Chapter 21: Trans-sphenoidal hypophysectomy

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Operations on the pituitary gland are now nearly always for the removal of pituitary tumours. This form of pituitary surgery is not a complete hypophysectomy, as ideally the normal pituitary is not removed. However, the term 'hypophysectomy' is too widely used and accepted to suggest any redefinition.

Pituitary operations are performed 'from below', which is trans-sphenoidally, or 'from above', which involves a craniotomy. The sphenoid sinus has been approached in a variety of ways, but two have emerged as the most satisfactory. The transethmoid method is used by otolaryngologists; it has the advantage of a wider access and exposure, but the disadvantage of a facial scar. The sublabial trans-septal route is mostly used by neurosurgeons, and there are some centres where otolaryngologists and neurosurgeons operate together.

History

The leading text books of 100 years ago described the pituitary gland as surgically inaccessible. Horsley (1906) was the first to decompress, by the transcranial route, a pituitary tumour which was causing blindness, but did not record this in print for some years. The threat of blindness was then the indication for operation. A number of surgeons tried modifications of the transcranial route, both intradurally and extradurally. Schloffer (1906, 1907) for example made an external incision across the eyebrows and then down to join a lateral rhinotomy. However, these operations seriously damaged nasal function and produced unacceptable scars on the face. In 1909 Cushing started his sublabial trans-septal operation. At about the same time, Hirsch (1911a,b) described an operation through the nose which was later modified to become much the same as the Cushing operation. Cushing (1932) continued with a large series of 159 trans-septal operations and 88 transfrontal operations. The 5-year recurrence rate was 35% from below and 13% from above. He therefore returned mainly to the transfrontal route in 1928. His overall mortality was only 5.8%. His name stands out as a great pioneer of pituitary surgery.

Chiari performed the first transethmoid trans-sphenoid operation in 1912, and this approach was taken-up later, in the 1950s, by a number of otolaryngologists who were removing the pituitary gland as part of the treatment for carcinoma of the breast and prostate. Angell-James (1967a,b), Bateman (1962, 1963), Briant (1964, 1968) and Williams (1978) had large series of operations at that time and it was their experience that reintroduced the transethmoid operations for pituitary tumours. Other approaches from below, such as the transantral operation described by Hamberger et al (1959, 1960, 1961) and the transpalatal operation by Trible and Morse (1965) have not generally been continued.

Indications

Surgery was initially the only method of dealing with pituitary tumours. Later radiotherapy by external beam with X-rays (Jenkins, 1972) or protons (Kjellberg et al, 1968; Lawrence, 1963, 1973) and by implantation of radioactive gold or yttrium (Wright et al, 1970) became effective and safe. Both surgery and radiotherapy were at first non-selective, just
destructive. Microdissection to remove the neoplastic portions and leave the normal parts was introduced, and the idea had great promise. However, for reasons discussed later, this is not always so successful. Radiotherapy is not selective and does not completely destroy a tumour leaving the normal gland intact, especially in the case of well differentiated neoplasms, but it does have a useful and effective role to play sometimes. The effectiveness of a number of drugs on pituitary function has revolutionized the treatment of various pituitary tumours. It is now possible to block certain selected pituitary and hypothalamic secretions and to shrink large pituitary tumours medically. However, the management of pituitary tumours today still requires the use of surgery, radiotherapy, and medication. It should be for the endocrinologist to decide how best to treat each case.

**Removal of normal pituitary gland**

Hypophysectomy for carcinoma of the breast and prostate with secondary metastases is now only rarely indicated. Before effective chemotherapy it was certainly a worthwhile procedure, so long as the time interval between the original diagnosis and the appearance of secondary spread was more than 2 years and that these were in bone only. Those with liver disease did uniformly badly. Dramatic remissions were achieved in only two out of three patients operated on, even when these indications were right. This operation is still occasionally worthwhile, especially in carcinoma of the prostate with secondary tumours in the bone with pain, where it may be possible to obtain a remission of a year or two after all other treatments have been exhausted. Diabetic retinopathy, if at the proliferative stage, can be arrested by removing the pituitary; however, laser surgery has made this indication redundant. In theory there are other hormone-dependent tumours which might be affected by hypophysectomy, but this has not met with any success especially in the case of malignant melanoma.

