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The History of the Treatment of Pituitary Adenomas

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It is conceivable that the day is not far distant when our present methods of dealing with hypophyseal enlargements, with scalpel, ronguer and curette—new as these measures actually are and as brilliant as the results may often be—will seem utterly crude and antiquated, for it is quite probable that surgery will, in the end, come to play a less, rather than a more important role in ductless gland maladies

Harvey Cushing (1912) (1)

The immense history leading to our current understanding and treatment of pituitary pathology is inextricably linked to the evolution of the understanding of the numerous functions of the hypophysis cerebri as the "master gland" of the endocrine system. When the anatomists of old encountered this small organ sequestered "like a nugget in the innermost of Chinese boxes" *(2)* at the base of the brain, they had no inkling of its importance in the control of multiple target organs in the human body. It would ultimately take two millennia and a vast amount of clinical and laboratory research for its role in the body to eventually become more completely appreciated.

Key Words: Pituitary; pituitary adenoma; medical history; treatment.

Primitive Concepts

L'organe enigmatique

Van Gehuchten (3)

For more than 2000 yr our understanding of the pituitary gland was based largely on very primitive concepts initially formulated in the 4th century BC. Hippocrates of Kos (460–370 BC) associated the brain with intelligence, thoughts, and dreams. He was the first to consider the brain a cooling organ that performed its function by secreting one of the four bodily humors, namely phlegm or *pituita (4).* These primitive concepts regarding the pituitary's physiological role remain historically preserved in the anatomical term for the pituitary, the hypophysis cerebri, or the *pituitary body*. Galen of Pergamum (130–200 AD), the father of experimental physiology, advanced this hypothesis along the same lines. He propounded that "nature" had established a special space for the gland hypophysis. According to Galen, the sella turcica of the sphenoid bone was pierced by foramina, through which blood vessels carried residues of *pituita (5).* The *pneuma*, or spirit, was brought into the body via the lungs. Blood flowed to and fro in the arteries carrying *vital spirit* to the various parts of the body. *Animal spirit* was formed from *vital spirit* in the brain by the *rete mirabile*, which Galen described as "the most wonderful of bodies." This encircled the gland hypophysis and covered the whole of the base of the brain. It was not a simple structure but rather a meshwork. The waste products of this chemical reaction flowed to the base of the brain, down the pituitary stalk, and so to the pituitary gland. From this "phlegmatic glandule" the waste products were supposed to be passed by ducts through the sphenoid and ethmoid bones to the nasopharynx where they emerged as *pituita* or nasal mucous *(6).*

Galen's Concepts Challenged

The first to challenge this ancient view of the role of the pituitary was Conrad Viktor Schneiber (1614–1680) of Wittenberg *(7,8)* and Richard Lower (1631–1691) of Oxford *(9).* In their work on the anatomy and physiology of the nose, they disproved the existence of a communication between the ventricles of the brain and the nasopharynx. Interestingly, as early as 1670, Lower together with his friend and colleague Thomas Willis (1621–1675) proposed that substances passed from the brain through the infundibulum to the pituitary, where they were distilled back into the blood. This early theory of neurosecretory substances was, in fact, acknowledged by Geoffrey Harris (1913–1972) 300 yr later in Oxford when describing the hypothalamic–hypophyseal portal circulation *(10).* It was, however, questioned by Hans Simmer in his book, *The Beginnings of Endocrinology*. Credit really hinges on the translation of a passage by Willis, describing the transit of blood past the pituitary gland: "Sanguis…seri superflui partem aliquam glandulae pituitariae demandet, partemque aliam in furculos venosis, versus cor reducendam insillet" *(11).* Cushing translated the passage as reading "The blood…takes some part of the superfluous serum *of* the pituitary gland…." Pordage in his 1681 translation and publication of Willis' works, read this as "*to*" instead of "*of*" the pituitary gland *(12).* Willis thus spoke of uptake by the pituitary, not of discharge—a receptive,

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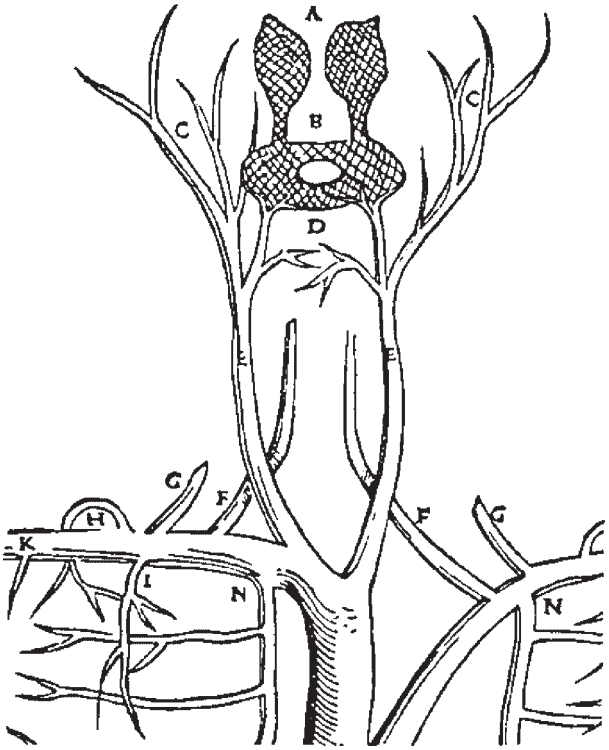

Fig. 1. Versalius' initial representation of the hypophyseal body (1538).

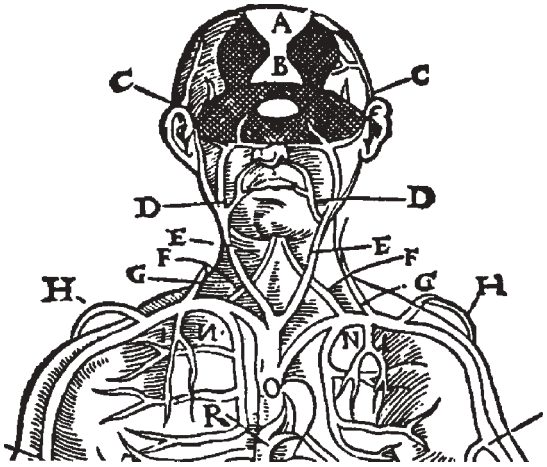

Fig. 2. Ryff's version of Versalius' pituitary. The *wonderful network* superimposed on an outline of the human body (1541).

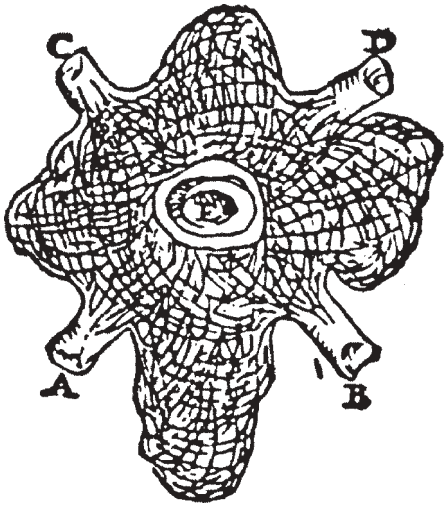

Fig. 3. Versalius' representation of the hypophysis cerebri in his work *De Humani Corporis Fabrica Libri Septem* showing the portal (E) for receiving pituita from the brain.

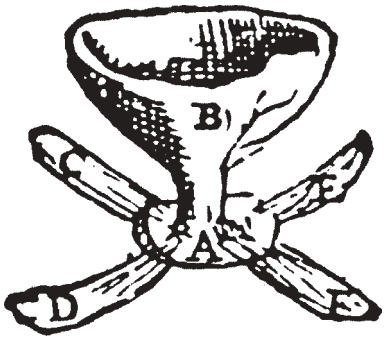

Fig. 4. Versalius' representation of the infundibulum. The cup or *cyathus* distils pituita from the brain into the funnel shaped receptacle provided by the gland. Drainage is facilitated via the ducts for easier drainage of pituita.

not a secretory function *(13).* Although the pituitary gland was known to Galen from his anatomical studies, it was first really described as a separate entity by Andreas Versalius (1514–1564). He termed it the "glandula pituitam cerebri excipiens," also accepting the doctrine of its role in secreting pituita through the nose *(6,14).* Galen believed that mucous was filtered through the cribriform plate of the ethmoid. Versalius, however, disagreed because of the anatomical relationships of the pituitary. He proposed a more likely anatomical pathway through the palatine canal and superior orbital fissure into the sphenopalatine fossa and out through the nose *(15).* In 1538, Versalius first illustrated the pituitary gland as the "rete mirabile, in quo vitalis spiritus ad animalem preparatur" (Fig. 1) *(3,13).* This diagram was later plagiarized by Walter Ryff of Strasburg who transposed it line for line onto an outline of the human body (Fig. 2). Versalius was infuriated and before publishing *De Humani Corporis Fabrica Libri Septem,* Basilae in 1543, removed the illustration, instead including another two schematic diagrams of the *rete*, one of which was a drawing illustrating the process of pituitary distillation (Figs. 3 and 4) *(4).*

The only other notable milestone of this era with respect to the pituitary was put forward by Franciscus Sylvius (1614–1672), professor at Leyden, and Raymond Vieussens (1641–1715) of Montpellier. This regarded the function of the pituitary. Thomas Gibsons in his book *Anatomy of Humane Bodies Epitomised*, summarized their theories on the structure and function of the pituitary indicating that they believed the pituitary was concerned with formation of cerebrospinal fluid explaining its convenient location at the base of the third ventricle.

