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Treatment of Pituitary Tumors

History

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Over the past century our understanding of the pituitary disease has undergone an amazing evolution, accompanied by impressive advances in the therapeutic approaches to pituitary tumors. This historical review aims to provide insights into the contributions of key medical and scientific pioneers, their occasionally serendipitous discoveries, and the lively global debates, which have ultimately improved the therapeutic targets and the long-term outcome of these patients. The development of the three main modalities is discussed (surgery, irradiation, pharmacotherapy). More recent experimental data, which may provide a path to a stronger therapeutic armamentarium for these undoubtedly challenging tumors, are also briefly reported.

Key Words: Pituitary tumors; treatment; history.

Introduction

Diseases are usually described long before their pathological basis is understood and therefore, before rational treatment can be contemplated. This is particularly the case in pituitary disease. Since 1886, when Professor Pierre Marie described acromegaly and its association with pituitary tumors *(1)*, our insight into the dysfunction of the "master gland" has significantly expanded, accompanied by a similar enrichment of our therapeutic armamentarium. This review aims to describe the evolution of the three main therapeutic modalities for pituitary tumors (surgery, irradiation, and drugs) and the important contributors.

Surgical Management

Since the first attempts to operate on the hypophysis over a century ago, pituitary surgery has undergone an amazing evolution allowing the improvement of the therapeutic targets; initially the goal was to find a route of access to the sellar region and perform life-saving decompression, later it was to remove as much tumor as possible for prevention of recurrence. It is only recently that safe, complete tumor resection and preservation of pituitary function have been achievable targets.

Marie's landmark paper on acromegaly sparked the beginning of neuroendocrine physiology and resulted in the development of various surgical approaches to the pituitary gland *(2)*. In 1889 Sir Victor Horsley undertook the first successful attempt to expose a pituitary adenoma via temporal craniotomy, but he did not report this major achievement until 1906 *(3)*. The first published surgical intervention was in 1893 by F. T. Paul, honorary surgeon at the Royal Infirmary in Liverpool. Paul with the encouragement of Horsley, performed a temporal decompression on a 33-yr-old female with acromegaly and features of raised intracranial pressure *(4)*. Removal of the pituitary tumor was not attempted and the wound never healed. However, the patient reportedly benefited from decompression of the cranium, and the remaining 3 mo of her life were "comparatively comfortable." Over the next 20 yr Horsley treated at least 10 patients with pituitary tumors using craniotomy techniques *(5)*. In some cases he attempted to remove the pituitary tumor, not just to perform decompression. He reported only two deaths, neither of which was apparently due to the operation. Horsley's patients presented at advanced stages in their disease; he vigorously advocated early surgical treatment, especially due to the lack of other alternatives. In 1904 F. Krause in Berlin used the first frontal transcranial approach to reach the sella tursica in a living patient *(2)*. Four years earlier he had used the same approach to remove a bullet lodged near the right optic canal, fired by a 22-yr-old man intending suicide; he realized then that this would be a useful method for resection of pituitary adenomas *(6)*. This provided the basis for the majority of subsequent variations on transcranial pituitary surgery by Heuer, Dandy, and Frazier *(7)*.

Craniotomy was initially afflicted with unacceptably high morbidity and mortality (ranging from 50% to 80%), making surgeons seek safer extradural approaches to the sella tursica. After preliminary work in cadavers by several surgeons, in 1907 Professor Hermann Schoffler (Innsbruck, Austria) performed the first transnasal transsphenoidal partial removal of a pituitary tumor using a blunt spatula *(8)*. His patient, a 30-yr-old male, presented with headaches and

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visual compromise due to a massive tumor. Unfortunately, he died 10 wk later from hydrocephalus due to obstruction at the level of the foramen of Monro by a large intra- and suprasellar tumor. Illumination of the operative field and visualization of structures of the sellar region was limited during this procedure. Furthermore, the poor existing preoperative examinations (skull X-rays and neurological examination) had not suggested such a large tumor making Schoffler state that "the selection of the right cases for surgery is of primary importance for further development of the surgical technique" *(9)*. In addition, complications such as meningitis and unsatisfactory cosmesis, prompted further modifications on the transnasal approach subsequently performed by von Eiselberg, Hochenegg, and Kocher *(7)*. The Viennese rhinologist Oscar Hirsch, another key pioneer in the transsphenoidal approach to the sella, introduced endonasal pituitary surgery in 1910 *(8)*. His first exposure to the sella was via the nasal cavity, and this was later changed to the transseptal technique, in order to work in a clean area *(9)*. Inferior nasal approaches avoiding externally visible excisions were soon developed and in Chicago Allen Kanavel and Albert Halstead devised first an infranasal and then a gingival approach *(8)*.