**Pituitary tumours**

The indications for the removal of pituitary tumours may be for their local effects or for medical reasons. Locally, if a pituitary tumour enlarges upwards, it will result in bitemporal hemianopia and restriction of the visual fields leading to total blindness. There will of course be the intracranial pressure effects of headache and papilloedema. When these tumours extend laterally into the cavernous sinus they will affect the cranial nerves III, IV and VI. Large downward extensions may present in the nasopharynx and sometimes cause cerebrospinal fluid leaks and recurrent meningitis. It may be necessary therefore to decompress, if not completely remove, large pituitary tumours for their serious local effects.

**Medical indications for the removal of pituitary tumours**

**Acromegaly and gigantism**

If it is possible to remove the tumour completely by trans-sphenoid surgery, this is now the most effective treatment for acromegaly. There are large series reported by Hardy (1973, 1975, 1978, 1979) and Williams (1974, 1975) indicating nearly 80% cute, that is reduction of growth hormone to normal, by surgery. High energy radiotherapy and especially proton beam therapy are certainly partially effective treatments for tumours causing acromegaly. So far medical treatment for acromegaly has met with limited success. It is
sometimes possible to shrink these tumours and lower the growth hormone to a variable extent but the results of medical treatment are not predictable. Maybe in the future the medical treatment of acromegaly will become as effective as it is with prolactin-secreting tumours.

**Cushing's disease and Nelson's syndrome**

Cushing's syndrome may be caused by a pituitary tumour, adrenal tumour, ectopic ACTH-producing tumour, and the administration of steroids or certain other drugs. The diagnosis of the cause of Cushing's syndrome is not always straightforward. However, the endocrinologist may ask the surgeon to treat Cushing's syndrome by removing a pituitary tumour. These tumours may be microtumours not apparent on plain X-ray but showing on computerized tomography (CT) scans, or they may be large invasive tumours. Usually the tumour is small and provides the possibility of a successful microdissection with removal of the tumour and sparing the normal pituitary. Large invasive tumours are very difficult to cure surgically or in any other way. If an adrenalectomy has been performed for Cushing's syndrome primarily due to a small pituitary tumour, then some months or years later the pituitary tumour is liable to grow. The result is high adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH) levels with generalized pigmentation as well as the local problems associated with the development of the pituitary tumour - this is Nelson's syndrome (1958, 1960). The results of trans-sphenoid surgery for Cushing's disease can be highly satisfactory with a complete cure of a very serious medical condition. These patients may, however, be extremely unwell on first presentation and it may be advisable to block the production of cortisol medically for some weeks or months until the patient is fit for operation.

**Prolactinoma**

Before the discovery of prolactin, these tumours were included with chromophobe tumours and it was thought that they did not have any hormonal effects. Prolactin-secreting tumours as their name implies actually secrete the hormone directly in large quantities. However, any suprasellar tumour interfering with the control of prolactin can cause hyperprolactinaemia, but the prolactin level in this case is not as high as with a prolactin-secreting tumour. In women, hyperprolactinaemia mainly causes amenorrhoea and infertility, but sometimes galactorrhoea as well. In men, hyperprolactinaemia may cause impotence, gynaecomastia and skin changes. Before medical treatment for prolactinoma became so effective, surgery was widely used, especially in the USA and Canada. This is where microdissection first came into its own and pressure was put on the surgeon by the endocrinologist to remove the tumour to allow a woman to become pregnant, but not to remove all the normal pituitary. The results of microdissection were sometimes most satisfactory but they depended on the size of the adenoma. Hardy (1979) had a cure rate of 90% with non-invasive tumours of less than 10 mm size, dropping to zero for large invasive tumours. A microadenoma with a piece of normal pituitary attached, which was thought to have been completely removed is shown. However, with special staining it was possible to show that in other parts of this pituitary there were abnormal clumps of prolactin-secreting cells which could have grown into another microadenoma. Prolactin-secreting tumours are now generally treated medically and it is only when this medical treatment cannot be tolerated
by the patient that surgery is occasionally necessary. Even large tumours causing pressure effects will shrink with medical treatment.

