Neurology of the pituitary gland

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This review will focus on those aspects of pituitary disease immediately relevant to neurologists and neurosurgeons when assessing and counselling patients. It is essential to adopt a multidisciplinary approach to the diagnosis and management of pituitary disease as emphasised by the recently published guidelines from the Royal College of Physicians of London.1–4

Range of pathology presenting in the sellar region

The commonest lesions presenting in this region are pituitary tumours (incidence of 15–20/million/year), including adenomas and craniopharyngiomas, aneurysms, and meningiomas, but many other diseases need to be considered (table 1).

Neurological presentations of pituitary disease

"Pituitary incidentalomas" may be disclosed when investigating unrelated disease (fig 1). Although figures from 5% to 27% have been quoted for the incidence of subclinical adenomas at postmortem, far fewer are of significant size—that is, over 5 mm in diameter with deviation of the stalk and unilateral enlargement of the gland. Careful endocrine and visual assessments are required and, where no abnormalities are found, most can be managed conservatively with follow up MRI.5–8

Pituitary disease often presents insidiously and in retrospect might have been detected earlier. The symptoms of hormonal hypersecretion in endocrinologically active tumours will obviously present before evidence of suprasellar or parasellar extension. Although somatic changes usually bring the growth hormone secreting adenoma to medical attention first, the neurologist may encounter nerve entrapment (particularly the carpal tunnel syndrome), proximal myopathy (weakness disproportionate to the increased body mass), peripheral neuropathy (muscle atrophy, distal sensory loss, and neuropathic joints) and the psychological and emotional sequelae of the disease.9 It has been debated whether the emotional sequelae reflect a specific interaction between growth hormone and the limbic system.10 The headaches are often bitemporal, periorbital, or referred to the vertex, and do not seem to correlate with the size of the mass.11 Fronto-occipital headaches have also been described that may be exacerbated by coughing. More remotely, acromegaly may present with the neurological complications of diabetes mellitus and hypertension. Some patients may present with symptoms drawn from more than one endocrinopathy when there is dual secretion by the pituitary adenoma—for example, of growth hormone and prolactin. Finally, not all growth hormone hypersecretion is the product of a pituitary adenoma—a rapidly progressive

| Differential diagnosis of neoplasms and “tumour-like” lesions of the sellar region |
| Tumours of adenohypophyseal origin | Cysts, hamartomas, and malformations |
| Pituitary adenoma | Rathke’s cleft cyst |
| Pituitary carcinoma | Arachnoid cyst |
| Granular cell tumour | Epidermoid cyst |
| Astrocytoma of posterior lobe and/or stalk (rare) | Dermoid cyst |
| Tumours of non-pituitary origin | Gangliocytoma |
| Craniopharyngioma | Empty sella syndrome |
| Germ cell tumours | Metastatic tumours |
| Glioma (hypothalamic, optic nerve/chiasm, infundibulum) | Carcinoma |
| Meningioma | Plasmacytoma |
| Haemangioendothelioma | Lymphoma |
| Chordoma | Leukaemia |
| Haemangioendothelioma | Inflammatory conditions |
| Lipoma | Infection/abscess |
| Giant cell tumour of bone | Mucocoele |
| Chondroma | Lymphocytic hypophysitis |
| Fibrous dysplasia | Sarcoïdosis |
| Sarcoca (chondrosarcoma, osteosarcoma, fibrosarcoma) | Langherans’ cell histiocytosis |
| Postirradiation sarcoma | Giant cell granuloma |
| Paraganglioma | Vascular lesions |
| Schwannoma | Internal carotid artery aneurysms |
| Glomangioma | Cavernous angiomata |

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history over a few months suggests an ectopic tumour.

The clinical manifestations of Cushing’s syndrome are well known. The patient usually presents at the microadenoma stage with remarkably little if any abnormality on MRI. Symptoms can fluctuate, particularly in teenagers. Weakness from proximal myopathy, psychiatric disturbances including anxiety and panic attacks, the neurological consequences of obesity and hypertension, and benign intracranial hypertension may bring the patient to a neurologist.

A neurologist will usually see prolactinomas and endocrinologically inactive tumours when they have already reached a size sufficient to impinge on the normal pituitary and extrasellar structures (visual failure, ophthalmoplegia, trigeminal sensory loss, and hydrocephalus). Hypogonadal symptoms, weakness, fatigue, or headache may be the presenting feature. Hypogonadism may be compounded by mild hyperprolactinaemia resulting from the effect of raised intrasellar pressure on the normal pituitary gland (see later). The neurological manifestations of hypothyroidism include carpal tunnel syndrome, slowing of cerebration, and, less commonly, myotonia and myopathy.

The neurological consequences of hyperthyroidism including exophthalmos may herald a thyrotrophinoma, the great majority of which are macroadenomas and hence may be accompanied by headache, visual field defect, and galactorrhoea. However, other conditions may be associated with hyperthyroidism plus a detectable concentration of serum thyrotrophin and specialist expertise is required to differentiate them.

Children with pituitary and third ventricular lesions may present with precocious puberty, growth retardation, diabetes insipidus, denial of visual failure, and the symptoms and signs of either high or low pressure hydrocephalus.

Some diagnostic pitfalls

Although most patients with a pituitary problem fall within well defined categories, a minority present with manifestations of one of the myriad of small print diagnoses. Ectopic tumours may cause not only Cushing’s syndrome but also acromegaly. Primary hypothyroidism may be accompanied by pituitary gland swelling as the result of overstimulation from the hypothalamus leading to visual symptoms, hypopituitarism, headache, and less commonly, diabetes insipidus, syndrome of...
inappropriate antidiuretic hormone secretion (SIADH), and precocious puberty. To add to the confusion, one third of such female patients may have menstrual irregularities as a reflection of modest hyperprolactinaemia leading to a misdiagnosis of prolactinoma. The pituitary swelling resolves with thyroxine and surgery is unnecessary.

The stalk compression syndrome refers to the symptoms and signs of hyperprolactinaemia in the presence of moderately raised prolactin concentrations and a sellar or suprasellar mass but distortion of the pituitary stalk alone does not correlate with prolactin concentrations.\textsuperscript{2,5,11} It is not clear why it is the prolactin inhibitory system alone of the hypothalamo-anterior pituitary control systems that is predominantly affected. Direct measurements of intrasellar pressure made during trans-sphenoidal surgery have shown that the intrasellar pressure may be raised above the presumed perfusion pressure of the anterior pituitary gland.\textsuperscript{14} The anterior pituitary is only supplied by thin walled portal vessels (derived from the superior and inferior hypophyseal arteries) that can easily be obstructed by CSF/intrasellar pressures above about 20 mm Hg. Dynamic CT after contrast injection discloses rapid enhancement of the posterior pituitary (direct arterial supply from the inferior hypophyseal arteries) followed by progressive enhancement of the anterior pituitary as the contrast supplied through the portal circulation extravasates through the defective blood-brain barrier in the anterior pituitary gland.\textsuperscript{15} There is no specific concentration of prolactin that distinguishes stalk compression from a true prolactinoma but values of 2500–5000 mU/L are often quoted despite many exceptions in the literature. It is more important to take the concentration in the context of the imaging.\textsuperscript{16} If the macroadenoma is a prolactinoma, the prolactin concentration should be much greater than 2500 mU/L. If there is no significant intrasellar or suprasellar mass and the concentration is less than 2500, this cannot be the result of stalk compression or raised intrasellar pressure. In addition there are many other causes of hyperprolactinemia to be considered. Hopefully, the days are gone when patients with symptomatic hyperprolactinemia were treated with dopamine agonists without any radiological imaging—bromocriptine will suppress the galactorrhea of stalk compression hyperprolactinaemia whereas the craniopharyngioma gets bigger! Immunocytochemistry on the excised tumour is the final arbiter.