Harvey Cushing the well-known neurosurgeon from Boston, whose pioneering work within the field of pituitary surgery started in the early 1900s, initially performed eight subtemporal and five subfrontal approaches *(10)*. The results were disappointing and based on the work of his mentor Halstead, he adopted the alternative transsphenoidal approach. In Baltimore, he performed his first transsphenoidal operation using Scholffer's procedure on a 35-yr-old acromegalic farmer on March 26, 1909 *(11)*. He combined methods of several other surgeons adopting the sublabial incision, submucous paraseptal preparation to the sphenoid sinus, and use of a nasal bivalved speculae (self-designed) and of an electrical forehead lamp. He also stood behind the patient's head, which was slightly reclined from the supine position. This procedure known as the "Cushing's approach" to sellar lesions is essentially the same as the one followed by neurosurgeons worldwide today. Interestingly, Hirsch and Cushing first performed their submucous septal resection on the same day, June 4, 1910. The transsphenoidal approach was initially embraced and modified. However, despite Hirsch's and Cushing's initial impressive results, most surgeons abandoned it, due to poor visualization, high recurrence rates, and improvements in the alternative option of transcranial surgery. By 1927 even Cushing abandoned it after performing at least 200 operations with a mortality rate of 5.6% *(8,12)*. Over this period he had seen many patients with suprasellar tumors (commonly meningiomas and craniopharyngiomas), indistinguishable prior to surgery from large chromophobe pituitary adenomas; he reasoned that the transfrontal approach allowed confirmation of suprasellar tumors and a more extensive resection. Furthermore, a number of patients previously operated transsphenoidally returned with recurrence of their symptoms; repeated operation via the same route was considered difficult *(9)*. Therefore, in the later years of his active neurosurgical life, Cushing almost exclusively used the transfrontal route. Nearly all his pupils followed his example leading to a dramatic decline of the transsphenoidal operations for the pituitary gland over the next 25 yr. A few surgeons (Hirsch in Boston, James in London, Hamberger in Stockholm) continued to advocate the transsphenoidal method *(9)*. In fact, Hirsch promoted its benefits until his death in 1965, but he remained an "obscure voice in the wilderness" *(13)*.

The re-introduction of the "Cushing procedure" occurred largely due to Professor Norman Dott (Edinburgh); he had been awarded a Rockefeller fellowship and trained under Cushing for 1 yr in the mid-1920s. During this period he grew to appreciate the merits of the transsphenoidal technique and he continued to use it where appropriate *(13)*. He operated on more than 100 pituitary adenomas without mortality (probably partially attributable to the introduction of steroid replacement and antibiotics in the 1950s) and without recurrence (due to post-operative radiotherapy) *(9, 14)*. In 1956 Dott introduced Professor G. Guiot (a Parisian surgeon training with him in Edinburgh) to this method. Interestingly, Guiot suspected that Dott never reported his favorable results out of posthumous deference to his teacher Cushing *(9)*. The following year Guiot started performing this technique and eventually operated on over 1000 patients with pituitary adenomas *(7)*. He also refined the method by using X-ray image intensification and introducing the semi-sitting position. He later concluded that "in the evolution of surgical techniques the introduction of the transcranial approach was progress, however then abandoning the transnasal approach, as a matter of fact, has been a step backwards" *(9)*. Dr. J. Hardy, a pupil of Guiot, operated on several thousand patients in Canada using the transsphenoidal approach. By 1962 he introduced intraoperative fluoroscopy allowing the precise definition of the position of the operative field. By 1965 he adopted preoperative routine angiography, as well as intraoperative televised fluoroscopy and air encephalography. He first used the operating microscope for total hypophysectomy in 1965. No deaths or serious complications occurred in the first 50 patients, and CSF leakage was prevented by sealing the floor of the sella with a graft of cartilage or bone from the nasal septum. The introduction of fluoroscopy and microscopy effectively ended the debate on how to maximally expose the gland with the least morbidity. Hardy also introduced microadenomectomy for lesions invisible radiologically, made possible by the vastly improved illumination. In 1969 he reported pituitary exploration in three patients with acromegaly and one with Cushing's disease *(15)*. In each case the fossa appeared normal, but Hardy found and removed a microadenoma with apparent benefit.