**Chromophobe tumours (adenoma and germinoma) in children**

These tumours do not have any direct hormone effects but they may raise the prolactin level indirectly by pressure on the prolactin controlling mechanism. A germinoma is a rare pituitary tumour occurring in childhood and pituitary surgery is sometimes necessary to make the diagnosis so that the patient can then be treated with radiotherapy.

**Other pituitary tumours**

There are other rare pituitary tumours producing a mixture of hormones and these may have to be treated surgically.

**Craniopharyngioma and chordoma**

These tumours may occasionally require trans-sphenoid surgery.

**Contraindications**

It is not safe to proceed with trans-sphenoid hypophysectomy in the presence of nasal or sinus infection, and this should be cleared up first. The removal of a normal pituitary for secondary carcinomatosis of the breast or prostate is rarely indicated now, but is contraindicated if the time between the diagnosis of the primary lesion and the appearance of secondary deposits is less than 2 years. The liver may contain secondary deposits; if there is evidence of this clinically by jaundice, an enlarged liver, or biochemically, patients are not helped by hypophysectomy. The platelet count may be reduced by bone deposits, radiotherapy or chemotherapy and, if it is below 30 x 10⁹/litre troublesome bleeding can be expected. Although this may be overcome by platelet transfusions, it usually means that there will not be any worthwhile recovery. Partial pneumatization or non-pneumatization of the sphenoid is frequently quoted as contraindication to trans-sphenoid hypophysectomy. This is not the case. It is not difficult to pneumatize the sphenoid with a drill. The soft cancellous bone can be removed until the more compact wall of the sphenoid is encountered. Once the shape of the pituitary fossa has been identified the operation can proceed normally. Upward extensions of more than a few millimetres anteriorly or 1 cm posteriorly are not accessible from below, and this is usually a contraindication to a trans-sphenoid operation. The exception is a dumbbell tumour, needing surgery from below and above. It has been found better to stage these operation, starting trans-sphenoidally.

**Preoperative investigations**

**Medical**

Medical investigations include measuring all pituitary hormone levels and often an oral or intravenous glucose tolerance test with measurements of serum growth hormone and insulin levels, as well as blood sugars. These tests are usually arranged by the referring endocrinologist.
**Surgical**

A full blood count is necessary, including platelets, if there is any question of bone marrow disease or toxicity. Serum electrolytes are also required, because in some conditions, such as Cushing's disease, the potassium levels may be dangerously low for general anaesthesia. Liver function tests are indicated in patients with secondary carcinomatosis. It is safer to have two units of blood cross-matched.

Although blood transfusion is hardly ever required, it may be vital if there is serious bleeding from the cavernous sinus or carotid artery.

**Imaging**

Routine skull X-rays will show the outline of the pituitary fossa, the pneumatization of the sphenoid, and the size of the frontal sinuses. Sinus X-rays should also be taken to exclude infection. For pituitary tumours it is necessary to show the outline of the upper part of the gland, and the first method for doing this was by an air encephalogram. However, this investigation was not entirely without risk and has now been completely abandoned in favour of CT scans. High quality CT scans with sagittal reconstructions show the whole pituitary gland very satisfactorily. The degree of upward extension is important when deciding whether trans-sphenoid surgery is appropriate and an empty sella with the dura dipping right down into a large fossa is easily seen on a CT scan. A microadenoma of the gland can also be identified. Hardy (1979) has shown that growth-hormone-secreting tumours are more often in the lateral parts of the fossa inferiorly; prolactin-secreting tumours in the lateral part of the gland superiorly; and ACTH-secreting tumours more often central. The author has not found that this can be relied upon. Neurosurgeons prefer to have arteriography of the internal carotid arteries to show their position. There is certainly one occasion where this can be most informative, and that is if a tumour has been treated medically and has apparently regressed. The carotid arteries can then move towards the midline and the space between them may be only a few millimetres, with the residual tumour below. Although the carotid arteries can be identified positively during surgery it is helpful to know where to expect to find them.