Lymphocytic hypophysitis often presents at the end of pregnancy with visual failure and it has also been described in men. MRI shows an enlarged homogeneously enhancing pituitary gland but a specific diagnosis cannot be made by imaging alone. Management requires careful coordination between obstetrician, endocrinologist, ophthalmologist, and neurosurgeon—early delivery may lead to early shrinkage and avoid trans-sphenoidal decompression provided vision has not deteriorated too far. Lymphocytic hypophysitis represents an autoimmune attack on the adenohypophysis and manifests histologically as diffuse lymphocytic infiltration effacing and destroying the normal glandular elements with progression to fibrotic scarring.\textsuperscript{17} The infiltrate is polyclonal, predominantly T cell, but often includes lymphoid germinal centres, plasma cells, and foamy macrophages. A similar lymphocytic inflammatory process may be confused to the neurohypophyseal system, sparing the anterior pituitary. By contrast, granulomatous hypophysitis is characterised by non-caseating epithelioid granulomata and multinucleate Langhans-type giant cells. When restricted to the anterior pituitary this pathology probably overlaps with lymphocytic hypophysitis\textsuperscript{18} but in the posterior pituitary it is more often a manifestation of neurosarcoïdosis and invariably associated with involvement of the hypothalamus and basal meninges. In any inflammatory process, unusual infections, particularly mycobacterial or fungal, must be excluded but in western countries these are unlikely except in the context of immunosuppression.

The symptoms and signs of extrapituitary extension depend on its direction:

- **Downwards**—nasal obstruction or epistaxis; CSF leak
- **Upwards**—visual failure (see later); hypothalamic disturbance, third ventricular obstruction with acute hydrocephalus (symptoms and signs of raised intracranial pressure), or chronic hydrocephalus (gait apraxia, slowing of mentation, and incontinence)
- **Laterally**—cavernous sinus syndrome; complex partial seizures.

**Pituitary apoplexy (fig 2)**

As pituitary adenomas enlarge, they acquire a direct arterial blood supply in addition to the portal blood supply but their blood supply remains variable.\textsuperscript{21,23} There is a range of presentation of haemorrhagic infarction from subclinical infarction, noted at operation or on preoperative imaging (the prevalence of haemorrhage within adenomas is 9%–43% on MRI of which less than 30% are symptomatic), to full blown apoplexy that mimics subarachnoid haemorrhage. Indeed, the diagnosis may initially be missed. Many of these patients may not be aware of a pre-existing adenoma. In addition to abrupt headache with or without loss of consciousness, the clinical features include visual failure,\textsuperscript{19} cavernous sinus syndrome, focal neurological signs, and acute panhypopituitarism, sometimes with low blood pressure. Pituitary apoplexy can occur with a relatively small adenoma and is often spontaneous but may be precipitated by endocrine stress tests, bromocriptine,\textsuperscript{25,26} and anticoagulants. The unenhanced emergency CT usually shows an enlarged pituitary fossa with some blood or speckled density within the mass. Magnetic resonance imaging will then confirm the diagnosis and angiography is rarely needed to exclude a vascular abnormality. Haemorrhage appears as high signal on both T1 and T2 weighted imaging, and can be confused with craniopharyngioma and Rathke’s cleft cyst, especially as the signal changes can persist for
3–12 months, to be replaced by an area of hypointensity in the chronic phase. Management includes resuscitation, steroid replacement, and early transphenoidal decompression with craniotomy reserved for the very small minority of patients with a dumb-bell tumour.27

Empty sella syndrome (fig 3)

Empty or partial empty sella are terms used when the pituitary gland does not fully occupy the sella, and this is found in 6% of routine postmortems and MRI examinations when a midline sagittal image is obtained. It is more common in multiparous women, presumably due to repeated enlargement and involution of the gland with each pregnancy. Empty sella is a radiological diagnosis based on CT or MRI performed for headache, CSF leak, or late visual deterioration after surgery or radiation therapy for a pituitary lesion. The radiological diagnosis of an empty sella should be made with care—a cystic craniopharyngioma or Rathke’s cleft cyst may sometimes mimic the normal anatomical contours both within and above the sella. This distinction is particularly important in those 18% of children with neuroendocrinological abnormalities who could have an empty sella, cyst, or craniopharyngioma.28 29 This should be less of a problem with MRI than it was with CT. Primary empty sella conventionally is not associated with significant endocrine or visual abnormalities. Sensitive dynamic endocrine testing may disclose abnormalities but hormone replacement is seldom indicated.30 An empty sella is commonly seen in patients with benign intracranial hypertension31 and may be the sequel to pituitary apoplexy. About 50% of adult patients with a primary empty sella have antipituitary antibodies that indicate previous autoimmune hypophysitis.32 Postpartum necrosis of the pituitary gland may be followed by an empty fossa. Spontaneous CSF rhinorrhea may be associated with an empty sella with or without raised intracranial pressure.33 When there has been a previous cause for the empty sella, then there may be an associated endocrine abnormality (either hypopituitarism or hormone hyperscretion) if there is an accompanying pituitary adenoma, particularly when shrunk either by bromocriptine or somatostatin. Prior intrasellar surgery and radiotherapy may lead to an empty sella.

The optic chiasm may herniate down into the empty fossa but there is considerable debate as to whether such herniation itself can be responsible for visual field defects.34 Radiation necrosis and arachnoiditis are more likely to be the cause of visual failure in such circumstances. Although some good results from chiasmectomy have been reported,35 both for the relief of intractable headache and for visual failure, there have certainly been disasters, which inevitably go underreported.

Diabetes insipidus and SIADH

Neither of these fluid balance disturbances are common presentations of anterior pituitary pathology—they usually indicate hypothalamic or pituitary stalk pathology. The posterior pituitary gland and stalk are supplied by an arterial circulation and the rise in intrasellar pressure produced by a pituitary adenoma is insufficient to compromise such an arterial circulation except possibly after pituitary apoplexy. Vasopressin and oxytocin are produced in hypothalamic nuclei and are transported by their axons to be stored as neurosecretory granules in the posterior pituitary which appear as a high signal intensity on MRI. The normal high signal (see fig 1A) is absent in almost all patients with central and nephrogenic diabetes insipidus.36 This, however, should be interpreted with caution as the bright signal is also absent in 15%–20% of the normal population, albeit usually in the elderly age group who, although asymptomatic, have a high circulating plasma osmolality.37 The presence of the bright signal indicates normal vasopressin stores, implying an intact neurohypophyseal system, which eliminates central diabetes insipidus as a diagnostic possibility. Ectopic location of the posterior lobe is very rare as an isolated finding with normal pituitary function. Any process, however, that disturbs transport of hormones from the hypothalamus to the neurohypophysis as in transection of the stalk, after head injury or surgery, or destruction of the posterior lobe, can result in the accumulation of the high signal material proximal to the site of obstruction.38
growth hormone deficiency, there is a high incidence (43%) of ectopic posterior pituitary.

Diabetes insipidus is more common with metastases (33%) compared with adenomas (1%) (see fig 7F). Neoplasms of the posterior pituitary are rare. Low grade gliomas that closely resemble astrocytomas may occur in the posterior lobe or stalk (fig 4). Benign, granular tumours, also called choristomas, contain large PAS positive granules which are solely due to abundant large lysosomes.