The advances in neuroimaging techniques (CT since mid-1970s and MRI since early-1980s) offering accurate information on the localization and extensions of the pituitary tumors had a substantial impact on the success rates achieved by neurosurgical hands. More recently, the intraoperative MRI allowing performance of operations interactively by real-time MRI guidance has also provided promising benefits *(16)*.

The evolution of surgical therapy continues with the arrival of the endoscope-assisted microneurosurgery, a method providing panoramic visualization of the anatomical structures through a wide angle of view, as well as safer approach to parasellar lesions *(16)*. Guiot in 1963 was the first to report the use of an endoscope inserted into the sphenoidal sinus during sublabial transsphenoidal surgery aiming to improve the limited visualization capability in the surgical field *(17)*. Gamea et al. in 1994 reported its benefits as an adjuvant tool during their microscopic transsphenoidal operations and Jankowski et al. in 1992 described the first endoscopic pituitary surgery *(17)*; in the following years various techniques were developed and many pituitary surgeons adopted this promising modality either as a supplement for visualization or even without the operative microscope *(17)*.

The evolution of pituitary surgery is undoubtedly fascinating. Although often associated with polarization of opinions and lively discussions on the indications, merits, and pitfalls of each method, surgical intervention remains the treatment of choice for most pituitary tumors (benign or malignant).

Irradiation

Radiotherapy has a long track record for the treatment of pituitary tumors. Conventional external beam irradiation was first described in acromegalic patients independently by two French physicians in 1909—Gramegna and Beclere *(2,18)*. Gramegna reported a 45-yr-old acromegalic woman with severe headaches and rapid loss of vision. His equipment included an early Crookes tube with a tube voltage below 80 kV. The applicator was a long glass cylinder used intraorally and directed at the pituitary. The total dose to the pituitary gland did not exceed 200 roentgens offered in twice weekly sessions of 1 h for 4 wk. The patient had clinical improvement but symptoms recurred 1 yr later and were relieved by a further course of treatment; further recurrence 3 mo later did not respond to treatment *(18)*. Beclere treated a 16-yr-old female with gigantism complaining of violent headaches, dizziness, and vomiting; he used a five-field technique, enhanced the dose at depth by increasing the tube–skin distance, and hardened the beam by interposing a thin aluminum sheet *(18)*. He reported "the séances have been carried out once a week for ten weeks. At each séance the hypophysis was treated by cross fire through four or five different areas on the frontotemporal region, the skin dose on each being 3H. The attacks of cephalagia have completely disappeared. Still important is the improvement in visual troubles" *(19)*. The patient remained well 13 yr after treatment *(18)*.

Following this promising start the world literature over the next two decades carried numerous reports confirming the value of radiotherapy in the treatment of pituitary tumors. In 1925 Harvey Cushing published the first results of radiation therapy for a variety of intracranial lesions including pituitary tumors in substantial numbers of patients *(20)*. He concluded that given the difficulty of achieving surgical cure, "radiotherapy should often be employed as a supplementary measure." Four years earlier he pointed out that "it is not impossible that some form of therapeutic radiation may prove so effective as to take the matter entirely out of the surgeons' hands" *(18)*. However, within the following two decades his attitude toward radiation therapy became more ambivalent; instead he adopted more aggressive surgery by the transcranial–frontal approach. In 1939 Henderson reviewed Cushing's series and analyzed the outcome of 338 patients with pituitary tumors treated over the period 1913–1932 *(18,21)*. He conclusively showed that postoperative radiotherapy significantly reduced the incidence of recurrence, which came as a surprise to both Henderson and Cushing, influencing thinking on this issue on the European continent *(18)*. The use of radiation therapy for the treatment of patients with brain tumors was limited by the technology of the day; the available equipment was capable of delivering X-rays with energies in kiloelectron volts (keV) (orthovoltage radiation) resulting in high radiation doses to superficial tissues and significant local side effects. With the advance in physics in the 1950s, megavoltage equipment became available delivering X-rays in the million electron volt (MeV) range and producing ionization at a much greater depth. During the following years further advances in the delivery and treatment planning techniques using MRI improved the therapeutic ratio and reduced the radiation toxicity, rendering this modality particularly useful as adjuvant treatment after incomplete surgical excision.

