# Diagnosis of pituitary disease

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Pituitary adenomas are relatively uncommon and slow growing. The onset of symptoms and signs is often insidious, particularly with non-functioning adenomas, so patients tend to present late and there is often a delay in diagnosis. A high index of suspicion is therefore essential.

## Background

**Pituitary development:** epithelial tissue in the oral ectoderm, situated in the roof of the primitive buccal cavity, thickens, invaginates and becomes pinched off to form a vesicle (Rathke's pouch) that develops into the anterior pituitary gland. The absence of mesenchyme between Rathke's pouch and the midline ventral diencephalon allows these two structures to approximate, and the subsequent interaction leads to the development of the downwards extension of neural tissue from the brain that becomes the infundibulum (stalk) and the posterior pituitary.

**Pituitary structure:** the anterior pituitary comprises five hormone-secreting cell types:

- somatotrophs, which synthesize, store and secrete growth hormone (GH)
- lactotrophs, which produce prolactin
- corticotrophs, which produce adrenocorticotrophic hormone (ACTH) and other fragments of the pro-opiomelanocortin molecule
- thyrotrophs, which produce thyroid-stimulating hormone (TSH)
- gonadotrophs, which produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Portal vessels in the stalk connect the hypothalamus and the median eminence with the pituitary, and transmit releasing and inhibiting hormones to the anterior pituitary gland, which they regulate. The hormones of the posterior pituitary gland (vasopressin and oxytocin) and their carrier protein neurophysin are synthesized in the supra-optic and paraventricular nuclei of the hypothalamus and transported along the stalk in unmyelinated nerve fibres, to be stored and then secreted from the posterior pituitary. Anatomically, the pituitary sits at the base of the brain close to some critically important structures (Figure 1).

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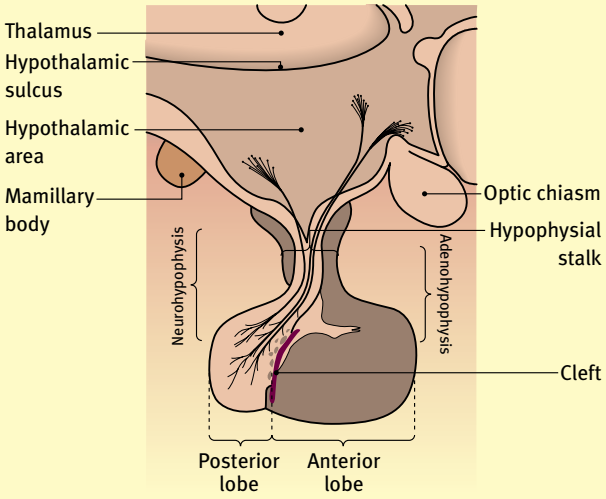
## Anatomy of the pituitary gland

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## Pituitary tumours

### Epidemiology

Pituitary tumours (Figure 2) are uncommon, accounting for about 10% of intracranial neoplasms, and have an annual incidence of about 25 per million population. They are generally benign, but up to 50% show histological evidence of capsule invasion. Less than 0.2% are malignant, with local spread into the CNS. The peak incidence is at age 30–60 years; presentation is earlier in women than in men.

### Aetiology

Rarely, ectopic hypothalamic releasing hormones induce pituitary disease; for example, GH-releasing hormone (GHRH) causes pituitary somatotroph hyperplasia, GH hypersecretion and acromegaly. It seems more likely that pituitary tumours arise as a result of abnormalities in the pituitary than in the hypothalamus. Characteristically, a pituitary adenoma is not associated with surrounding hyperplasia of the rest of the gland, lesions are usually solitary, and cure can be achieved with complete removal of the adenoma – all factors favouring a pituitary origin for the disease. Allelic X-chromosome inactivation analysis has shown that almost all pituitary adenomas are monoclonal in origin, supporting the view that the abnormality is in the pituitary and not the hypothalamus, and confirming that these tumours are true neoplasms, though characteristically benign in nature.

Research continues into identifying somatic mutations leading to neoplastic transformation in anterior pituitary gland cells. The best-studied examples of this phenomenon are the activating mutations of the alpha chain of the stimulatory G protein (Gsp), which links the somatotroph cell membrane GHRH receptor to adenylate cyclase and, by its activation, induces GH secretion. This Gsp-activating mutation has been identified in up to 40% of patients with somatotroph adenomas leading to acromegaly. Genetic predisposition to pituitary tumours can occur as part of familial multiple endocrine neoplasia type 1 (Figure 3).

## Pituitary adenomas

| Cell type | Prevalence (%) |
|---|---|
| • Lactotroph cell adenoma | 26 |
| • Null cell adenoma[1] | 17 |
| • Somatotroph adenoma | 14 |
| • Corticotroph adenoma[2] | 15 |
| • Plurihormonal cell adenoma[3] | 13 |
| • Oncocytoma[4] | 6 |
| • Gonadotroph cell adenoma | 8 |
| • Thyrotroph cell adenoma | 1 |

[1]No evidence of hormone excess; negative immunocytochemistry
[2]Can be functioning or non-functioning (silent)
[3]Particularly growth hormone and prolactin secreting
[4]Variant of null cell with marked mitochondrial accumulation

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## Pituitary hyperplasia

It is important to distinguish physiological and pathological hyperplasia of the pituitary gland from pituitary adenoma.

- Prolactin cell hyperplasia, which can lead to a doubling in size of the pituitary gland, occurs physiologically during pregnancy and lactation.
- In patients with long-standing primary hypothyroidism or primary gonadal failure, hyperplasia of TSH-producing cells or LH/FSH-producing cells, respectively, may result.
- GH cell hyperplasia may result from ectopic production of GHRH, though this is extremely rare.
- Up to 10% of patients with Cushing's disease have pituitary hyperplasia caused by ectopic production of corticotrophin-releasing factor.

## Multiple endocrine neoplasia type 1 and the pituitary

- Autosomal dominant disease
- *MEN1* gene
  - Tumour-suppressor gene
  - Mapped to long arm of chromosome 11
  - Mutations lead to altered menin protein
- Results in endocrine tumours (parathyroid, enteropancreatic tissue, anterior pituitary gland) and non-endocrine tumours (lipomas, angiofibromas, ependymomas)
- Pituitary adenoma cell type
  - Lactotroph – 62%
  - Somatotroph – 9%
  - Corticotroph – 4%
  - Mixed – 9%
  - Non-secretory – 13%
  - Gonadotroph – 3%
- Tumours may be aggressive (large and less responsive to treatment)

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