Visual failure

ANATOMY OF THE CHIASM

The chiasm (4 mm thick, 12 mm wide, and 8 mm long) lies about 1 cm above the pituitary fossa, inclining as much as 45° from the horizontal. In humans, about 53% of fibres decussate and there are about 2 million axons for both nerves. Because of the normal variation in the length of the optic nerves, the chiasm may be prefixed (overlying the tuberculum sella anteriorly) or postfixed (overlying the tuberculum sella posteriorly). Small tumours in this region or ophthalmic artery aneurysms may cause unilateral blindness by pressure on one intracranial optic nerve. A space of about 1 cm between the dorsum sella and the chiasm will accommodate a reasonably large tumour arising above the dorsum sella before it compresses the chiasm. Fibres from the macula comprise most of the fibres of the optic nerve, chiasm and optic tract. As a consequence, pituitary tumours compressing these structures will have field defects that affect the central 30° and so may be detected using the tangent screen and automated perimeters which test out to 24° or 30°.

The inferior nasal fibres which cross within the chiasm sweep forward into the opposite optic nerve and thence into the opposite optic tract, forming Wilbrand’s knee. Recent anatomical studies of the chiasm have emphasised that the exaggerated bulge of crossing fibres, which seems to involve the contralateral optic nerve, is partly an artefact caused by enucleation.

VISUAL SYMPTOMS OF PITUITARY TUMOUR

Some patients may be unaware of their field defects. The most frequent complaints of patients with chiasmal compression from pituitary tumours are progressive loss of central acuity and dimming of the visual field, especially in its temporal portion. However, the lack of a binocular temporal field may also cause difficulties with depth perception for near vision and diplopia. Convergence for near vision results in crossing of the two blind hemifields so that an object posterior to fixation apparently disappears—so called postfixation blindness. Patients often complain of difficulty with fine tasks such as threading a needle and cutting fingernails. Diplopia without an ocular motor paresis results from “vertical slip”. Patients with a bitemporal hemianopia do not have a link between the remaining hemifields so that vertical or horizontal separation occurs between the two intact nasal hemifields and visual sensory difficulties result. Diplopia may also result from involvement of the third, fourth, and sixth cranial nerves in the cavernous sinus causing a disturbance of ocular motility.

FIELD DEFECTS IN CHIASMAL LESIONS

The classic pattern of a chiasmal visual field defect is a bitemporal depression and greater
near fixation, but the effects may be peripheral, central, or a combination. The defects may be absolute or relative. Patients with chiasmal disease may have normal or reduced acuity and colour vision. The initial field defect usually occurs in the superior temporal quadrants and then to the inferior nasal and superior temporal quadrants.

The types of field defect with chiasmal lesions may be classified as:

1. **anterior angle of the chiasm**
   When only a small lesion involves the crossing fibres of the ipsilateral eye, the field defect is temporal with a midline hemianopic character; if only the macular crossed fibres are affected the field defect is paracentral and temporal. When both the crossed and ventral fibres from the contralateral eye are affected, there is a defect in the temporal field of that eye. If there is extensive involvement of one optic nerve, an extensive field defect or even blindness of that eye may result; when such a lesion extends to involve the chiasm, the earliest indication is a temporal defect in the contralateral eye.

2. **Lesions involving the body of the chiasm**
   These characteristically produce a bitemporal hemianopia that may be peripheral, central, or a combination of both with or without splitting of the macula. Usually the visual acuity is normal. In the field of the right eye, the defect progresses in a clockwise direction and, in the left eye, a counterclockwise direction. A complete bitemporal hemianopia is rarely seen except after trauma to the chiasm. Most compressive lesions cause relative bitemporal hemianopias.

3. **Lesions at the posterior angle of the chiasm**
   These lesions characteristically produce bitemporal homonymous scotomas often associated with peripheral bitemporal defects as well. Lesions affecting this area often also compress the ipsilateral optic tract.

4. **The lateral aspect of the chiasm**
   Compression of the lateral aspect of the chiasm affects both the uncrossed temporal fibres and the crossed nasal fibres causing a contralateral homonymous hemianopia.

**Psychophysical Abnormalities in Chiasmal Lesions**

Recent investigation with contrast sensitivity techniques has attempted to characterise changes in visual function resulting from chiasmal compression before visual acuity and visual field are affected. Studies of temporal contrast sensitivity have shown both uniform and low temporal frequency loss of contrast sensitivity in patients with chiasmal compression. Studies assessing spatial frequency sensitivity in lesions affecting the suprasellar region have found alterations either to be total or limited to low to medium spatial frequencies only. A recent study of psychophysical losses in foveal sensitivity found significant losses in chromatic, luminance, and temporal sensitivities in patients with suprasellar lesions without field defects.

**Fundal Signs**

Optic atrophy is a late sign of chiasmal compression from pituitary tumour; usually the optic discs are normal. Optic atrophy is weakly correlated with the duration of visual symptoms and strongly correlated with persistent postoperative decreased visual acuity. There is a characteristic optic atrophy found in advanced chiasmal compression—“bow tie” or “band” atrophy. The optic disc shows atrophy of the nasal and temporal margins with relative sparing of the superior and inferior portions where most spared temporal fibres (serving the nasal field) enter. A relative afferent pupillary defect may be detected when there is asymmetric compression of the optic nerves.

**The Mechanism of Chiasmal Compression**

The mechanism by which pituitary adenomas and other lesions damage selectively the decussating nasal fibres remains uncertain. Because the axons for the entire superior visual field are in the inferior portion of the chiasm, compression from below would be expected to produce a defect in the entire upper field; yet an altitudinal hemianopia is extremely rare. Thus, unless the decussating fibres are more vulnerable to compression than the uncrossed fibres, simple compression does not provide a complete explanation for bitemporal field defects.

There is evidence from animal studies of the effect of direct compression on the anterior visual system. In a macaque monkey a suprasellar meningioma compressed the optic nerves, chiasm, and tracts dorsally causing a selective loss of small diameter fibres. In cats, optic nerve pressure obstruction has been shown to disrupt large diameter fibres selectively. The vulnerability of the crossing fibres to compression from below may be related to the vascular supply; in humans, the central chiasm derives its blood supply from the inferior vessels. Alternatively, the attachments of the optic chiasm are such that expanding tumours produce tension on the crossing fibres only.

**The Prognosis for Visual Function After Trans-Sphenoidal Hypophysectomy**

After uncomplicated surgical decompression of the chiasm and optic nerves, visual acuity and visual fields usually improve rapidly over a few days. There may also be a slower improvement occurring over weeks and months. Visual recovery is usually complete by 4 months. Visual outcome is favourable in most patients; in a recent report of 67 patients, the vision was improved in 88%, the same in 7%, and worse in 4%. The extent of improvement depends on whether permanent damage to the optic nerve and chiasm has occurred. The extent of preoperative damage may be judged from a loss of arcuate nerve fibres surrounding the optic disc (the nerve fibre layer) and the degree of atrophy and pallor of the disc itself. The duration of visual loss and the degree of chiasm and optic nerve compression are the chief influences on the preoperative visual status. In cases of advanced visual failure and severe optic atrophy, it is wise to caution the patient that
decompression may prevent further visual deterioration but may not improve visual function. Rarely, visual function may deteriorate after trans-sphenoidal hypophysectomy particularly with second operations or after radiotherapy and all patients should be warned of this possibility before surgery. Visual deterioration after surgery is usually related to an intracapsular haematoma, possibly as the result of infarction of a tumour remnant, or direct surgical manipulation of the optic nerve or chiasm and its blood supply. Visual deterioration is more likely after craniotomy, particularly when radical removal of a capsule from the chiasm has been attempted.