**Visual fields**

Visual field defects begin to appear when the tumour extends upwards to the optic chiasma; this is an important sign as it usually means the trans-sphenoid operation is not indicated and that surgery is better performed from above. It is good practice to have visual fields routinely recorded and to compare them with any subsequent tests, in case for example there is a recurrence of the tumour.

**Drugs**

Adequate doses of steroids must be given to cover the operation and the postoperative period. For example a basic regimen of steroid cover would be: prednisolone 2 mg hourly intravenously for 24 hours and then prednisone orally 15 mg per day for 5 days, gradually reducing to a maintenance level over the next 2 weeks. However, the details of how this steroid cover is arranged are not critical. Experience has shown that if trans-sphenoid surgery is covered by prophylactic antibiotics, infection is extremely rare. A pack will normally be
left in the nose for about 9 days and to prevent infection the combination of a broad-spectrum antibiotic and an antibiotic which diffuses easily into the cerebrospinal fluid is effective. These antibiotics should be continued until the pack is removed. Desmopressin (DDAVP) should be available for the first few postoperative days to treat diabetes insipidus. Water intoxication is however more dangerous than diabetes insipidus, so this drug should only be given when necessary. When the specific gravity of the urine is low and the urinary output exceeds 500 mL/h for 3 consecutive hours, this is a reasonable indication for the injection of desmopressin 2 microg. Also, a total output of more than 5 litres in 24 hours may indicate that the diabetes insipidus should be treated. Some patients may have been told that they may become thirsty and because of this they drink so much that they can simulate a diabetes insipidus.

**Anaesthesia**

Intubation during anaesthesia may be difficult because of the large tongue in patients with acromegaly, and large laryngoscopes and long endotracheal tubes should be available. Whether the ventilation is spontaneous or controlled is for the anaesthetist to decide, providing that the venous pressure can be kept low. Air embolism does not seem to be a problem because under direct vision it is possible to see if blood is coming from the cavernous sinus or if air is entering it, and the ventilation pressure can be adjusted accordingly. In the author's experience it is not necessary to monitor the neck veins with Doppler probes for air embolism. Hypotension can be most helpful during the dissection of the pituitary. However, in the early stages of the operation it is better to have a normal blood pressure so that all the superficial bleeding can be thoroughly controlled to avoid a subcutaneous haematoma.

**The operation**

**Tranethmoid approach**

The operating table is tipped about 25° head-up, and the neck slightly flexed to face the surgeon who stands on the right hand side of the patient. It may be necessary to perform a submucous resection of the nasal septum for access to the right side of the nose. An external incision is made, curved round the medial side of the orbit. The incision is deepened towards the nose medially, so that the lacrimal sac is avoided. Superiorly the supratrochlear nerve is also avoided by straightening the upper 1 cm of the incision. The incision is deepened to the bone by dividing the periosteum, which is then separated from the bone and dissected back past the orbital rim until the anterior ethmoidal artery is exposed. This artery runs through the frontoethmoidal suture and represents the upper limit of the roof of the ethmoids. The artery is sealed above and below by diathermy and is divided; there is usually no bleeding but there may be a small extravasation of fat. The dissection continues to the posterior ethmoidal artery which is left as a landmark. The lacrimal sac is lifted out of its groove and mobilized to avoid tension, when the retractor is inserted. A Luongo retractor is then placed in position. The paper plate of the ethmoid is removed up to the anterior ethmoidal artery and if necessary back as far as the posterior ethmoidal artery; the orbital rim is taken away with a drill or gouge. The frontonasal duct must not be opened widely in acromegalic patients for the soft tissues may later prolapse and obstruct the duct. This removal continues downwards as far as the posterior edge of the lacrimal fossa. A complete
external ethmoidectomy is performed. It is convenient to use forceps either through the external opening or through the nose lateral to the middle turbinate. It is not necessary to remove the middle turbinate unless a wide access is required for the larger tumours, when this step is indicated. The sphenoid sinus is opened through the posterior ethmoid cell and usually the right sphenoid is entered first. The position of the intersphenoid septum can be seen on the submentovertical X-ray of the skull, and it is nearly always necessary to remove this septum. The opening into the sphenoid sinus is widened and the rostrum of the vomer is removed either with back biting Ostrum's forceps or a drill, until full exposure of the front of the pituitary fossa is achieved.