Anatomical and Histological Observations and a Renewal of Interest

The invention of the microscope by Anton van Leeuwenhoek (1632–1723) greatly accelerated the understanding of human anatomy and allowed many ancient concepts to be challenged. The pituitary gland, however, seemed to attract little interest until the end of the 18th century. Joseph Lieutand (1703–1780), an anatomist and professor of medicine at the University of Aix-de-Provence, noted that the pituitary stalk was not canalized but a solid cylinder of grey matter surrounded by pia mater. He also had an early but perhaps unappreciated view of the hypothalamo–hypophyseal portal system, commenting on many small longitudinal blood vessels communicating with the pituitary gland *(16,17).* He proposed the term "tige pituitaire" (pituitary stalk), stating "I have given the name pituitary stalk to this part because I believe that the term funnel would not be suitable for it" *(6,16,17).*

As it became apparent that Galen's theory regarding the role of the pituitary gland was mistaken and considering its unique central anatomical location in the sella, the pituitary began to generate more interest among physicians and scientists. This initially led to further speculation regarding its functions and associated pathologies. Franz Joseph Gall (1758–1828), a noted French physician and anatomist of phrenology fame, believed that the pituitary to be a large ganglion *(6,13,14).* The term "hypophysis cerebri" was introduced in 1778 by Samuel Thomas von Soemmering (1755–1830). An attempt in 1823 at renaming it "l'appendice sus-sphenoidal" by Pierre-Francois-Olive Rayer (1793–1867) of Calvados, was rapidly forgotten *(13,18).* At least these were advances on the term "l'organe enigmatique" advanced by Van Gehuchten *(2,18).* Joseph Wenzel (1768–1808) suggested the pituitary as a cause of epilepsy *(13,18).* In 1839, in his doctoral thesis, Joseph Engel proposed that the pituitary was actually a small cerebellum assisting in the coordination of balance and movements. This was based on the observation that alcoholic patients frequently had pituitary diseases—possibly anticipating the earliest observation of Cushingoid features in alcoholics by nearly 140 yr *(6,13,18).* Carl Gustav Carus (1789–1869) proposed that the small gland was the rostral projection of the nervus sympaticus *(6,13,18,19).* Ernest Burdach (1801–1876) proposed that this small gland was the beginning of the spinal cord and that the anterior and posterior lobes were replicas of the anterior and posterior tracts of the spinal cord *(6,13,18).* Johann Friedrich Meckel the Younger of Halle (1781–1833) believed the pituitary produced fluid that nourished the brain.

At this point in time, pituitary pathology and its presentation began to be documented. In 1797, Mathew Baillie (1761–1823), royal physician to King George III and nephew to William Hunter, recorded in his text *Morbid Anatomy (20)* that "this gland is very little liable to be affected by disease." He reported finding only one patient in which the gland had enlarged to "twice the normal size of fibrous tissue" *(6,20).* The secondary pressure effects of pituitary pathology on neighboring structures, especially optic chiasm compression and visual failure, were well recognized before the various clinical disease entities were described. Early accounts of blindness caused by pituitary enlargement were published by Jean Louis Petit (1674–1750), first director of the Academie de Chirurgie in Paris. He had also observed that in most cases of hydrocephalus, the pituitary was "squirrheuse" (scirrhous) *(6,21).* Other accounts were also reported by Vieussens in 1705, Johan Jacob Wepfer (1620–1695) in 1681, Theophile Bonet (1620–1689) in 1705 and in 1833, by TH Hedlund (1791–1847) *(6).* Anton de Haen (1704–1776), professor of medicine at the University of Vienna, reported finding a pituitary tumor at postmortem examination in a 20-yr-old female patient who presented with amenorrhea, visual failure, severe headaches, nausea, and vomiting. No discrete cause was identified, but the case was published in his *Pars Quinta Rationis Medendi (6,22).*

The Evolution of Pituitary Histopathology

The understanding of the histological characteristics of the pituitary gland progressed as slowly as did understanding of its physiological role. In 1844, Adolph Hannover (1814–1894) recognized two distinct cell types in the adenohypophysis *(23).* Shortly afterwards, European histologists began describing in more detail the cellular components of the anterior pituitary. In 1884 and 1886, using hematoxylin and eosin and other stains, Flesch, Lothriger, and Dostoiewsky first described the two types of cells as either nongranular, clear chromophobe cells or granular chromophil cells *(6,24–26).* Shortly thereafter, Schonemann divided the chromophil cells into eosinophil, staining with acid dyes, and basophil, staining with basic dyes *(6,26,27).* Once different types of adenomas had been distinguished histologically, the next step was to associate them with certain clinical features. In 1900, Carl Benda (1857–1933) discovered that pituitary tumors were composed of specific pituitary cells and were thus true adenomas of the gland itself *(28).* He demonstrated that the adenomas in acromegalics stained eosinophilic *(26,28)* and became the first to emphasize the necessity of using histological techniques to study such tumors and to correlate histopathological features with the clinical presentation. This heralded the era of histopathological examination of the pituitary gland *(13).* As Harvey Cushing and Herbert Olivecrona amassed hundreds of cases of surgically treated adenomas, it became readily apparent that certain histological subsets of these lesions had unique clinical characteristics. Correlation of the staining characteristics with the clinical presentation led to the popularized schema that acidophil adenomas resulted in acromegaly, basophilic adenomas were associated with Cushing's disease, and chromophobe adenomas were hormonally inactive tumors presenting with mass effect and hypopituitarism. In

three separate papers between 1929 and 1950, Rasmussen went on to describe the relative frequencies of the cell types in the pituitary gland, in both sexes and at different ages and stages of sexual development.

Despite theses advances, during the period 1930–1950, investigations of the pituitary–adrenocortical axis could only be conducted by means of histology, pathology, clinical observation, historical data, orthodox biochemistry, and analysis of urinary 17-ketosteroids. As a consequence, circumstantial evidence was often all that one could obtain, resulting in a number of controversies. This was particularly the case with respect to the complex etiology of Cushing's syndrome relative to other conditions such as acromegaly.

The classification of pituitary adenomas based on hemotoxylin and eosin staining on light microscopy persisted until its limitations were highlighted by discordant findings of "fugitive acromegalics" and patients afflicted with Cushing's disease harboring chromophobe adenomas *(29, 30).* During the 1960s and 1970s, the development of biological markers for assessing serum hormone levels in conjunction with the development of electron microscopy and immunohistochemical techniques led to the development and popularization of a new classification based on the functioning of the adenoma—particularly among endocrinologists. Adenomas became categorized into those with signs of endocrine activity or clinically *functioning* adenomas and those that did not display any activity or clinically *nonfunctioning* adenomas. Further differentiation of the nonfunctioning group relied on ultrastructural evaluation for the presence of secretory granules and oncocytic change.

Owing to the early sometimes unreliable nature of immunohistochemical analysis and acknowledgment that the classification of pituitary adenomas based on light microscopy was oversimplified and restricted, Kalman Kovacs and Edith Horvarth then introduced a morphologic classification taking into account structure–function relationships using electron microscopy *(31,32).* This led to the first ultrastructural classification of pituitary adenomas and enabled the validation of immunohistochemistry in its infancy. As the production of monoclonal antibodies and polyclonal antisera became more refined resulting in less cross-reactivity and false positivity, results from immunohistochemistry yielded more accurate and reproducible results *(33).* Together with electron microscopy ultrastructural analysis where necessary, this provided us with the WHO classification for pituitary tumors as we know it today *(34).*

Experimental Pituitary Studies

Despite the paucity of investigations of pituitary function available, insight based primarily on numerous clinical and laboratory observations and necropsy investigation continued to accrue. Reports of patients with pituitary adenomas but "without acromegaly" were published. In 1900, Joseph Babinski (1857–1932), a pupil of Charcot, reported

Fig. 5. Harvey Cushing (1869–1939). From personal collection Dr. E. R. Laws—with permission.

a case of an obese young woman with genital hypoplasia. She had a pituitary region tumor, very adherent to the pituitary and most likely a craniopharyngiona *(35).* In 1901, Alfred Froelich (1871–1953) described a pituitary tumor in a patient without acromegaly that in retrospect was a classical description of dystrophia, adipose-genitalis *(36).* Neither considered that these patients' features were a result of hypofunction of the pituitary gland and much confusion ensued. Cushing (Fig. 5), in a moment of inspiration, was able to detect the similarity between the latter patient and hypophysectomized puppies in his laboratory. In June 1909, Cushing addressed the American Medical Association on "The Hypophysis Cerebri" comparing the experimental findings in dogs and the clinical features of pathological conditions in humans *(2).* He introduced the terms "hyper- and hypopituitarism" and in his summary stated: "Two conditions, one due to a pathological increased activity of the pars anterior of the hyypophysis (hyperpituitarism), the other to a diminished activity of the same epithelial structure (hypopituitarism) seem capable of clinical differentiation" *(2).*

Two relatively basic methods were developed to study the physiology of the pituitary gland. The so-called "positive method" involved the introduction of a part of a gland itself or an extract thereof into an organism or fed to the subject. This was designed to stimulate and replicate normal glandular activity. The other "negative method" involved the gland being partially or completely removed. Experimental hypophysectomies were thus carried out on a number a different animals *(37).* The challenge with respect to experimental hypophysectomy was predominantly technical. Achieving a clean lesion in a suitable animal model without complication and thereby producing contradictory results, proved to be very difficult. Different approaches,

both transcranial and transoral, were utilized on numerous different animals—most dying of operative complications. Midline approaches from below through the nasal, buccal, hyoid, and pharyngeal regions or from one side by a lateral pharyngeal and sphenopalatine route, were all attempted. A transfrontal approach was adopted in 1881 by Julius Michel, but the morbidity and mortality remained high, and it was difficult to judge exactly what had been removed. Using the alternative "positive method," Emil Goetsch (1883–1963) fed rats 0.05 g of acetone dried powder of whole pituitary glands. He observed that growth and sexual development were transiently stimulated *(38).* These observations were, however, subsequently challenged *(39).*