The relatively low energy of the initially used orthovoltage devices encouraged the use of brachytherapy (i.e., implantation of radioactive isotopes) in patients with brain tumors *(20)*. Notably, two pioneers of hypophyseal surgery —Horsley and Hirsch—provided the groundwork for the development of stereotaxic methods. In 1908 Horsley, with the engineer Richard Clark, first proposed the system of stereotaxic localization within the brain using a rigid reference framework fixed to the skull *(22)*. In 1921 Hirsch in an attempt to reduce the size of the residual tumor, used a rudimentary device attached to the teeth holding a radium capsule within the sphenoidal sinus under the sella tursica; between 1910 and 1956 a total of 413 patients were treated with the combination of the transseptal approach and local

application of radiation *(13)*. Between 1917 and 1932 Cushing treated 12 cases by application of radium to the roof of the nasopharynx; 9 as part of their initial treatment following the transsphenoidal surgery and 3 for late recurrence *(18,19)*. The method was effective but there were four deaths from infection and necrosis of the bone, leading to its discontinuation *(18)*. In the 1950s various stereotactic procedures were developed to insert radioactive isotopes into the pituitary fossa for the destruction of the normal gland aiming for the treatment of diabetic retinopathy, breast cancer, or prostatic cancer. Interestingly, in 1955 Talairach and his collaborators at Hospital Sainte Anne (Paris) reported the first stereotactic destruction of the normal hypophysis under X-ray guidance *(22)*. This method was adopted by a variety of centers where destructive radioactive implants were used for the treatment of pituitary tumors. Currently, brachytherapy is rarely used, mainly due to its low efficacy and high rate of complications.

In an effort to reduce the complications of conventional radiotherapy and achieve more effective radiation therapy, stereotactic radiosurgery was developed. This method, initially introduced by the Swedish neurosurgeon L. Leksell in 1951, involves the delivery of high radiation doses to the tumor and lower doses to the surrounding normal tissue using stereotactic mapping for precise target definition *(23)*. Currently, this can be performed by using multiple narrow beams from radioactive sources (gamma knife), by moving an X-ray source through a series of arcs (linear accelerator-based system), or by using heavy, charged particles (proton or helium beams). In 1968 Leksell reported the first patient with an adenoma treated by gamma knife *(24)*. Early experience with gamma knife radiosurgery was limited by the available imaging procedures (pneumoencephalography and polytomography) *(24)*. The introduction of MRI in the late 1980s and of sophisticated computer-guided planning techniques revolutionized its efficacy enabling its spread in many centers. The therapeutic role of this modality remains to be established.

Medical Management

In 1887 Victor Horsley stated "the main factor which acts most powerfully in suggesting the advisability of surgical treatment is the utter hopelessness of any other drugs proving of any value" *(3)*. At that time the only available medical therapies included iodine, arsenic, mercury, strychnine, and caffeine for acromegaly; these often extremely toxic medications were unsuccessful in altering the course of disease.