Trans-septal approach (Cushing's)

A gingival incision is made. The peristomeum is elevated with the mucosa to expose the mucosa of the pyriform opening and floor of the nose. The dissection is continued to the front of the nasal septum. Firm retraction is needed to elevate the upper lip and tip of the nose, using small right-angled retractors. The mucosa is separated from the floor of the nose, to both sides and from the nasal septal cartilage. The bony opening of the front of the nose is thus exposed, and can then be enlarged inferolaterally with a bone punch or drill. This is not always necessary, and may cause temporary or occasionally permanent denervation of the incisor teeth. A submucous resection of the nasal septum is then performed, holding the flaps apart with a large Killian's speculum. A Hardy bivalve speculum is inserted. The anterior wall of the sphenoid sinus is opened with a gouge or drill and removed laterally as far as possible. The pituitary fossa is not identified as easily from this angle as from the ethmoids, especially if the pneumatization is not full. From this point the operation is the same whichever approach is used, except that with the transethmoid approach straight instruments can be used, but with the sublabial approach angled instruments are better. This is because the microscope view and all instrumentation are through the same relatively small opening trans-septally.

Opening the pituitary fossa and dissection

A Zeiss operating microscope with a 300 mm objective lens is positioned, viewing through the external incision where a transethmoid approach has been used. The bone over the pituitary fossa is drilled away using a small cutting burr and this does not damage the dura. A layer of bone is removed extending above to the top of the sphenoid sinus, sideways until the bone thickens, and the full width of the fossa is reached, and downwards to the floor. The floor is not removed, as this is needed to support the muscle plug at the end of the operation. Large tumours often erode through the bone and sometimes through the dura presenting in the sphenoid sinus. At this stage the front of the pituitary fossa may be seen as a pulsating sheet of dura. The carotid arteries are occasionally exposed laterally and can be identified by their thicker appearance. The cavernous and intercavernous sinuses can usually be seen through the dura and the incision made to avoid them. Bleeding from the cavernous sinuses can be a problem but is lessened by good anaesthetic technique and adequate head-up position. The author has never found it necessary to abandon an operation because of bleeding. The venous sinuses are less obvious with expanding tumours than with small normal-sized pituitary glands. If there is an almost 'empty sella', care must be taken to enter the gland or tumour and not the subarachnoid space. If possible a cruciate incision is made, but if there is insufficient space between the superior and inferior intercavernous sinuses, a
transverse incision is adequate. A diathermy incision helps to seal the two layers of dura, but some surgeons prefer a knife.

When the gland is opened a tumour will extrude whereas a normal-sized gland just presents itself. Angell-James dissectors are especially shaped to separate the floor and sides of a normal gland and are useful for microdissection. Where a large tumour is present the normal pituitary is not easy to find, and probably enough of it resides in the diaphragm where the stalk emerges. It is best therefore to remove all the tumour that can be found but not to clean the diaphragm too thoroughly, if tumour does not appear to be attached to it. Where there is some upward extension, and when the tumour has been decompressed the diaphragm may well come down into view. Downward extensions can be followed easily and removed; they may even extend out into the basisphenoid and occiput, and can be drilled away under direct vision. Lateral extensions are more difficult and it is often not possible to see completely the lateral extent of a tumour. Dissection therefore has to be blind. For this situation Hardy curettes are useful but great care has to be taken not to curette too firmly out of sight, or serious bleeding can result. For microtumours, microdissection is often possible. This involves removing the tumour and leaving an adequate quantity of normal pituitary gland behind. The tumour can usually be identified as a separate adenoma appearing different from the normal gland. Experience is required to be confident about this identification but the tumour may be whiter and of a softer consistency. A plane of cleavage may appear, but it is advisable to take some adjacent normal pituitary for it has been shown histologically that, if a cleavage plane is followed, some tumour may be left behind. If there is doubt in identifying the tumour from the normal gland small pieces may be sent for frozen section. Cerebrospinal fluid will escape if the diaphragm is breached. This can be sucked away until pressure is lowered so the flow will then stop, and the operation can proceed.