A debate relating ablation of the pituitary with survival ensued. The first major contribution on this subject was by Marienesco, an associate of Marie. After mentioning experiments by Dastres who approached the gland transorally without success, he discussed his own experiments. Via a buccal route and after dividing the soft palate, the sella was opened and the gland destroyed using heat. Three animals in Marienesco's operations survived—for 3, 5 and 18 d. He concluded that pituitary ablation was compatible with life for only a limited period *(40,41).* Studies then attempted to determine the symptoms of apituitarism. Giulio Vassale (1862–1912) and Ercole Sacchi in 1892 and 1894, respectively *(42,43)*, adopting a similar approach to Marianesco, observed apathy, motor retardation, muscle twitching, hypothermia, polydipsia, anorexia, weight loss, and coma. The conclusion was that the pituitary produced a substance essential for life. Using a very elegant transcranial route and dividing his animal models into partial and complete ablation groups, Nicolas Paulesco (1869–1931), a physiologist from Bucharest, reproduced these results *(44).* Two years later Redford and Cushing reported 20 cases of experimental hypophysectomy from the Hunterian Laboratory *(45).* The results once again confirmed that life could not be sustained in the absence of a pituitary. Death was preceded by loss of appetite, loss of weight, and listlessness, which was defined as "cachexia hypophysiopriva" *(2).* In 1912, Ascoli and Legnani noted atrophy of the adrenal cortex after hypophysectomy *(46).* In 1917, William Bell (1871–1936) reported that clamping the stalk had the same effect of hypophysectomy with atrophy of the uterus and ovaries *(47).* Bernard Ascher (1883–1960) in 1912 improved the technique of hypophysectomy and proceeded to undertake more extensive and elegant experiments. He described immediate postoperative arrest of growth, failure of the epiphyseal cleft to close, and infantilism in hypophysectomized puppies. He concluded, "it follows for human pathology, that the surgeon…can extirpate the entire pituitary without endangering life, this has not yet been done." Astutely, he also believed that acromegaly was a consequence of hyperfunction and not hypofunction of the pituitary *(48).*

Cushing's next step was to successfully prolong the life of hypophysectomized animals by injection of glandular extracts or emulsions of animal pituitaries and by auto- or homotransplantations of pituitary tissue *(40).* The availability of adrenal substitution (17-hydroxtcorticosterone, *Kendal Compound E*) for clinical use by 1948 completely changed operative morbidity and mortality *(49).* It was now able to be used for replacement of cortisol in cases of hypopituitarism, following bilateral adrenalectomy and in patients with hypophysectomy for cancer treatment *(50).*

Fig. 6. Cushing's first acromegalic patient: (**A**) some years before presentation and (**B**) on admission. From Cushing, H. *The Pituitary Body and its Disorders.* Philadelphia: J. B. Lippincott, 1912.

"Prosopectasia" and Enlightenment

In 1864, the Italian Andrea Verga provided one of the earliest reports of the clinical features now associated with acromegaly in a female patient. He termed the entity "prosopectasia" derived from the Greek "prosopon" (face) and "ektasis" (enlargement) *(51).* At postmortem examination, a pituitary tumor was encountered that had both eroded into the sphenoid sinus and was compressing the optic chiasm. Verga incorrectly assumed that the syndrome and the tumor had been caused by her early loss of menses *(52).* A further similar report by Vincenzo Brigidi emerged in 1881 on the autopsy findings on the Italian actor Ghirlenzoni, who had a clinical description consistent with acromegaly *(53).* He misinterpreted the tumor for hypertrophy, considering the etiology to be a primary disease of bone. It was left to the great French neurologist Pierre Marie (1853–1940) to coin the term "acromegaly" (Fig. 6) from the Greek "akron" (extremity) and "megas" (great) from his report of two such patients treated at the Salpetriere Hospital of Paris *(54).* However, Marie was unaware of the associated pituitary pathology until 1891 when he and Georges Marinesco described the autopsy findings of an acromegalic patient *(55).* He found that the pituitary gland had been replaced by adenoma and concluded that the normal function of the gland was to inhibit somatic growth and that gigantism was due to a lack of inhibition. The existence of a pituitary tumor, correctly termed an "adenoma," had already been described in 1884 by Fritzche and Klebs, who had indicated that this was a

consistent finding in patients with gigantism. In 1891 Marie collaborated with his former Brazilian pupil, Jose Dantos de Souza-Leite, who had described 48 acromegalic patients in his doctoral thesis and published their combined experience in *Essays on Acromegaly (56).* Neither understood the cause of the disease appreciating only that the pituitary gland was a regulator of growth admitting, "we have nothing definite" *(56).* Although their assumption was the exact opposite of the truth, the importance of this historic error was that it was instrumental in focusing interest on the pituitary and directing further examinations as never before *(13).*

Oscar Minkowski (1858–1931), who first described diabetes mellitus after pancreatectomy, advanced our understanding recognizing a consistent relationship between acromegaly and enlargement of the pituitary *(57).* The syndrome continued to be considered as a glandular insufficiency until 1894 when Augustino T. Tamburini (1848–1919) suggested that acromegaly was caused by an overactivity of the gland *(13,58).* Woods Hutchinson noted that in 19 giants and acromegalics the anterior lobe of the pituitary gland was uniformly enlarged and that "disturbances of the pituitary's metabolism are the principal factors in both acromegaly and gigantism, the principal difference between the results being simply due to the stage of development at which the disturbance of function begins" *(59).*

Pituitary "Basophilism"

In 1910, amenorrhea–galactorrhea was observed by Oskar Hirsch (1877–1965) in a 35-yr-old woman *(60).* At surgery, however, only a cyst and no adenoma was encountered. A true adenoma was later discovered at postmortem *(61).* By 1911, Hirsch had differentiated the three most important pituitary-related clinical entities at the time: (1) acromegaly, (2) adiposogenital dystrophy, and (3) a condition with visual defects only and no changes in general appearance *(62).*

In 1933, Harvey Cushing (1869–1939) *(63)* described a 33-yr-old woman suffering from post-partum amenorrhea and continuing galactorrhea caused by a mixed eosinophilic/chromophobic "pregnancy cell" adenoma. He suspected that this tumor secreted large quantities of lactogenic hormone, prolactin, isolated by Riddle a year earlier *(64).* The syndrome of amenorrhea–galactorrhea and low urinary levels of follicle stimulating hormone—the syndrome caused by prolactinomas—was further characterized by Argonz and Del Castillo in 1953 *(65)* and Forbes in 1954 *(66).*

In 1912, Cushing introduced the term polyglandular syndrome, implying "nothing more than that secondary functional alterations occur in the ductless-gland series whenever the activity of one of these glands becomes primarily affected" *(1).* The case alluded to was a 23-yr-old woman (case XLV) suffering from "a syndrome of painful obesity, hypertrichosis and amenorrhea with overdevelopment of secondary sexual characteristics" (Fig. 7) *(67).*

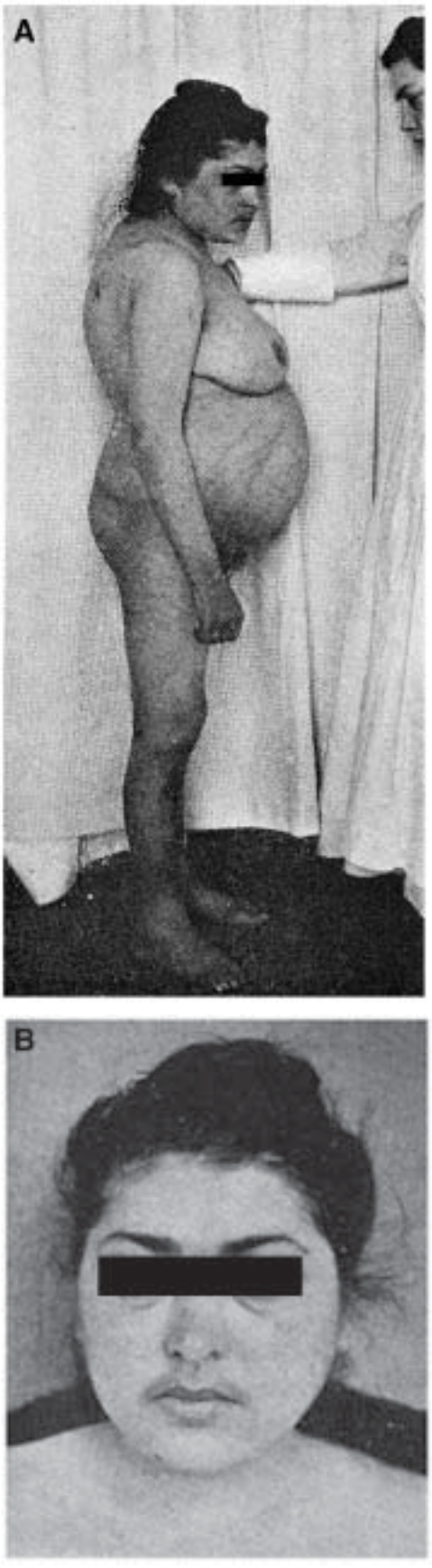

Fig. 7. Cushing's first patient with his syndrome: Case XLV—"Minnie G." From Cushing, H. *The Pituitary Body and its Disorders.* Philadelphia: J. B. Lippincott, 1912.