The other important concern in follow up is whether patients with persistent bitemporal field defects should be allowed to drive. According to the current criteria of the United Kingdom Driver and Vehicle Licensing Authority, if there is a bitemporal field defect its blood supply. Visual deterioration is more likely after craniotomy, particularly when radical removal of a capsule from the chiasm has been attempted.

The other important concern in follow up is whether patients with persistent bitemporal field defects should be allowed to drive. According to the current criteria of the United Kingdom Driver and Vehicle Licensing Authority, if there is a bitemporal field defect affecting the central 20°, patients should be advised that they will not be permitted to drive.

Investigations
ENDOCRINOLOGY

Patients with pituitary tumours should be assessed by a multidisciplinary team. They often require long term supervision, and early referral to the appropriate endocrinologist is sensible. The only urgent endocrine test required in a patient with visual failure and a large suprasellar mass is a basal prolactin concentration. Endocrine tests should be tailored to the individual patient and not ordered uncritically. The conventional dynamic endocrine tests may precipitate pituitary apoplexy, as most sleep deprived pituitary surgeons can testify. Inferior petrosal sinus sampling for Cushing’s syndrome uses a percutaneous bilateral femoral approach and requires obsessional attention to detail if useful results are to be obtained. In experienced hands, the procedure is safe but cavernous sinus thrombosis and brainstem infarction have been seen—heparin and a gentle contrast injection technique are essential.

IMAGING

Magnetic resonance is the first choice for imaging the pituitary and parasellar region as no ionising radiation is involved and bone induced artefact is avoided. Plain skull radiology is seldom indicated except for surgical planning in selected cases. Computed tomography is reserved for emergency use and for the claustrophobic, the MRI incompatible, those too large for the bore of the magnet, and for specialised indications when bone details are useful (CSP leaks and surgical planning). Each neuroradiology department has a standard MRI protocol but this has to be refined for specific clinical indications and close communication between radiologist and clinician is essential if errors are not to occur. Particular care is required with long term, multidisciplinary follow up when miscommunication can so easily occur with missed or mislaid scans making accurate comparisons and timely management decisions difficult.

Clinicians should be aware of the age related changes in pituitary size and characteristics from childhood through puberty and pregnancy to old age. The maximum allowable pituitary height is 6 mm in children, 8 mm in men and postmenopausal women, 10 mm in women of child bearing age, and 12 mm in late pregnancy and the postpartum period. Microadenomas, defined as less than 10 mm in diameter, are 400 times more common than macroadenomas. Magnetic resonance imaging is emerging as a superior technique to CT for the detection of microadenomas. The detection rate varies in the literature from 65% to more than 90%. This is related to the technique used, the continuing improvement in equipment, the use of contrast, and the size of the microadenoma. Most microadenomas are visible by virtue of their hypointensity on TI weighted sequences in relation to the normal pituitary tissue (see fig 1B). Focal enlargement of the gland and convexity of the diaphragma sella are less specific adjuvant signs. Infundibular tilt and sella floor thinning or erosion are less useful criteria. Microadenomas as small as 2–3 mm can now be detected in 75%–90% of cases (with a false negative rate of about 13%), which is very important for surgical planning in patients with pituitary driven Cushing’s disease when combined with bilateral inferior petrosal sinus sampling. Serial MRI studies have shown that about 7% of microprolactinomas progressively expand over 2–8 years.

The immediate T1 weighted scan after gadolinium, with the use of thin slices, is the most useful sequence to increase the sensitivity of detection of small intrasellar lesions: the enhancing normal glandular tissue allows the low intensity microadenoma to become more conspicuous (fig 5). The ability to obtain a dynamic series of images in seconds rather than minutes has overcome some of the limitations of conventional postcontrast imaging (fig 6).
Images obtained less than 2 minutes from the start of injection have a detection rate of 90% compared with 60% at 5 minutes. However, some adenomas become less visible, as they also enhance to be isointense with the gland. A few microadenomas show more rapid arrival of contrast material than the normal pituitary tissue suggesting perhaps the development of a direct arterial blood supply. Precontrast TI weighted images remain important to detect both the few adenomas (5%) which are hyperintense to the normal gland and haemorrhagic lesions.

Computed tomography and MRI are equivalent in detecting the full extent of a macroadenoma (fig 7). The margins tend to be lobulated in at least two thirds of the cases (23% in meningiomas). Sellar enlargement is seen in 94%-100% of pituitary macroadenomas. This is only helpful as a distinguishing feature in a suprasellar mass when it is absent, because its absence favours neoplasms other than a macroadenoma but does not exclude an aneurysm! The presence of hormone hypersecretion and an adenoma on CT does not exclude the presence of an associated vascular abnormality or intrasellar aneurysm, particularly in patients with acromegaly. Visual symptoms are seen when there is chiasmatic displacement greater than 8 mm above a line from the frontal base and posterior clinoid in the sagittal plane and 13 mm above the upper surface of both internal carotid arteries in the coronal plane. Magnetic resonance imaging is very helpful in defining the extent of cavernous sinus involvement, documenting the anatomical effects of medical treatment (bromocriptine, somatostatin), and for surgical planning. The interpretation of early postoperative scans can be difficult and are best left for 3 months unless early radiotherapy is contemplated.

Rathke cleft cysts and craniopharyngiomas probably have a common origin from Rathke’s pouch with occasional cases of ciliated craniopharyngiomas showing features of both. Rathke cleft cysts are mostly small and intrasellar and lined by a single layered cuboidal or columnar ciliated epithelium that may include goblet cells. Squamous metaplasia may transform the lining or the lining may degenerate. Occasionally larger cysts project beneath the optic chiasm. Such cysts are often asymptomatic but are increasingly recognised with the wider use of MRI. Small lesions should not be mistaken for microadenomas and the larger ones with suprasellar extension should be distinguished from craniopharyngiomas as the surgical approach may be different and postoperative radiotherapy is not necessary. Diagnostic features on MRI include a sellar epicentre, smooth contour, the absence of both calcification and enhancement, and, when present, an anteriorly displaced pituitary stalk. The MR signal intensities are typically reduced on T1 and increased on T2 though in more than half of the cases there is hyperintensity on T1 and varying signal on T2.

Cranioopharyngiomas are benign squamous epithelial neoplasms that are predominantly suprasellar but sometimes show an intrasellar extension. There are two histological patterns of craniopharyngioma, adamantinomatous and papillary. The first is composed of lace-like strands of stellate epithelial cells with a basal pallisade enclosing many cystic spaces. Degenerative changes are associated with the deposition of cholesterol crystals that confer an oily appearance to the cyst fluid. Masses of eosinophilic, necrotic, keratinised cells that accumulate within the epithelium often become heavily calcified and may dominate the histology of a small biopsy. The less common papillary craniopharyngiomas usually occur in adults and are formed by mature squamous epithelial cells encasing a fibrovascular core. This type does not calcify and only rarely involves the sella. In keeping with the varied histological constituents of craniopharyngiomas, the MR appearances are quite diverse. A prominent cystic component and varying signal intensities of the mixed cystic and solid components are typical features, occurring in nearly 80% of cases. Areas of homogeneous T1 hyperintensities and enhancement of solid as well as the thick wall of the cystic components are highly suggestive of the diagnosis (see fig 7D). Calcification is common especially in childhood tumours and is best demonstrated by CT. The pituitary gland can often be seen separately from the tumour especially by MRI. Suprasellar epidermoids are much rarer tumours but often cannot be radiologically differentiated.