Insertion of a piece of muscle into the fossa stops bleeding and escape of cerebrospinal fluid. It also supports the diaphragm and prevents postoperative headache due to stretching. This muscle should be placed in the fossa lightly rather than packed lightly. A large plug may extrude. The muscle can then be covered with Sterispon to prevent adherence of the pack. A 1.25 cm (half-inch) ribbon gauze pack is inserted into the sphenoid sinus, coming out through the right side of the nose. More packing should be placed in the nose to keep the sphenoid pack in position. The sphenoid pack stays in for 9 days but the nasal packs can be removed sooner especially with a Cushing's approach, depending on the stability of the sphenoid pack. With the transethmoidal operation the pack should fill the ethmoid and not bulge into the orbit. Only the skin requires suturing. Padding and bandaging the eye for 12 hours helps to reduce postoperative swelling, but care must be taken not to apply the bandages too tightly and compress the eye.

Postoperative care

The patient's temperature often rises during the first 12 hours but this does not necessarily indicate infection and it is probably due to some hypothalamic disturbance. From the second to about the eighth postoperative day the temperature is often subnormal for the same reason. After the nasal packs are removed on the ninth day the treatment is the same as for any other intranasal operation. It is sometimes necessary to remove crusts from the nose, but with saline nose sniffs for 2 or 3 weeks the nose usually becomes clean and healed. Looking into the nose the pulsations of the pituitary may be seen for up to one month
postoperatively. Medically, steroids ought to be continued until the normal pituitary function has been tested, usually about 6 weeks after operation. The preoperative tests are repeated to assess the effect of the operation and whether it is necessary to continue with steroids and/or thyroxine. After surgery for large pituitary tumours about 25% of patients may have some pituitary hormone deficit and require replacement therapy.

Complications

Some patients develop a superficial haematoma or black eye but this is outside the orbital periosteum. It may look alarming for a few days but usually settles within 5 days. If the eye becomes completely closed it is important to test the vision and eye movements to exclude excessive intraorbital pressure. Temporary diabetes insipidus occurs in up to one-third of patients. Cerebrospinal fluid leaks are rare but if they occur following removal of the nasal packs the treatment should be conservative, with the continuation of the antibiotics. The leakage usually settles within 3 weeks. Only if the muscle pack has come out completely would it be necessary to take the patient back to the operating theatre and insert another muscle plug. In the author’s experience this has only occurred once in over 300 tumours operated on and the reason was that the patient decided to restore himself to his normal health. It was on the fiftieth press-up on the tenth postoperative day that the cerebrospinal fluid started to leak. This was followed by meningitis. No other case of meningitis has been encountered in this series and it is generally a very rare complication. Frontal sinusitis occurs especially in acromegalic patients if the frontonasal duct has been opened too widely. With proper operative technique this should be avoided but if it does occur, an operation some months or years later to reopen the frontonasal duct may be necessary. In experienced hands the mortality of this operation is less than 1%.

Conclusion

Trans-sphenoid pituitary surgery is a most effective way of treating some pituitary tumours which extend downwards into the sphenoid sinus. Neurosurgeons usually approach the sphenoid via the nasal septum, but otolaryngologists use an external ethmoidectomy approach. CT scans have made it possible to localize microtumours which can often be dissected leaving the normal pituitary intact. The overall management of pituitary tumours should be by an endocrinologist, with a surgeon who can operate trans-sphenoidally, a neurosurgeon and a radiotherapist. The treatment of pituitary tumours should be restricted to centers where these specialists are available.