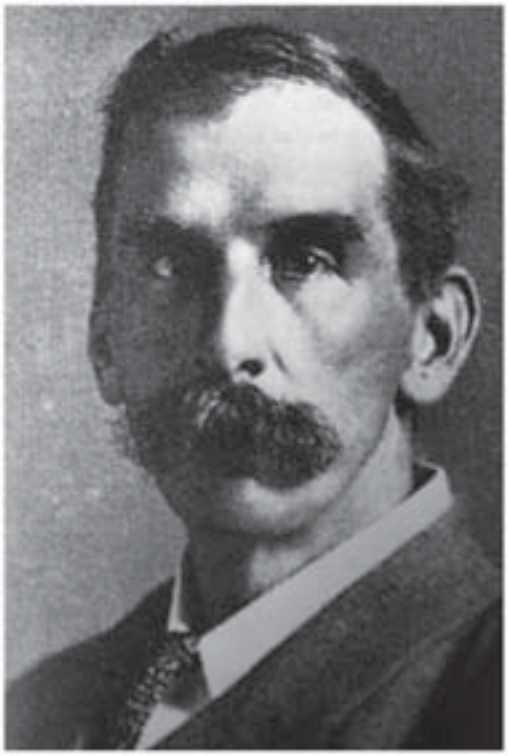

Fig. 8. Sir Victor Horsely (1857–1916). From personal collection Dr. E. R. Laws—with permission.

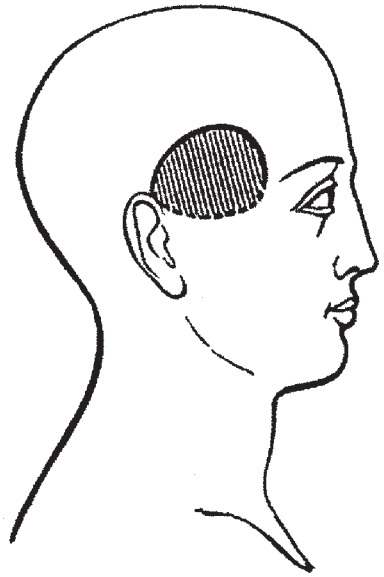

Fig. 9. A diagram of the craniotomy site in a female acromegalic patient treated by Caton and Paul. The surgery entailed a two-stage lateral subtemporal decompression. From Caton, R., et al. *BMJ* 1893; **2:** 1422—with permission.

"Whether these symptoms were chiefly attributable to disordered pituitary, adrenal, pineal or ovarian influences was uncertain" *(2).* After painstakingly collecting 15 further cases from his own files and from the literature over the next 21 yr, Cushing *(68)* concluded that some of the cases were definitely due to adrenal tumors that improved after tumor resection, but that a similar syndrome may accompany basophilic adenomas of the pituitary with accompanying hyperplasia of the adrenal glands—what we now recognize as "Cushing's *disease*."

Pituitary Surgery

By the 19th century, laboratory work had begun investigating the effect of canine hypophysectomy *(69).* In 1889, Sir Victor Horsely (1857–1916) (Fig. 8) became the first surgeon to operate on a pituitary tumor. He used a bifrontal craniotomy approach and a technique he described as "cerebral dislocation" encountering a cystic adenosarcoma that he described as inoperable. The patient died a few years later and a subsequent autopsy revealed considerable softening of the frontal lobe. Horsley blamed this on the fact that he had found it necessary to sacrifice polar veins draining into the superior sagittal sinus in order to gain access. As a result he abandoned the transfrontal route in favor of a transtemporal approach *(62).* Despite presenting this work at numerous medical meetings, he waited 17 yr before publishing the case report, describing the approach as a "prehistoric way" *(69).*

The first actual recorded attempt of the surgical resection of a pituitary tumor was by Frank Thomas Paul (1851–1941), honorary surgeon at the Royal Infirmary, Liverpool. In 1893 he operated on a patient of Richard Caton's, his physician colleague *(70).* Using a subtemporal approach suggested by Horsely (who was consulted on the case) (Fig. 9), he operated on a young woman with acromegaly. She had presented with headaches, facial pain, and visual failure. The surgery entailed a two-stage lateral subtemporal decompression. Unfortunately the tumor could once again not be accessed and the patient, blind as a consequence but with her facial pain having resolved, died 3 mo later. In 1903, Otto George Theobald Kiliani, a New York surgeon, began practicing a bifrontal intradural approach to the pituitary region on cadavers *(71).* His first live operation was on a patient presenting with severe pituitary apoplexy complicated by subdural extension of the hemorrhage. After encountering blood over the convexity and failing in the placement of a ventriculostomy drain to help contain brain swelling, he abandoned the procedure and the patient died 8 h later. In 1900, in Berlin, Fedor Victor Krause (1857–1937) undertook an extradural right frontal approach to access and remove a bullet lodged in the region of the right optic foramen on a patient who had survived a suicide attempt with a handgun due to lovesickness *(72).* The patient did remarkably well and Krause was quick to appreciate the significance of the view he had obtained of the sella turcica: "As I had succeeded in reaching the optic foramen from the front, in order to extract the bullet, it seemed feasible to approach the pituitary in the same way." In 1905 he performed the first successful transfrontal pituitary oper-

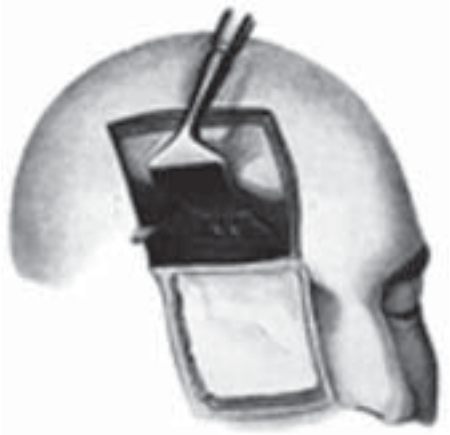

Fig. 10. The osteoplastic right frontal craniotomy flap developed and used by Fedor V. Krause (1857–1937). From Krause, F. V. *Surgery of the Brain.* Vol. 1. New York: Rebman, 1990.

ation, choosing an extradural approach to avoid injury to the brain (Fig. 10) *(73).* This procedure provided the basis on which the majority of subsequent variations of the transcranial approach were developed *(74).* He later changed to a frontolateral intradural approach before eventually changing to the superior transnasal approach of Schloffer. For tumors with large suprasellar extensions, however, he maintained the use of a transcranial approach. Between 1904 and 1906, Horsley operated on 10 pituitary tumors, utilizing both subfrontal and lateral middle fossa approaches with a mortality rate of 20%, exceeding the results of colleagues who hitherto had experienced prohibitive mortality rates ranging from 50% to 80% *(75,76).* He advocated surgical intervention for pituitary region lesions emphasizing the importance of relieving mechanical pressure on the chiasm exerted by the tumor in order to avoid blindness —similar obligations that are still pertinent today *(77).* Horsley's approach, however, did not gain universal popularity, Cushing finding it impracticable *(78).* In 1907, after performing a number of cadaver studies, Wilhelm Braun was convinced that the pituitary should be reached via a transtemporal approach through the cavernous sinus. This, however, invited unacceptable morbidity and mortality necessitating division of the maxillary branch of the trigeminal nerve as well as ligation of the carotid artery in the neck. In 1908, in approaching a pituitary adenoma, Louis Linn McArthur (1858–1934) turned a right frontal osteoplastic flap and resected the supraorbital rim together with part of the orbital roof. The entire approach was extradural until 5 mm proximal to the chiasmatic sulcus *(79,80).* Charles Frazier (1870–1936) initially adopted this approach but later changed to an intradural frontobasal approach *(81).* Upon experiencing unexpected hypotension, even in patients who had not experienced significant bleeding, he later changed to a two-stage procedure *(82).* He later concluded that the transnasal operation, with which he accrued some experience, should not be used for patients with visual symptoms, a view later shared by Cushing.

In 1910, after a number of experimental hypophysectomies in dogs, Silbermark suggested an approach to the hypophysis through the Sylvian fissure *(62,83).* In May 1914, George Heuer (1882–1950) of Baltimore, Maryland, applied Silbermark's proposal and performed an intracranial intradural approach to the chiasm *(84–87)* followed shortly afterwards by Alfred Adson (1887–1951) of the Mayo Clinic. After being conscripted to France in 1917, Heuer's experience of 20 cases was presented by Walter Dandy before the Johns Hopkins Medical Society on February 4, 1918 on the insistence of Halstead. The advantages of the pterional approach to lesions in the suprasellar area or inferior third ventricle region, using the natural tissue planes along the sphenoid wing at the frontotemporal junction, eventually became apparent and this approach has become the most frequently used transcranial approach to the sella region *(88).* The pterional approach as we know it today was subsequently refined and described in detail by Gazi Yasargil, minimizing brain retraction by splitting the Sylvian fissure and opening the basal arachnoid to allow egression of cerebrospinal fluid *(89).*