Suprasellar and intrasellar meningiomas arise from the diaphragma, tuberculum, and the dorsum sella as well as the dura of the adjacent cavernous sinuses (see fig 7E). They are
isointense with the grey matter on T1 weighted images but invariably show homogeneous dense enhancement. Obtuse dural margins and dural tail enhancement, in 68% of lesions involving the sella, are helpful in the preoperative diagnosis although they are not specific.\textsuperscript{72} \textsuperscript{82} Adjacent hyperostosis, best seen on CT, is present in more than one third of cases and is a helpful sign.

Hypothalamic/optic gliomas in the paediatric age group and young adults are slowly growing, benign pilocytic astrocytomas. They are related to neurofibromatosis type I in at least 30% but invariably if there are bilateral optic nerve gliomas. In adults, hypothalamic gliomas tend to be more aggressive. The full extent of the lesion and invasion of the optic tracts, lateral geniculate bodies, and optic radiation can be readily assessed by MRI (see fig 4).

The table lists the many other lesions that may present in the sellar region which unfortunately do not have pathognomonic imaging characteristics (fig 8) even though their management may be different, reflecting, for example, the radiosensitivity of most germinomas\textsuperscript{83} and the disseminated nature of a metastasis. Finally, the development of specific radiolig-
ands suitable for positron emission tomography (PET) imaging may contribute to the functional diagnosis and localisation of pituitary lesions and their follow up.

**Management**

Management ranges from the conservative finding of “incidentalomas” through medical, surgical, and radiotherapeutic strategies depending on the tumour type, size, and invasiveness. The objectives of treatment include restoration of a feeling of wellbeing, relief of pressure symptoms, treatment of hormone excess symptoms, restoration of or substitution for specific system deficits, prevention of tumour regrowth, and reversal of increased long term mortality. Results between series can be compared only if the anatomical, neuropathological, and endocrine characteristics are specified. The definition of a “cure” depends on the specific lesion:

- Non-functioning tumours—no remnant on sequential MR scans; lack of enlargement of a known remnant after surgery and radiotherapy suggests that control has been achieved but longterm follow up is still required.
- Acromegaly—the criteria have become more stringent and now include a glucose suppressed growth hormone less than 2 ng/ml and normalisation of insulin-like growth factor (IGF-1).
- Cushing’s disease—reversal of hypercortisolaemia but care has to be taken with the interpretation of the results.
- Prolactinoma—correction of hyperprolactinaemia; maintained shrinkage of adenoma on sequential MR.
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**Grading systems**

Hardy’s original and robust classification was based on skull radiography and CT and for all practical purposes requires only minor modifications to create more elaborate systems:

1. Microadenoma less than 10 mm in diameter
2. Macroadenoma without suprasellar extension
3. Macroadenoma with suprasellar extension
4. Macroadenoma with localised destruction of the floor of the sella
5. Macroadenoma with diffuse invasion
6. Giant adenomas extending more than 40 mm above the planum sphenoidale or with multidirectional extensions.

Any grading system will be imperfect because no imaging modality can yet distinguish displacement of the cavernous sinus from invasion of the dura. Such invasion can occur even with a small, laterally placed microadenoma.
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Neuropathology and biological behaviour

The original classification of adenomas as acido-
phil (GH & prolactin), basophil (adrenocor-
ticotrophin (ACTH)) and chromophobe (pro-
lactin, non-secretory α-subunit) was based on
histological features determined by nature and density of the
cell type and cytoplasmic characteristics. The combined approaches
electron microscopy, immunocytochemistry,
and molecular biology have served to elucidate and characterise the plurihormonal nature of
many adenomas with expansion of their classi-
fication to include at least 16 different types.55
Molecular biological studies have shown that
pituitary adenomas are mostly monoclonal.
initiated by genomic mutation of a single
adenohypophyseal cell and stimulated to prolif-
erate by various hypothalamic, peripheral
endocrine, and paracrine factors. Individual
tumour cells often contain and may secrete more
than one active hormone, in addition to
fragments of various precursor molecules. For
example, many growth hormone adenomas
also contain prolactin and thyrotrophin and
many secrete the non-functioning α-subunit
that is common to all glycoprotein hormones as
confirmed by studies of primary monolayer
cultures of human anterior pituitary cells. Such
findings are important for advancing our under-
standing of the role of cell specific transcription factors such as PTF-1 in the
development of pituitary adenomas.88

Individual adenomas may show either a monomor-
phous or mixed cell population with variation in
fine structure and immunophenotype. Cyto-
plasmic granularity and positive immunostain-
ing indicate hormone synthesis and storage but
not necessarily release and hence there may be
poor correlation with serum concentrations of
the paramount hormones or their systemic
derived effects. Whereas macroadenomas
tend to be endocrinologically more inert, there
is emerging evidence of greater proliferative
activity and other differences from smaller but
systemically more active adenomas.89

Sparsely granulated tumours may be less well differen-
ciated and more aggressive than the densely
granulated adenoma as has been documented
in acromegaly. To complicate matters, the stem
cell chromophobe adenoma synthesises both
growth hormone and prolactin but, unlike the
common prolactinoma, does not respond to
dopamine agonists, and shows both oncotypic and more aggressive growth.59
An unusual growth hormone variant contains both
typical adenomatous cells and also clusters of
large, sometimes dysmorphic, neurons inter-
preted as gangliocytoma. The neurons
contain growth hormone releasing hormone and
support the hypothesis that hypothalamic
releasing hormones promote tumorigenesis in
the anterior pituitary.90

Cushing’s disease may be produced by a tiny microadenoma but
islands of hyperplasia may be seen—the
concept of endocrine cell hyperplasia preced-
ing neoplasia is fully accepted elsewhere, for
example, in thyroid C cell hyperplasia. There
are at least two other unusual ACTH adeno-
mas that are clinically silent, usually large, and
only established by immunostaining to synthe-
sise ACTH. One is a basophilic granulated
tumour that has a marked tendency to undergo
spontaneous haemorrhage and is a cause of
cerebellopontine angle lesion. The other is a chromo-
phobe adenoma showing only weak ACTH
immunoreactivity but stronger reactivity for
β-endorphin, which is also a derivative of the
ACTH precursor pro-opiomelanocortin.92

Thyrotrophinomas are the rarest of all adeno-
mas and only a few are hyperfunctioning.
Immunoassertion may reveal sparse thyrotrophs
in growth hormone adenomas. Both thyro-
thropinomas and prolactinomas may become
heavily calcified.93

Some 20%-30% of all adenomas are endo-
crinologically inactive and include the silent
ACTH adenomas, growth hormone tumours,
gonadotrophinomas, null cell adenomas, and
oncocytomas.94

Null cell tumours resemble chromophobe adenomas but show negligible
immunoreactivity or ultrastructural evidence
of hormone production. Oncocytic cells con-
tain abundant large mitochondria that impart
cytoplasmic granularity and eosinophilia which
could be mistaken for an acidophilic growth
hormone adenoma.95 Such tumours may
mimic prolactinomas clinically but prolactinoma-
emia is due to raised intrasellar pressure or stalk
compression.