The medical treatment for pituitary adenomas gained momentum in the early 1970s following the introduction of dopamine agonists as the primary therapy of prolactinomas. Bromocriptine, a semisynthetic ergot alkaloid, was the first such drug used. Ergots, produced by the fungus *Claviceps purpura,* have toxic and medicinal properties described for centuries. Interestingly, it was noted that nursing mothers who developed St. Anthony's fire (ischemic limb pain associated with ergot poisoning) after consuming grain contaminated with *C. purpura*, stopped breast feeding *(25)*. It was as early as 1676 when Dodart stopped milk production in a lactating woman by administering ergot *(25)*. During the 1950s and 1960s a series of experiments showed that ergotamine suppressed prolactin release and prevented egg implantation in the rat *(25)*. In 1968 Fluckiger demonstrated that bromocriptine (CB-154) inhibited prolactin secretion *(25)*. That same year bromocriptine was introduced for the treatment of puerperal and in 1971 of non-puerperal hyperprolactinemia, opening a new chapter in the therapy of pituitary tumors *(26–28)*. The interest was initially focused on the normalization of hyperprolactinemia, re-establishment of gonadal function, and fertility. The improvement in preexisting bitemporal visual defects suggested accompanying tumor shrinkage and CT proof of prolactinoma shrinkage was first described in 1979 *(25)*. It is now well recognized that the pituitary D_2 receptor activation reduces prolactin secretion, has antimitotic effect, and causes rapid involution of the cellular protein synthetic machinery resulting in rapid and sustained tumor shrinkage *(29)*. Bromocriptine probably remains the most widely used dopamine agonist globally; however, other longer-acting and better tolerated drugs, such as cabergoline, are changing this pattern, at least in the Western world *(29)*. Medical therapy provides the greatest risk/benefit ratio for prolactinomas and is generally considered their first-line treatment when some intervention is indicated. In fact, absence of prolactin normalization is encountered in 10–25% and failure to achieve at least 50% reduction in tumor size in nearly 10–35% of the patients *(30)*.

In the late 1960s and early 1970s several research groups attempted to apply the growing knowledge on the hypothalamic–pituitary axis to the development of new medical treatments for acromegaly. Based on experiments suggesting that in some patients growth hormone (GH) hypersecretion is partly under hypothalamic control, drugs known to disrupt the hypothalamic signals, as medroxyprogesterone, catecholamine antagonists, and dopamine antagonists, were used; these proved ineffective in the majority of the cases *(2)*. Despite the well-known GH stimulatory effects of dopamine agonists in normal subjects, Liuzzi et al. found that L-dopa paradoxically inhibited GH secretion in some acromegalics *(31)*. Subsequent studies showing substantial GH suppression by bromocriptine *(32)* led to the adoption of dopamine agonists in the pharmacotherapy of acromegaly *(33)*. Three decades later these agents still form part of our medical repertoire, achieving normal IGF-I in at least 10% of the patients *(34,35)*. In 1968 Krulich et al. during their efforts to isolate GH promoting activity, incidentally detected a substance in ovine and rat hypothalamic extracts that inhibited GH release from rat pituitaries in vitro *(36)*. In 1973 the responsible peptide, somatostatin, was sequenced

and, importantly, in one experiment it significantly inhibited the release of GH by enzymatically dispersed cells derived from the pituitary of a patient with confirmed active acromegaly *(37)*. Hall et al. in 1973 reported that continuous intravenous administration of somatostatin reduced substantially GH levels in acromegaly indicating a therapeutic potential for this peptide *(38)* and opening the avenues for a "new treatment for an old disease" *(39)*. The limitations of the clinical use of the native peptide (short half-life, need for intravenous administration, and post-infusion rebound hypersecretion of hormones including GH, insulin, and glucagon), lead to the development of cyclic somatostatin analogs with longer duration of action *(*40*)*. Thus, in 1984, Plewe et al. reported the effectiveness of SMS 201-995 (now known as octreotide) to induce prolonged GH suppression in acromegalic patients *(41)*. A large number of subsequent studies confirmed this beneficial effect, and also demonstrated tumor shrinkage. Other slow-release forms, with a better pharmacokinetic profile and greater potency for GH suppression, followed *(42,43)*; currently available analogs for clinical use (as primary or adjuvant therapy) are octreotide LAR, lanreotide SR, and an aqueous formulation of lanreotide (lanreotide Autogel). It should be noted, however, that effective control of disease activity by these agents is achieved in around half of the cases *(44)*, thus necessitating the development of novel pharmacological strategies. Elegant studies since the 1990s provided an alternative treatment option in the form of pegvisomant; its development represents a remarkable story taking place during attempts to develop a GH superagonist by causing mutations to the hormone molecule. It was initially noted that transgenic mice exhibiting a dwarf phenotype with decreased IGF-I concentration, expressed GH with mutations in amino acid residues of the third helix in the region of binding site 2 *(45)*. Further experiments demonstrated that glycine at position 120 of human GH (in the region of binding site 2) was essential for its growth-promoting activities, and substitution by any other amino acid except alanine resulted in a GH antagonist *(46)*. Finally, when mutations in this region were combined with amino acid substitutions in binding site 1 (providing increased affinity for the GH receptor), highly potent GH-receptor antagonists were produced *(46)*. One of these compounds, B2036, conjugated to polyethylene glycol is pegvisomant (B2036-PEG). The existing data suggest that pegvisomant normalizes IGF-I in 97% of the patients *(47)*. Recent interest has focused on novel somatostatin analogs with a more universal somatostatin receptor binding profile, such as SOM30. In vitro experiments have demonstrated inhibition of GH secretion from GH-secreting adenomas, offering further treatment options *(48)*.