Eventually, on 16th March 1907 in Innsbruck, Austria after publishing a review on the topic of pituitary surgery *(90)* and influenced by Davide Giordano (1864–1954), Herman Schloffer (1868–1937) performed the first successful transsphenoidal removal of a pituitary tumor *(91).* The patient was a young man with hypopituitarism who had visual failure, headache, loss of libido, and loss of body hair. Examination revealed a bitemporal hemianopia and genital atrophy. A left nasal rhinotomy was performed, and the nose was reflected together with the bony nasal dorsum toward the right-hand side (Fig. 11). The transsphenoidal technique subsequently underwent a number of modifications culminating in the description by Halstead of the oronasal rhinoseptal approach with a sublabial gingival incision subsequently adopted by Cushing (Fig. 12). After initial disappointments with transcranial procedures, Cushing adopted this approach. Combining suggestions from various surgeons and using the submucosal dissection technique advocated by Eisenberg and Kocher, Cushing went on to perform 231 such procedures over a 15-yr period from 1910 to 1925 with a reported mortality of 5.6% *(74).* Cushing later, in fact, abandoned the transsphenoidal approach, reverting to the transcranial approach, believing that it enabled the optic apparatus to be more readily decompressed. Owing to Cushing's enormous influence at the time, transsphenoidal pituitary surgery became largely neglected. Norman Dott (Fig. 13), however, who had worked under Cushing, remained committed to the transsphenoidal approach. Out of deference to his mentor, he never publicized his preference, eventually passing on these skills to Gerard Guiot (1912–1996) *(92)* and Jules Hardy *(93).* They in turn then introduced fluoroscopy and the operating microscope to the procedure, with Hardy pioneering selective adenomectomy as we know it today. Although this transsphenoidal

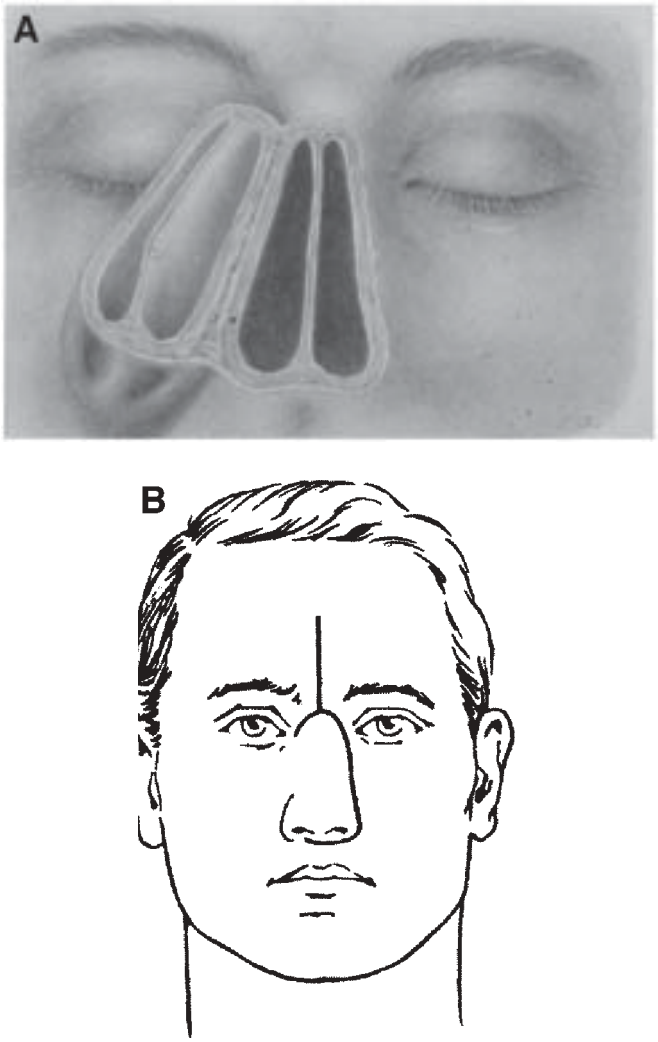

Fig. 11. Schloffer's transnasal transsphenoidal operation. An incision is made along the left nasolabial furrow around the left nostril and continued up to the glabella. The whole external nose is reflected exposing the septum. From Cope, V. Z. *Br. J. Surg.* 1916; **4:** 107–144.

approach has been universally adopted as the standard approach for almost all sella tumors, a role for transcranial approaches has, nevertheless, persisted.

The Advent of Roentographic Evaluation

Performed under the guidance of localization theory alone, neurosurgery at the end of the 19th century was associated with significant mortality and morbidity *(94).* The traditional diagnostic and localization modalities of percussion, palpation, and auscultation did not apply to intracranial pathology. Furthermore, the fragility and eloquence of the brain restricted the use of exploratory procedures *(94).* Until the late nineteenth century, noninvasive investigation of the pituitary gland was unavailable. The 8th November 1895 provided the inception of neurodiagnostic imaging. Wilhelm Conrad Roentgen (1845–1923), while studying the phenomena accompanying the passage an electrical current through gas at extremely low pressure, noted that this induced fluorescence in barium platinocyanide crystals lying on a nearby table. This rapidly led to a major medical milestone with the sensational discovery of X-rays. This was announced to the world on 6 January 1896 and was greeted with universal enthusiasm. In 1901 Roentgen was awarded the Nobel Prize for physics for this work *(95,96).* Very rapidly, every region of the body was extensively investigated, including the cranium and the first published skull radiograph appeared in 1896 in William Morton's book *The X-Ray (97).* In 1896, Cushing was a house officer at the Massachusetts General Hospital (MGH). He very rapidly appreciated the importance of the discovery and the diagnostic possibilities, relaying his enthusiasm in a letter to his parents *(98).* In 1896, he personally assisted financially in the procurement of a unit for MGH. After the conservative MGH staff refused to re-imburse him, he took the unit to the Johns Hopkins Hospital where he took up residency in the same year.

In 1899, Hermann Oppenheim (1858–1919), a leading German neurologist and diagnostician, noted and described dilatation of the sella turcica as a consequence of hypophyseal tumors *(99).* This initially became evident in patients with acromegaly but soon it became appreciated that even patients "without acromegaly," and furthermore with other recognizable and definable symptoms, could possess pituitary fossa's expanded by hypophyseal tumors. This association next became apparent to gynecologists and ophthalmologists. Women presenting with idiopathic secondary amenorrhea, frequently complained of visual disturbances and would be referred for a formal ophthalmological evaluation. This would reveal fairly constant visual field defects —typically a bitemporal hemianopia. Gradually the relationship of patterns of visual failure to compression of various parts of the optic chiasm also became recognized and the importance of routinely performing skull roentograms to assess for enlargement of the pituitary fossa was appreciated. As understanding of the presentation of pituitary pathology evolved, so were the foundations for the new specialty of neuroophthalmology being laid. Throughout his career, Cushing understood the extent to which the visual pathway was represented in the brain and its importance in localization of brain tumors. All his patients had their visual fields and acuities meticulously assessed and recorded. The similarities with regard to sexual dysfunction, infertility, other features of hypopituitarism, and visual impairment in men soon also became apparent *(3).*

As clinical neuroendocrine syndromes became better defined, the advent of roentographic skull studies meant that pituitary-related symptoms and signs could now be correlated with indisputable radiological evidence of a pituitary region mass lesion. This had important implications for management as confirmatory radiological studies data now meant that surgical intervention became a viable option

