antonacci C, *et al*. Hypophysial pathology in AIDS. *Histol Histopathol* 1992;**7**:291–300.
- 105 **Murialdo G**, Tamagno G. Endocrine aspects of neurosarcoidosis. *J Endocrinol Invest* 2002;**25**:650–62.
- 106 **Murakami K**, Muraishi K, Ikeda H, *et al*. Plasma cell granuloma of the pituitary gland. *Surg Neurol* 2001;**56**:247–51.

A poem for pathology

Winds of change

There once lived a pathologist by name Joe Pearson,
Like the back of his hand, he knew every lesion.
He knew them all; he’d seen them all,
A great teacher, his students he’d enthrall.
“REAL” lymphomas to “pseudo” tumours he was the master,
There was no man who could be faster.
Our good old man had but one vice,
That he’d firmly shut his mind’s eyes.
Never a new thought could he entertain,
The winds of change—he treated with disdain.
Stagnant and resistant, the frog-in-a-well,

Till one day, the curtain of wax fell.
He’d made a mistake, which was certainly fatal—
putting a newborn through the gates of hell;
He was left a loner in his ivory tower,
Deprived of his glory, shorn of his power.
His work of a lifetime stood by him no more,
‘cos he’d refused to learn and he’d chosen to ignore.
A heavy price he paid, to fathom the secret of living—
That if you want to go places, you must keep moving!

T Rajalakshmi,

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Winds of change

T Rajalakshmi

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