Aggressive adenomas and carcinomas— micro-
scopical extracellular extension of pituitary
adenomas is common but these tumours tend
to displace brain, optic nerves/chiasm, and ves-
sors rather than invade them. Adenomas that
invade the sphenoid or cavernous sinuses can
be regarded as unduly aggressive and pituitary
carcinomas are defined by evidence of cranios-
phenial, or systemic metastases, or both. As with
other endocrine tumours, nuclear and cellular
pleomorphism alone are not reliable markers of
invasive potential, but frequent mitoses gener-
ally constitute an adverse prognostic sign. Vari-
ous cell proliferation markers, including prolif-
erating cell nuclear antigen, Ki-67 or MIB-1
staining for Ki-67 antigen have been employed
in attempts to predict the likelihood of recurrences. High proliferation indices tend to
correlate with more aggressive growth but
sampling error is a problem and presently, par-
ticularly in tiny biopsies, the results are not suf-
ficiently reliable to provide a clear prediction in
an individual case.96 The very rare pituitary
carcinomas are most often prolactinomas or
ACTH secreting tumours emerging in Nel-
som’s syndrome.97 Molecular biological studies
disclose multistep mechanisms of
tumorigenesis—for example, ras oncogene mu-
		nation and activation are uncommon in pri-
cary pituitary tumours but have been identi-
ifed in metastases.98 Proliferation indices and
p53 expression also tend to be higher in the
metastases.99

Medical management

Dopamine agonists are the first line of manage-
ment in patients with hyperprolactinemia— particular those with a microprolactinoma.
Cabergoline, a newer ergot based dopamine
agonist, is taken twice weekly as opposed to daily
with bromocriptine and is associated with fewer
side effects. Quinagolide is a non-ergot dopamine agonist which has been shown to be effective—particularly in bromocriptine resistant cases—but can be associated with neuropsychiatric side effects when administered in high dosage. Medical therapy is also the mainstay of management for most macroprolactinomas, but with careful coordination between endocrinologists and pituitary surgeons. Clearly, pituitary apoplexy into a macroprolactinoma is an indication for urgent trans-sphenoidal decompression, as bromocriptine can hardly be expected to shrink a haemorrhagic infarct. On the other hand, there is one case report of a third nerve palsy due to apoplexy, treated with bromocriptine to good effect and chiasmal compression secondary to prolactinomas is certainly reversible with medical therapy.99 Brain MRI indicates that a significant number of patients have small haemorrhages into the adenoma which are usually asymptomatic but may form the basis for subsequent fibrosis. There is evidence that bromocriptine treatment for 6–10 weeks increases the degree of fibrosis, leading to a greater surgical morbidity thereafter.100, 101 Therefore, early pituitary surgery should be considered in patients with visual or cranial nerve problems if there is either no improvement or an increase in tumour size despite maximal dopamine agonist therapy, or in the few patients who are intolerant or non-compliant with drug therapy.102

Trans-sphenoidal microsurgery (see later) is the primary therapeutic modality of choice in Cushing’s disease and specific medical management is very limited. It is useful to treat patients preoperatively with metyrapone, which blocks 11β-hydroxylase, to reduce the surgical morbidity resulting from the effects of high cortisol concentrations on tissue healing, blood pressure, and immunity.103 Metyrapone, ketoconazole (inhibits steroidogenesis), and mitotane (cytotoxic to adrenal cortical cells) cannot be used long term because of their side effects and centrally acting drugs (bromocriptine, cyproheptadine, sodium valproate) are seldom effective. Long-term cure rates of up to 80% are being reported after surgery,104 reflecting several improvements in management: firstly, inferior petrosal sinus sampling has proved particularly useful in making a firm preoperative diagnosis—particularly in difficult cases; secondly, recent studies indicate that an undetectable morning serum cortisol postoperatively correlates most closely with the likelihood of long-term cure. A non-suppressed postoperative cortisol (>150 nmol/l) may therefore be an indication for an early second exploration with more radical pituitary surgery. Ectopic adenomas in the suprasellar part of the pituitary stalk105 or multiple areas of corticotrophic hyperplasia may contribute to surgical failure. Failed pituitary surgery usually leads to local radiotherapy, particularly as corticotrophic adenomas may be radiosensitive and it is essential to protect against the development of Nelson’s syndrome. Radiation treatment takes many years to exert its effect, necessitating the use of bilateral adrenalectomy to achieve biochemical remission of Cushing’s disease in the interim. The recent advent of laparoscopic techniques for adrenalectomy may reduce the morbidity associated with this operation.

Trans-sphenoidal hypophysectomy is also the treatment of choice in acromegaly.106 The likelihood of a surgical response seems proportional to tumour mass and extrasellar spread, with a 70% cure rate for adenomas associated with circulating growth hormone concentrations of 100 mU/l but only a 40% cure rate with concentrations greater than 100 mU/l.107, 108 Once again, radiotherapy is used postoperatively when surgery has failed, but can take 10–20 years to achieve biochemical control. Moreover, it is now recognised that the increased growth hormone concentrations associated with active acromegaly are associated with considerable excess cardiorespiratory mortality and morbidity and possibly a risk of colonic neoplasia.109 Accordingly, medical therapy is used to reduce mean growth hormone to safe concentrations of less than 5 mU/l. A minority (10%) of acromegalic tumours, especially those that also secrete prolactin, respond to bromocriptine.110 For the remainder, octreotide (a somatostatin analogue),111 is administered by thrice daily injection, but newer highly effective fortnightly or monthly depot preparations are now available. Octreotide treatment can also be used preoperatively to shrink extrasellar tumour extension, but it is not known whether this improves the surgical outcome. Octreotide may also have a role as the primary long-term treatment modality, despite the risk of gall stones and the expense, in an older patient with mild acromegaly, a circumscribed tumour without local compression, perhaps with added factors (for example, cardiac failure) which constitute a poor operative risk. Finally, octreotide is also highly effective in controlling hyperthyroidism due to rare pituitary thyrotrophin secreting adenomas which have not been controlled surgically.

Although many of the non-functioning adenomas are derived from the gonadotroph lineage, they are generally unresponsive to medical therapies including dopamine agonists, growth hormone, and somatostatin analogues. In this context, radiotherapy plays an important part in arresting growth of the postoperative tumour remnant but this needs careful follow up with serial MRI as there are no circulating hormonal markers which can be measured to monitor residual tumour activity.108

Surgical management

Surgical approaches for “sellar” lesions have evolved since Sir Victor Horsley’s first craniotomy in 1889 and range from the straightforward transphenoidal operation to the complex multidisciplinary anterior skull base and transventricular/transcallosal approaches (fig 9). Subspecialisation is required if the patient is to be offered safe, appropriate treatment. Modern transphenoidal surgery, of which there are many excellent accounts,2, 111 is very safe, with a mortality in well trained hands of 0.2%-1% depending on the case mix, and is suitable for the great majority of pituitary tumours. It is also inexpensive when compared
with drug therapy. Transnasal, sublabial transseptal, and transethmoidal approaches each have their advocates—it is useful to be able to use each route in selected cases particularly for reoperations. Transnasal endoscopy has not yet been widely adopted except for repair of some CSF leaks. Refinements such as intraoperative hormone assays are not generally available.

Contraindications to the transphenoidal approach include dumb-bell tumours (tight diaphragma prevents access to the suprasellar extension from below), inaccessible extrasellar extensions (subfrontal, subtemporal, retrostellar—where a combined or staged approach is preferable—see later), and intrasellar vascular lesions including aneurysms and “kissing” carotids. With the use of an image intensifier and the awareness that this ensures safety only in the anteroposterior plane, it is possible and reasonably safe to drill through an incompletely pneumatised sphenoid air sinus. Chronic sinusitis and polyps should be rigorously dealt with by an ear, nose, and throat colleague before transphenoidal surgery. Particular care needs to be taken with reoperations especially if the first operation has been undertaken elsewhere and the midline anatomical landmarks have been removed, circumstances in which the information from preoperative CT with bone windows is useful.