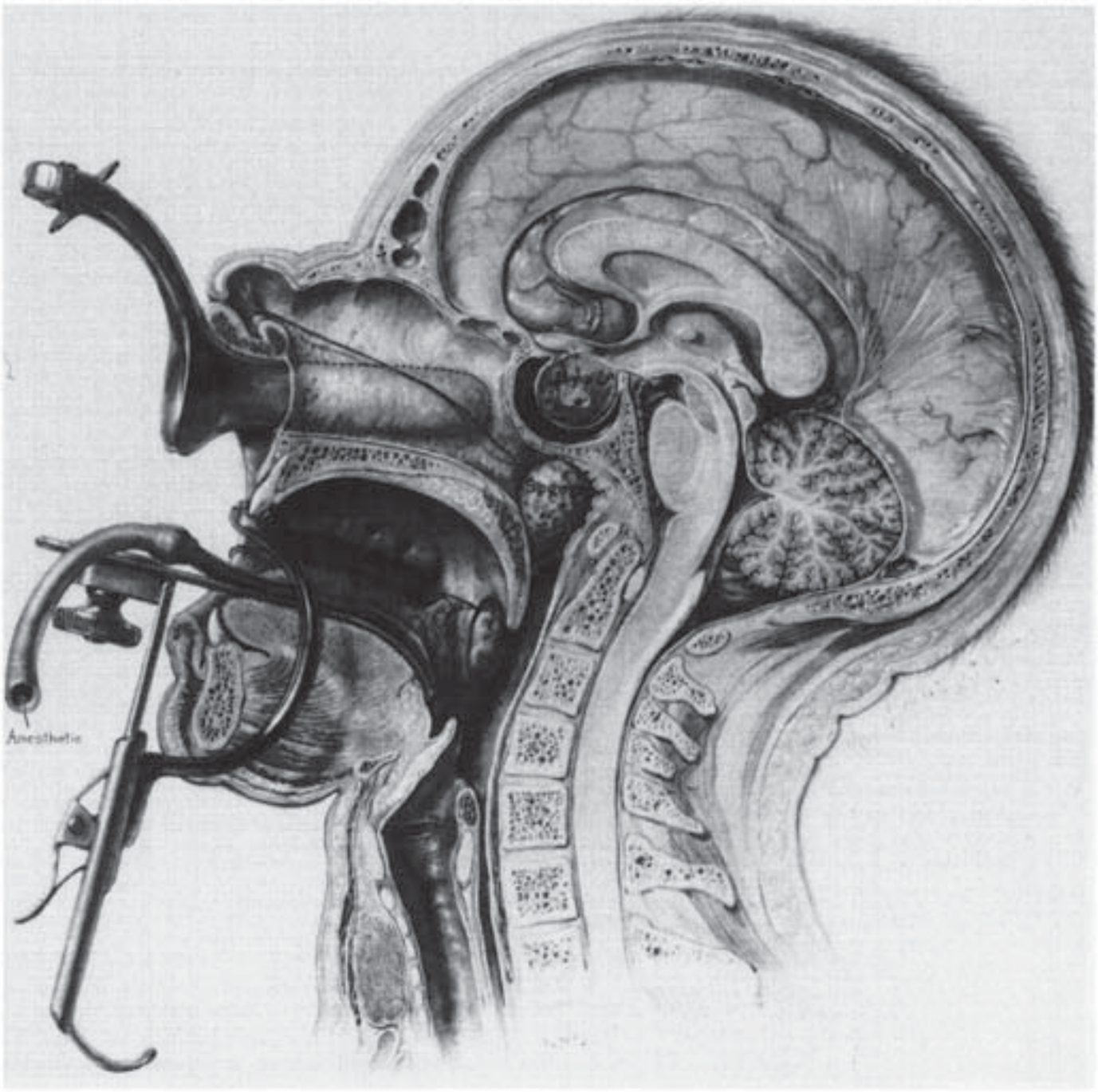

Fig. 12. Drawing made in 1912 by renowned medical illustrator Max Brodel showing Cushing's adaptation of the transsphenoidal approach to the pituitary. The sagittal diagram shows substitution of the two lateral retractors for a self-retaining bivalve speculum. From Cushing, H. *JAMA* 1914; **63:** 1515–1525.

in management. For microadenomas *(100)*, however, a problem with respect to radiological diagnosis, localization, and evaluation persisted. The presence of an adenoma with a diameter of less than 10 mm could only be confirmed by additional radiological techniques. Hypocycloidal tomography evolved as the most popular radiological technique for detecting these lesions by demonstration of focal changes, namely, deformation and/or thinning of the sellar floor *(101)*. However, the dilemma remained in determining the degree of suprasellar extension.

In 1913, W. M. Luckett reported a case of post-traumatic pneumocephalus in a patient struck by a tram *(102,103)*. The skull radiograph showed a clear outline of a very dilated ventricular system filled with air and requiring drainage. This was the first demonstration of intracranial structures by an intracranial contrast medium. Five years were to pass

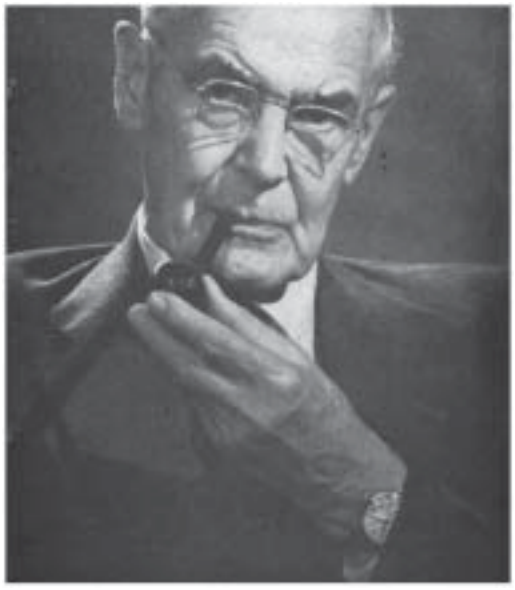

Fig.13. Professor Norman McOmish Dott of Edinburgh (1897–1973). From personal collection Dr. E. R. Laws—with permission.

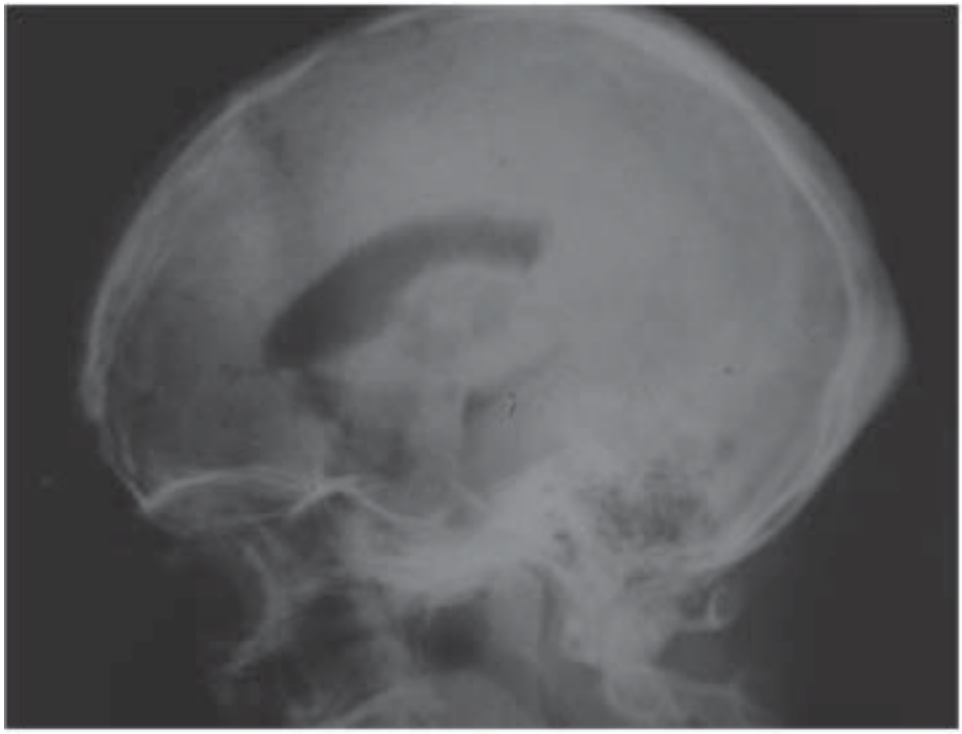

Fig. 14. Skull pneumoencephalogram clearly demonstrating the outline of the suprasellar extension of a pituitary macroadenoma projecting into the suprasellar cistern filled with air introduced via lumbar puncture. From personal collection Dr. I. F. Martin—with permission.

before Walter Dandy (1886–1946) would describe pneumoventriculography, crediting William S. Halstead (1852–1922) for introducing him to the technique *(104).* In the absence of contrast media, Dandy found that radiographs were only helpful in 45% of cases—a result of having to rely on calcification, bony erosion, or pineal displacement. In 1919, he began experimenting with the introduction of air into the subarachnoid space via lumbar puncture generating pneumoecepholography as opposed to pneumoventriculography *(105).* This produced a clear outline of the extension of pituitary adenomas into the suprasellar cisterns (Fig. 14). By using a combination of pneumoventriculography and pneumoencephalography, Dandy predicted that no intracranial tumor would be able to escape detection *(105).* The procedure was, however, not without difficulty. Patients often described the investigation as being far more

painful than the operation, dictating the universal use of general anesthesia. Despite these advances in largely outlining intracranial lesions, the narrow range of cerebral densities, especially on a plain skull radiograph, meant that the soft tissues of the brain remained indistinguishable. The first advance toward a solution came with the concept of plain film tomography by Ziedes des Plantes in 1921 *(106,107).* He believed that interpretation of shadow tomography could be simplified by eliminating superimposed shadows by visualizing a single plane at one time, blurring all shadows cast by tissues anterior and posterior to the area of interest. The first tomogram was subsequently built in 1931 *(107).*

In 1961, William H. Oldendorf (1925–1992) of the Wadsworth Veterans Administration Hospital in Los Angeles, tired of performing endless angiograms and pneumoencephalograms and wanting to find and research a new imaging technique, adapted tomographic images to brain scanning. This rotated a radiation source and detector around an axis allowing tissue at the intersection to contribute a constant component of radiation absorption. He later had to abandon work on this project after being unable to obtain financial backing *(107).* In 1963, Allan M. Cormack (1924–1998) adapted the mathematical principles regarding Fourier transform of Ronald N. Bracewell (born 1921) to radiology *(108,109).* This facilitated the development of the first computerized tomography scanner by English computer expert Sir Godfrey Hounsfield (1919–2004) in 1970 *(110).* They later shared the 1979 Nobel Prize for Medicine. Pneumoencephalography was thus rapidly replaced by this new noninvasive diagnostic modality computed tomography and then ultimately by magnetic resonance imaging. Both these modalities are able to further enhance resolution using contrast media. The additional resolution of dynamic sequence MRI scanning for pituitary adenomas now enables detection and localization of microadenomas 3 mm in size. The detection and intrapituitary localization of hypersecreting adenomas with diameters of less than 3 mm—the resolution limit of modern-day imaging techniques—have been further facilitated for Cushing's disease by the use of an interventional neuroradiological technique —bilateral simultaneous inferior petrosal sinus ACTH sampling enhanced by corticotrophin-releasing hormone stimulation *(62,111).* This detects a gradient between central and peripheral ACTH levels before pituitary secretion gets diluted.

After Dott had introduced Guiot to the Cushing technique of transsphenoidal pituitary surgery, Guiot introduced intraoperative radiography and later, together with Jules Hardy, image intensification *(112–114).* This was a tremendous advance for transsphenoidal surgery. It assisted the surgeon with regard to the intraoperative approach and resection in the sagittal plane. This surgical adjunct was further advanced by the technique of intraoperative air encephalography to both increase intracranial pressure in order to reduce the diaphragma sella with the rostral suprasellar extension of a pituitary macroadenoma down into the operative field and to provide an air encephalogram enabling evaluation of the position of the diaphragma *(115).*

The imaging dilemma for the pituitary surgeon, however, remained identification of the anatomical midline and navigating to the sella between the internal carotid arteries, particularly in reoperative cases. To a large extent this has been overcome by the development of intraoperative frameless stereotaxy, which enables the surgeon to navigate intraoperatively relative to a preoperative X-ray in one plane *(116)* or a preoperative CT or MRI scan in three planes, making transsphenoidal procedures quicker, safer, and more effective *(117).* The most recent development has been the introduction of intraoperative magnetic resonance imaging providing virtually real time navigation and assessment of surgical progress and the extent of tumor resection *(118).* This, however requires a totally non-ferromagnetic theater environment, and the considerable cost involved puts it beyond the budgets of most neurosurgical units.