Proven effective medical therapy targeting the corticotroph adenomas is not currently available. In the 1970s neuromodulatory agents, such as cyproheptadine, bromocriptine, and valproic acid acting on the pituitary or hypothalamus were unsuccessfully used. Since the early 1980s, several groups studied the usefulness of somatostatin analogs without being able to provide consistent data that would allow their widespread clinical use in Cushing's disease *(49,50)*. Therefore, the efforts focused on the elimination of hormone excess by pharmacologic agents. In 1949 the observation by A. Nelson that dogs treated with the insecticide dichloro-diphenyl-dichloroethane (DDD) had adrenal cortical atrophy led to the development of the adrenolytic agent mitotane in the late 1950s *(49)*. During the following three decades a number of steroidogenic blocking drugs (metyrapone, aminoglutethemide, trilostane, ketoconazole, and etomidate) were introduced. Reports showing expression of the nuclear hormone receptor peroxisome proliferator-activated receptor-gamma in human ACTH-secreting pituitary tumors, as well as suppressive effects of the thiazolidinedione compound rosiglitazone on ACTH and corticosterone secretion in mice *(51)*, have focused attention on the role of these agents in the treatment of Cushing's disease. Limited studies have provided some favorable results, but the value of these drugs is far from being proven *(52)*. Recent studies demonstrating the selective expression of somatostatin receptor subtype 5 in human corticotroph adenomas, in combination with the inhibitory effect of SOM230 on ACTH secretion, may provide another potential medical therapy for Cushing's patients *(53)*.

The pharmacotherapy for gonadotroph or non-functioning adenomas initially included dopamine agonists (first tried in 1979) *(54)* with subsequent agents being somatostatin analogs (since 1988) *(55)* and gonadotrophin-hormone releasing hormone analogs (first tried in 1984) *(55)*. A number of studies suggesting rather limited efficacy has prompted restriction of their role as primary therapy. Still, treatment with dopamine agonists seems promising in the prevention of residual tumor enlargement in patients operated for non-functioning adenomas *(56)*.

Drug treatment for the uncommon TSH-omas relies on the dopamine agonists or more successfully on the somatostatin analogs, introduced in the 1980s *(57)*.

Finally, in the rare cases of pituitary carcinomas, medical therapy directed against tumor growth (chemotherapy and non-chemotherapy-based regimes) has been applied since nearly the early-1980s with relatively poor results *(58)*.

Conclusions

The history of the treatment of pituitary tumors is unquestionably exciting and didactic; creative pioneers, unexpected observations, serendipitous discoveries, hot debates and admirable achievements, have all ultimately led to the enrichment of the therapeutic armamentarium with subsequent improvement of targets. The horizons have been further expanded by the arrival of novel diagnostic tools posing new challenges for both the physicians and surgeons caring for patients with pituitary tumors. Each treatment modality has undoubtedly a role in this field; however, experience

over the past century has clearly confirmed that successful treatment has to be an interdisciplinary challenge involving endocrinology, neurosurgery, and radiation oncology in established centers of excellence. Further advances are eagerly awaited.

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