Patients should be counselled that there is a small risk of infection of 1%-2% (meningitis; sinusitis; sepal or pituitary abscess) and that there is no evidence that prophylactic antibiotics are of any value except perhaps in patients with Cushing’s disease or recent sinusitis. Septal perforation, numb teeth, and a saddle nose are potential late complications but much less important than those of subfrontal retraction via a craniotomy. Significant haemorrhage is unusual (<1%). Damage to the internal carotid artery or rupture of an unsuspected intrasellar aneurysm can be readily controlled with a muscle pack. When intraoperative arterial injury is suspected, postoperative angiography is essential to forestall any delayed, life threatening epistaxis. The usual cerebrovascular techniques may be required including balloon occlusion, clipping or coiling of an aneurysm, and embolisation of a torn sphenopalatine artery. Arterial injuries should be avoided by introducing deamin-D-arginine vasopressin first at night. Patients should be counselled that there is a small risk of infection of 1%-2% (meningitis; sinusitis; sepal or pituitary abscess) and that there is no evidence that prophylactic antibiotics are of any value except perhaps in patients with Cushing’s disease or recent sinusitis. Septal perforation, numb teeth, and a saddle nose are potential late complications but much less important than those of subfrontal retraction via a craniotomy. Significant haemorrhage is unusual (<1%). Damage to the internal carotid artery or rupture of an unsuspected intrasellar aneurysm can be readily controlled with a muscle pack. When intraoperative arterial injury is suspected, postoperative angiography is essential to forestall any delayed, life threatening epistaxis. The usual cerebrovascular techniques may be required including balloon occlusion, clipping or coiling of an aneurysm, and embolisation of a torn sphenopalatine artery. Arterial injuries should be avoided by introducing deamin-D-arginine vasopressin first at night.

Delayed hyponatraemia may occur spontaneously up to 2 weeks postoperatively in about 2% of patients. The original concept was that this reflected release of antidiuretic hormone from degenerating posterior pituitary neurosecretory terminals (SIADH) or was the result of overenthusiastic cortisol withdrawal particularly in patients with Cushing’s disease whose receptors had become adjusted to a very high cortisol concentration. However, antidiuretic hormone concentrations may not be raised. Treatment is by mild fluid restriction and salt replacement. Patients should be warned that they may need second operations, long term follow up and long term hormone replacement as well as adjuvant therapy (for example, bromocriptine, somatostatin, radiotherapy). It is difficult to give a precise risk of postoperative hypopituitarism as it depends on the preoperative status and tumour type and morphology but an overall figure of up 10% is sensible. There is the potential for improvement in pituitary function in a minority of patients after transphenoidal decompression of non-functioning pituitary adenomas (16%-57% depending on the series and pituitary sector investigated). It would be unusual for there to be any deterioration in pituitary function after transphenoidal marsupialisation of an intrasellar cyst in a young person. By contrast, it would be intended that reoperation for refractory Cushing’s or Nelson’s disease would result in hypopituitarism.

In addition to trans-sphenoidal surgery, more complex tumours including craniopharyngiomas require various approaches (fig 9) that may carry very significant risks. The judgement and experience of a multidisciplinary team is invaluable. There is a temptation with multilobular suprasellar extensions...
of pituitary adenomas, for example, to chase every lobule via pterional, subfrontal, translaminar terminalis and subtemporal routes but the morbidity and mortality may be unacceptable to the patient. Great care has to be taken when dissecting around the chiasm. A more conservative transphenoidal decompression plus a restrained craniotomy followed by radiotherapy may achieve a much better quality of life for the patient even if the postoperative scans are less impressive. Lateral extensions invading the cavernous sinus and engulfing the carotid artery are seldom amenable to any surgical route and are the province of the radiotherapist.

**Current issues in radiotherapy treatment of pituitary tumours**

There is a consensus that radiotherapy should not be given routinely postoperatively and each patient must be considered individually. With the hypersecreting adenomas, there is a tumour marker to guide adjuvant therapy. With the “non-secretors” in which there has been complete tumour removal at operation as judged on postoperative imaging, detectable recurrence occurs in 16% but further therapy was only required in 6%. If a small residual tumour is seen on postoperative imaging, radiation may be withheld until a change indicating evident growth is seen or repeat surgery offered without radiotherapy. Postoperative imaging can be deceptive and not all residual tissue is a tumour remnant. Radiotherapy is useful for the very occasional patient who is too frail for surgery.

Radiotherapy has a very high therapeutic ratio, defined by the balance of tumour control rates which are very high, and normal tissue complication rates which are extremely low. For non-functioning adenomas, tumour control is defined as lack of progression of macroscopic disease. For hormone secreting adenomas, reduction of hormone production is also required. After radiotherapy, rates of freedom from progression are extremely high, and should be around 95% at 10 years, and 88% at 20 years. Secreting tumours fare marginally worse in some series, 89% versus 97% at 10 years and 69% versus 96% at 20 years, though others record equal control rates of over 90%. Survival rates are excellent, although there is a slightly increased relative risk of death in patients with pituitary tumours requiring radiotherapy.

Despite the excellent rates of tumour control, control of hormone secretion is poorer, with up to 20%-40% of patients failing to gain control of hypersecretion, even with protracted follow up. These rates of hormone control can be improved by a further 20% by the addition of medical treatment. The effects of radiotherapy on tumour hormone production may take several years to become maximal, so the timing of assessment of this end point must be chosen carefully. As hormone concentrations are reduced by about a first order reaction, the initial hormone concentration will in part determine the time required for normalisation, if control is achieved.

*Radiotherapy dose*

Doses of 45–50 Gy in 25–30 fractions are typical, well tolerated, and highly effective. The few studies which report results of a wider range of radiotherapy doses show a dose response, with lower rates of control associated with lower doses. The use of lower doses for patients with acromegaly has been investigated as a way to reduce the risk of pituitary insufficiency. A dose of 20 Gy in eight fractions seems to achieve relatively good control rates, though this has not been formally compared with conventional larger doses, and the long term outcome is not certain.

It is known that individual differences exist in normal tissue radiosensitivity in some tissues and it is very likely that this applies to the CNS also, but it is not yet possible to predict prospectively. Avoidance of damage to any patient thus requires the choice of dose which
LATE COMPLICATIONS

Visual impairment
In a series of 411 patients treated at the Royal Marsden Hospital with 45–50 Gy in 25–30 fractions, 305 patients had a detectable visual defect before treatment, and 55% improved after radiotherapy. Only two (0.5%) developed late deterioration of vision presumed to be due to radiotherapy, and both actually retained vision.124 In a large series from Princess Margaret Hospital in Toronto, out of 160 patients with non-functioning adenomas treated with a median dose of 45 Gy, there were no cases of visual damage, and of the 145 cases with secreting tumours treated with a median dose of 50 Gy one patient (who received 42.5 Gy in 22 fractions) developed deterioration in the vision of the left eye only.125, 126 Surgical exploration of this patient showed dense fibrotic tissue adherent to the left optic nerve and a postfixed chiasm, with herniation of the left optic nerve into the empty sella. This was considered to be due to the combined effects of surgery and radiotherapy,126 and gives an incidence of visual impairment of 0.3%.