Distillation of the Internal Secretions

A more comprehensive understanding of the function of the pituitary gland was essential for the treatment of pituitary pathology to be able to advance. The fact that the pituitary consisted of two discrete components seems to have been first appreciated by Thomas Willis *(119).* He belonged to the iatrochemical school that believed that the vital phenomenon was chemical in nature. The Venetian anatomist Giovanni Domenico Santorini (1681–1737) recognized as early as 1724 that the anterior pituitary was a discrete entity and not a continuation of the infundibulum *(6,13,119,120).* Albrecht von Haller (1708–1777) clearly distinguished the pars anterior from the pars posterior by 1766. In 1779, William Cullen (1712–1790) appreciating its extra-axial location, described the pituitary as an "appendix to the brain." An important advance in understanding the physiologic significance of the pituitary was made in 1895 by George Oliver (1841–1915) and Edward Schafer (1850–1935). They demonstrated a hypertensive response in animal models when injected with an extract of fresh pituitary under general anaesthetic—the vasopressive response *(121).* The participation of Schafer, a leading British professor of physiology, was a major turning point for endocrine research. This meant that organ extracts were now acceptable and rapidly became a serious occupation of the physiologist *(6, 13).* This belief was confirmed when Schafer, on 2 August 1895, subsequently addressed the British Medical Association on the topic: "My definite subject—that of internal secretions—is one of far reaching interest, although its full importance has only lately come to be recognized" *(122).*

Emil Goetsch (1883–1963), a co-worker of Cushings, claimed that the growth and sexual development of rats were stimulated by feeding them acetone-dried powder prepara-

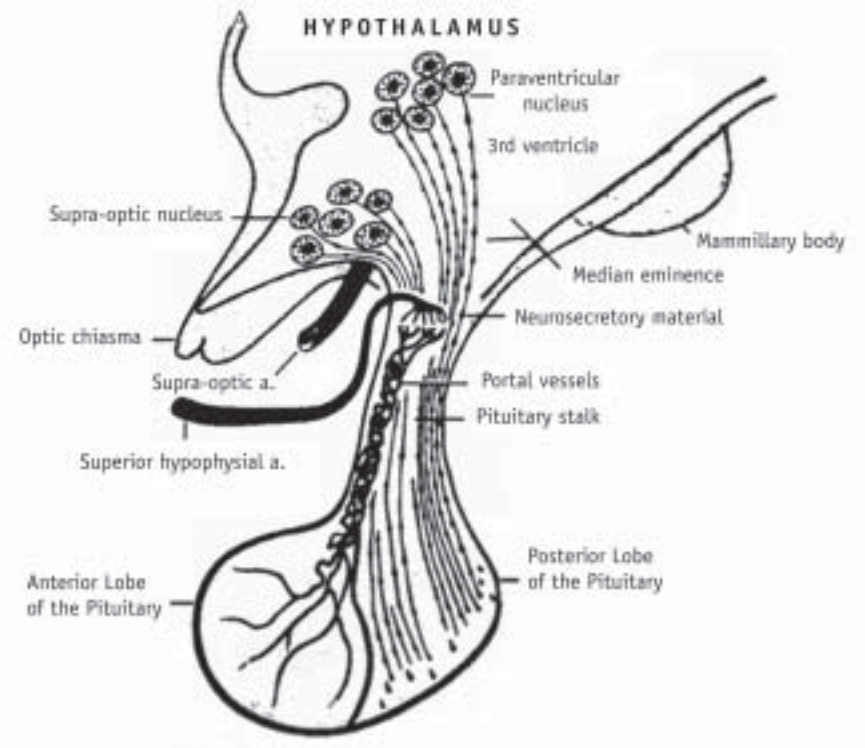

Fig. 15. The diagram used by Andrew V. Schally in his Nobel Prize lecture to represent the thalamohypophyseal portal circulation.

tions of whole pituitary glands *(38).* The natural extension of this work was to develop pituitary replacement therapy. In 1921, Herbert McLean Evans (1882– 1971) and Joseph Abraham Long managed to prove that the anterior lobe of the pituitary contained a growth-promoting hormone *(123).* Phillip Smith (1884–1970) and his colleague Earle Engle (1896–1957) demonstrated that hypophysectomy inhibited somatic growth as well as the development of the gonads, thyroid, and adrenal cortex *(124).* In 1933, Oscar Riddle identified the pituitary hormone controlling the secretion of milk as prolactin *(125).* His work eventually led to the development of a bioassay for prolactin *(126).*

Herbert Evans' laboratory continued to contribute to the understanding of pituitary physiology *(6,127).* In 1940, Choh Hao Li, Miriam Simpson, and Evans isolated the interstitial cell-stimulating (luteinizing) hormone *(128).* This amazing team went on to discover and isolate the adrenocorticotrophic, growth, and follicle-stimulating hormones in 1943, 1944, and 1949, respectively *(129–131).*

By the early 1950s, based on anatomical observations and physiological experimentation from several groups in the United States and Europe, it became abundantly clear that the endocrine secretions of the adenohypophysis—well known by then to control all the functions of all the target endocrine glands (thyroid, gonads, adrenal cortex) plus the overall somatic growth of the individual—were somehow entirely regulated by some integrative mechanism located in the neural elements of the ventral hypothalamus. Owing to the peculiar junctional anatomy of this region between the ventral hypothalamus and the anterior pituitary, the mechanisms involved in the hypothalamic control of adenohypophyseal function were best explained by proposing the existence of secretory products by yet uncharacterized neuronal elements of the ventral hypothalamus which reached the adenohypophysis via the capillary vessels of the hypothalamic–adenohypophyseal portal circulation. In 1977, Roger Charles Louis Guillemin (born 1924) and Andrew Schally (born 1926) shared the Nobel Prize for medicine for their joint discovery of the neuropeptide hormones (CRH, LH-RH, and TRH) and the endorphins (Fig. 15). Rosalyn Sussman Yalow (Fig.16), a medical physicist from the Bronx Veterans Hospital, was a co-recipient of the same prize for her invaluable contribution to endocrinology in developing a process called radioimmunoassay, enabling precise and fairly rapid measurement of circulating hormones. Slowly, the various components of the puzzle were being assembled and technology developed to facilitate further advances. Nowadays current technology is moving away from radioimmunoassay toward chemoilluminescent techniques.

In 1794, Johann Peter Frank (1745–1821) distinguished diabetes insipidus from diabetes mellitus *(132).* It was, however, Alfred Erich Frank, in 1912, who first clearly expressed the view that polyuria in patients with diabetes insipidus was probably caused by a hypophyseal lesion *(133).* In 1928, Oliver Kamm succeeded in separating the posterior lobe extract of pituitrin into vasopressor and oxytoxic fractions *(134).* The synthesis of vasopressin was achieved between 1953 and 1954 by Vincent du Vigneaud and his

Fig. 16. Rosalyn Sussman Yalow (1921–) Nobel laureate for her work on hormone radioimmunoassay.

co-workers *(135).* This accomplishment has subsequently contributed even further to the reduction of morbidity and mortality following pituitary surgery.

New Treatments

The use of improved diagnostic methods and the introduction of modern pituitary microsurgical techniques have led to an unparalleled increase in primarily transsphenoidal pituitary adenoma operations *(100).* Evaluation of neurosurgical resident logbooks in the United States indicates that 19% of primary brain tumor operations are now being performed transsphenoidally and personal series in excess of 1000 cases are no longer uncommon *(136).* The introduction of antisecretory drugs, predicted as early as 1912 by Cushing, has, however, stemmed this tide. In 1954, Mordechai C. Shelesnyak published a series of classic pharmacological experiments showing that ergotoxine inhibited deciduoma formation and implantation of the fertilized ovum in the rat. From this he deduced that prolactin was required for maintaining the corpus luteum and that ergotoxine would inhibit prolactin release and prevent decidua formation. This was before dopamine was recognized as a neurotransmitter and before dopamine receptors had been described or characterized. Fluckinger, working at Sandoz (the forerunner of Novartis), took this observation and developed bromocriptine as a selective prolactin inhibitor, avoiding the oxytocic and other adverse effects of the ergot alkaloids. He did this at a time when there was uncertainty as to whether prolactin actually existed as a pituitary hormone separate from growth hormone. In addition, there were no immunoassays for prolactin. Only bioassays were used measuring inhibition of lactation and prevention of deciduoma formation. Bromocriptine was subsequently introduced as a specific inhibitor of prolactin secretion. In 1972, Robert M. McLeod, at the University of Virginia Health Sciences Centre, while investigating the effect of various agents on in vitro culture of pituitary adenomas, found that the addition of dopamine caused tumor regression in prolactinomas. This helped identify dopamine as the prolactin inhibiting hormone—an observation that led *inter alia* to his new colleague Michael O. Thorner, speculating that bromocriptine was acting as a dopamine agonist. This was at a stage when dopamine was being introduced for the treatment of parkinsonism. When clinical trials started, interest was initially focused on normalization of hyperprolactinemia, reversal of gonadal dysfunction, and fertility. However, improvement of pre-existing visual field defects suggestive of tumor involution began being reported as late as 1975 by Corenblum *(142).* Thorner's main contribution was in subsequently confirming the rapid tumor involution of macroprolactinomas treated medically rather than surgically *(141).* This then led to the development of primary medical therapy for prolactinomas and not just its use to lower prolactin levels. Absolute proof of tumor regression was finally documented by CT in 1979 *(62,143).*

The somatotropin release-inhibiting factor (SRIF) somatostatin was detected by Brazeau in 1973 in hypothalamic extracts that reduced growth hormone synthesis in pituitary cultures *(144).* The therapeutic use of this polypeptide was unfortunately not practical due to its biological half-life of only 2–3 min *(145).* Systemic fragmentation and derivation of the minimal essential amino acid sequence of SRIF by Vale in 1978 *(146)* and studies designed to increase its functional activity, eventually resulted in the synthesis of octreotide, 70 times more active than SRIF and with a biological half-life increased to 113 min. This enabled treatment of many patients with acromegaly who had failed either surgery, radiotherapy, or both and in whom the mortality was two to four times that of the average person. In 1988, utilizing the knowledge of the structure of growth hormone and the growth hormone receptor, John J. Kopchick from the Edison Biotechnology Institute of the University of Ohio attempted to identify a molecule that would block the GH receptor using a molecular modeling technique *(147).* By substituting nine amino acids he was able to produce a substance (B2036-PEG) that preferentially blocked the GH receptor preventing dimerization of the two GH receptor arms and the generation of the cascade resulting in the production of IGF-1. This new growth hormone receptor antagonist pegvisament may now supercede the role for somatostatin in the management of refractory acromegaly with an ability to normalize IGF-1 levels in 92% of patients *(148).*

External Radiation Therapy

In many respects the management of GH-secreting pituitary adenomas in patients with acromegaly provided a historical precursor to subsequent treatments of other pituitary adenomas. The first reported case of a pituitary adenoma being treated with radiotherapy was by Gramegna *(149).* This occurred in 1909 in Venice, the same year, incidentally, that Krause performed the first successful intracranial operation on a patient with a pituitary tumor *(73).* Gramegna's patient was a young female acromegalic presenting with

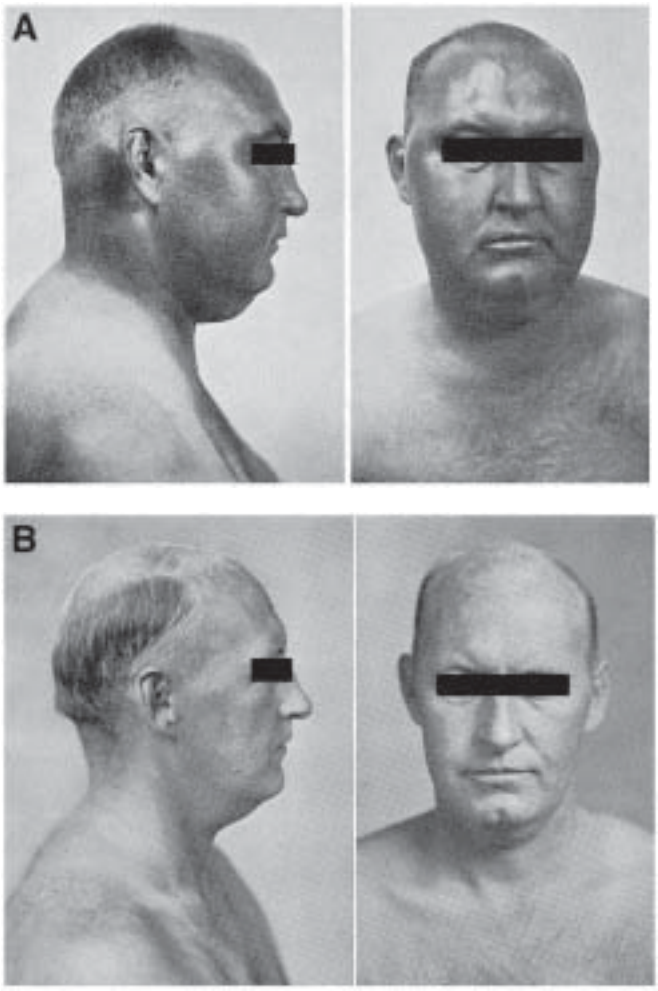

Fig. 17. Woodyatt and Colwell's patient (case 11): a 30-yr-old dentist showing the tense, plethoric and painful adiposity of the face (**A**) with resolution of Cushingoid facies after hypophyseal irradiation (**B**)—further confirmation of the association of hypercortisolism with a pituitary adenoma. From Cushing, H. *The basophil adenomas of the pituitary gland and their clinical manifestations (pituitary basophilism). Bull. Johns Hopkins Hosp.* 1932; **50:** 137–234.

severe headaches. She received two courses of radiotherapy transorally, responding incrementally after each treatment. Jaugeas *(150)* and Beclere also treated acromegalic patients with irradiation the same year, Beclere delayed publishing until 1922 *(151).* His patient had a remarkable response. The patient was a young acromegalic female, afflicted by visual failure and headaches. X-ray treatment was successful and 13 yr post-irradiation she was doing well, her visual failure and acromegalic symptoms having regressed, and her menstruation having returned. Such cases were, however, isolated and anecdotal, and it was several years before clinicians began systematically evaluating the effectiveness of irradiation. Despite this, as early as 1912, Cushing wrote already appreciating that "in certain forms of hypophyseal tumor prolonged rontgenization has a notable effect in ameliorating the neighbourhood symptoms, due in all likelihood to a definite shrinkage of the growth" *(1).* The importance of radiotherapy at this stage was not just its potential therapeutic role but also its important diagnostic role with regard to Cushing's syndrome. It was the success of pituitary irradiation of patients with Cushing's disease, however transient, that supported the argument for a pituitary etiology for the hypercortisolism (Fig. 17).

The first significant series of patients undergoing irradiation of pituitary tumors was reported by Heinisman and Czerny in 1926 *(152).* Further publications followed *(13, 153–158).* The general opinion was that radiotherapy should be considered as an adjuvant to surgery and only considered preoperatively if the patient did not have an acute or progressive clinical status. Nevertheless, at this stage not only did radiotherapy become the first-line of treatment at many centers because of its apparent low morbidity and efficacy in relieving the outward signs of the disease but also because it provided a non-invasive means of confirming the diagnosis of a suspected pituitary origin to the pathology *(6).* Many, however, remained skeptical. Charles Frazier (1870–1936) warned physicians about the limitations of irradiation as a means of preserving vision. Cushing, by 1932, had also begun to appreciate many limitations of radiotherapy writing: "So far as concerns radiotherapeusis, at least in the case of the chromophobe adenomas, it is safe to say that it will come to be discarded just as radiation for exophthalmic goitre has been, so soon as neurosurgeons as a class perfect themselves in the details of the operative procedure" *(159).* So in some respects he was correct but in others very wrong. While conventional external beam radiotherapy has begun to assume an increasingly smaller role in the management of pituitary lesions, so has stereotactic radiosurgery *(160)* begun assuming a steadily increasing role.

Future Developments

Despite the many advances already made over the past century with regard to the pathology and treatment of pituitary adenomas, there is still an immense amount to be learnt and done. The future lies predominantly in the field of molecular biology and in elucidating the pathogenesis of pituitary tumors and developing markers for predicting and understanding their behavior. This understanding at a molecular and genetic level will in turn facilitate the development of tumor control mechanisms and allow further advances in designer pharmacology such as with pegvisomant and more recently SOM 230, a somatostatin analog with high affinity for sst5 subtype somatostatin receptor for the treatment of Cushing's disease. It will also allow exploitation of these insights to develop other novel therapies and imaging techniques. Simultaneously, surgery has evolved to the point at which operations are now able to be performed via minimally invasive approaches using three-dimensional "brow-up" endoscopes. The use and accuracy of surgical adjuncts such as frameless stereotaxy has also

advanced so that they are now being used routinely to assist intraoperatively with both navigation during the approach and tumor resection. Conventional radiotherapy for pituitary lesions has also largely been superseded by stereotactic radiosurgery techniques, which are becoming standard for most neuroendocrine units. Most important, the patient benefit and cost effectiveness of providing specialist neuroendocrine centers with coordinated care by a team of neurosurgeons, endocrinologists, neuroradiologists, pathologists, oncologists, radiosurgeons, nursing, and theater and support staff is being appreciated *(161).*

Conclusion

It would require volumes to do justice to the many important historical contributions that have brought the medical community to the point where we now stand with regard to our understanding of the pituitary gland and the treatment modalities we have available. There would doubtless be many important contributions beyond the scope of a synopsis such as this or contributions possibly even neglected. It is well appreciated that the accrual of medical knowledge follows an accelerating trend. In few other spheres is this as evident as in the field of neuroendocrinology, where the entire evolution seems to have taken place over just a century. Despite all these advances, the amazing complexity of what remains one of the smallest organs in the human body—by virtue of size but not stature—makes one appreciate just how much more we still have to learn. This will hopefully provide inspiration to the many physicians and scientists worldwide concerned with pituitary related work that will no doubt soon lead to Cushing's prophetic words in 1912 becoming a reality.

Acknowledgments

It would be difficult for anyone to write a comprehensive history on any endocrine subject without drawing on Viktor Medvei's work: *The History of Endocrinology*. I am very grateful to him for the assistance it provided. I would also like to thank both Dr. Ian F. Martin and Prof. Mary Lee Vance for reviewing my manuscript and providing invaluable advice.

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