Brain necrosis
Radiation necrosis has been described in patients having pituitary irradiation, but most cases occurred many decades ago, with what would now be considered poor techniques, often with low voltage machines (for example, 250–300 kV, rather than 6 MV typically used now), and with higher doses than currently prescribed.134 Provided the dose is 50 Gy or less, and the fraction size is 2 Gy or less, the risk of necrosis should be extremely small or absent.134, 135

Hypothalamic pituitary axis dysfunction is dependent on radiotherapy dose and also on dose per fraction
With clinical doses, failure occurs in many patients after pituitary radiotherapy, and is certainly dose dependent.136 As noted above, smaller doses (20 Gy in eight fractions) have been used to treat acromegaly,132 on the basis that the risk of dysfunction of the hypothalamic pituitary axis will be reduced and its onset delayed relative to "conventional" doses. This warrants further investigation in a clinical trial setting. It may be that a similar dose but given with a lower dose per fraction will further reduce the risk of hypothalamic pituitary axis insufficiency. As well as total dose, the dose per fraction has an additional effect,136 such that larger doses per fraction, especially doses over 2 Gy per fraction, produce a disproportionate effect on the axis. Even with dose fractionation schedules which relatively spare the axis, there is a high incidence of failure, which rises with time and probably has no plateau (fig 10), even beyond 15 years. Some 50%–70% of patients require replacement of gonadotrophins, glucocorticoids, and thyroxine.124, 125, 127 This high incidence is the product of initial tumour damage and surgery, as well as the effects of radiotherapy which probably accounts for 10%–20% of patients who develop it.125, 126 Associated with dysfunction of the hypothalamic pituitary axis

Complications of radiotherapy
Complications of radiotherapy can be divided into “acute”, occurring during or just after the course of radiotherapy, or “late”, occurring 6 months up to many years after treatment. Acute side effects are rarely serious and include a mild skin reaction, loss of temporal hair, and secretory otitis media, due to inflammation of the anterior part of the eustachian tube. This normally settles spontaneously but requires a myringotomy in 2%–3%.125, 126 However, it is the late complications which determine safe doses and define the therapeutic ratio.

Figure 10 Probability of hypothalamic-pituitary axis dysfunction after treatment for pituitary adenoma. A (redrawn from Latley et al124) shows data from 165 adults treated with radiotherapy doses of 37.5–42.5 Gy in 15–16 fractions with a median follow up of 4 years, which is relatively short. B (redrawn from Tsang et al125) shows data for 160 patients with a median follow up of 8.5 years. Radiotherapy doses were typically 45 Gy in 22–23 fractions for minimal residual disease (in 95), 50 Gy in 25 fractions for gross residual disease (in 41), and 40–42 Gy in 25 fractions for unspecified reasons. There are obvious differences between the two series which may reflect the different dose fractionation schedules used.

is safe for even the most sensitive patient. This variation in individual sensitivity is probably the major reason that higher doses have been given to some patients without inflicting damage.

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is hyperprolactinaemia, although this is usually not permanent or extreme.\textsuperscript{137} Also striking is the complete loss of growth hormone production by 5 years. It is virtually unknown for patients to develop diabetes insipidus as a result of radiotherapy for pituitary tumour.\textsuperscript{138} Hypopituitarism in adults does carry a slight survival disadvantage, which is not fully eliminated by replacement with cortisol, thyroxine, and sex hormones, and it is possible that growth hormone deficiency is a factor.\textsuperscript{139}

Vascular damage
Damage to the large vessels around the pituitary gland has not been noted with radiotherapy, but such damage at other sites is described, although typically with higher doses than standard pituitary treatment.\textsuperscript{140} Occlusion of one or both carotid arteries might have catastrophic consequences, and is one reason against the use of stereotactic radiosurgery for the initial treatment of large target volumes or for retreatment for tumours close to these large vessels.

Cognitive dysfunction
Impairment of memory and executive function has been found in patients with pituitary tumours. One recent study suggested that neither surgery nor radiotherapy alone affected cognitive function, but that combined treatment caused some dysfunction.\textsuperscript{142} However, other detailed psychometric studies suggest that pituitary radiotherapy does not lead to impairment of cognitive function.\textsuperscript{141, 142}

Risk of second tumour
Exposure to radiation, including therapeutic radiation, carries a small but significant risk of developing a second tumour, extending for at least two decades after exposure. In one series of 334 patients treated with conservative surgery and radiotherapy and followed up for a median of 11 years, a total of five second tumours occurred, although only three of these were malignant. This gives a cumulative risk of second tumour of 1.3\% in the first 10 years after radiotherapy and 1.9\% over 20 years.\textsuperscript{143} Summing the cases in the relevant literature, a total of 1510 patients followed up for an average of 10 years developed 13 new second tumours, giving an approximate incidence of 0.86\%.\textsuperscript{144-147} The absolute risk may in fact be slightly lower than this, as developments in radiotherapy techniques and equipment have almost certainly reduced the risk below these concentrations.\textsuperscript{146}

Newer developments in radiotherapy
STEREOTACTIC RADIOSURGERY
It is difficult to see how this technique could improve the outcome for pituitary tumours in most circumstances, especially as standard external beam radiotherapy gives such good results.\textsuperscript{152} Stereotactic radiosurgery is characterised by the use of a large dose of radiotherapy given as a single fraction and delivered with high accuracy. The use of a large single fraction may be effective against tumours. Indeed, the technique was originally developed as a method of giving a dose designed to cause necrosis of the target, and its therapeutic ratio is provided by the rapid drop from high to low dose (called the penumbra) which occurs over a distance of just a few millimetres, and which allows avoidance of critical structures. However, large single fractions are the antithesis of fractionated treatment and can be extremely damaging to normal tissues if they are inadvertently treated. Thus the technique, even with its high precision, is far from ideal for treatment in which the target has to include tumour extension onto or around the critical normal tissues. Relatively few patients with pituitary disease have tumours which are truly confined to the pituitary fossa without some encroachment laterally or superiorly. The optic nerves and chiasm, the nerves associated with the cavernous sinus, and possibly the carotid arteries, are highly susceptible to radiation damage, particularly when the dose per fraction is large, as in stereotactic radiosurgery. If a tumour abuts the optic chiasm, for example, it is possible to limit the dose at the edge of the tumour to safe levels, but this is at the expense of lowering the dose to part of the tumour. Thus, stereotactic radiosurgery is unlikely to improve tumour control over conventional radiotherapy.

Many patients with pituitary adenomas have apparently been successfully treated using stereotactic radiosurgery.\textsuperscript{149, 150} However, as yet there is no evidence that it produces superior results. Proton and heavy ion beams which can deliver relatively focused radiotherapy have also been employed, though likewise do not necessarily confer any particular advantage.\textsuperscript{150} Despite some enthusiastic reports, catastrophic damage has been described after stereotactic radiosurgery. Rocher et al.\textsuperscript{153} treated 135 patients with stereotactic radiosurgery, including 36 with pituitary adenomas. Over a short period of follow up, the rate of pituitary tumour control was comparable with conventional external beam radiotherapy. The complication rate, however, was excessive. Twelve patients (33\%) had serious visual complications, including two who developed bilateral blindness. These complications were directly attributable to the proximity of the tumour, and hence the high dose volume to the chiasm. This group has now abandoned the use of stereotactic radiosurgery for pituitary tumours.

CONFORMAL RADIOThERAPy
Conformal radiotherapy uses advanced radiotherapy treatment planning in three dimensions to achieve better conformation of treatment volume to target volume. This allows reduction in the volume of normal tissue irradiated around the target. Conventional dose fractionation is normally used with conformal radiotherapy. As conventional external beam radiotherapy is so safe and effective, conformal radiotherapy would not be considered necessary in most cases. However, it is likely that the indications will expand with time. It is possible that the technique might lower doses to the hypothalamus, although this requires formal evaluation. Conformal
radiotherapy is likely to have an advantage for treating children, by reducing cognitive dysfunc-
tion. Currently, its place may be in treating particularly extensive tumours, for retreatments, or for treating children.
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