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Highlights from Endocrine Surgical History

Richard B. Welbourn, M.A., M.D.*

Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, University of London, London, U.K.

Abstract. Endocrine surgery includes excision of diseased or sometimes normal endocrine glands and occasionally the transplantation of endocrine tissues. Male castration was performed for social reasons in prehistoric times, and thyroid operations were described during the twelfth century. Until the end of the nineteenth century most operations were undertaken to relieve the local effects of pathologic enlargement of the thyroid, ovaries, pituitary, and adrenals; and with the development of anesthesia, antisepsis, and effective hemostasis, thyroidectomy for benign, nontoxic goiter was perfected. Thyroid deficiency followed total thyroidectomy, and thyroid replacement therapy was developed. Toxic goiter was sometimes relieved by partial thyroidectomy. After the discovery of hormones early this century, knowledge of endocrinology increased, and many syndromes of hormonal excess were described. Surgeons began to operate to relieve them. Results improved with mastery of surgical technique, especially for operations on the thyroid, parathyroids, and pituitary; with the development of methods for diagnosis of syndromes and the localization of lesions; with teamwork; and with the use of hormones, drugs, and radiotherapy as alternative or additional forms of therapy before, during, and after operation. Notable advances followed adequate resection of thyroid tissue and the use of iodine and antithyroid drugs before operation for toxic goiter. The use of cortisone rendered adrenalectomy safe for the relief of cancer of the breast and prostate and of Cushing's syndrome. For about 40 years increasing numbers of surgeons have specialized in endocrine surgery as a discipline within general surgery, and results of treatment have improved greatly.

Samuel Clark Harvey (1886–1953) (Fig. 1) was Professor and Chairman of the Department of Surgery at Yale from 1924 to 1947. He was a serious student of history, a subject he incorporated in his surgical teaching. He joined the staff of the Department of the History of Medicine at its foundation in 1951 and began to write a general history of surgery. Unfortunately, he died without completing it [1–3].

At that time general surgeons operated on the thyroid and most other endocrine glands, but for technical reasons operations on the pituitary were usually undertaken by neurosurgeons and ear, nose, and throat (ENT) surgeons. Harvey, however, was a general surgeon and, having trained with Harvey Cushing (1869–1939), included transcranial hypophysectomy in his surgical repertoire. No one then singled out operations on the endocrine glands as a special branch of general surgery, as many do today [4a].

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Present address: 2 The Beeches, Tilehurst, Reading RG31 6RQ, U.K.

Endocrine operations began in antiquity with castration, and Aristotle (384–322 BC) described its effects in men and animals but not in women [5]. This mutilating procedure, however, was performed only as a social or religious rite. Eunuchs were well known, but the ideas of ductless glands, internal secretions, and hormones had not yet been conceived. Surgeons did not begin to remove the testes or the ovaries therapeutically until the nineteenth century.

Thyroid Surgery: Phase 1

Goiters and their life-threatening complications have been known since ancient times. Surgeons have long tried to bring relief, and thyroid operations have always formed the backbone of endocrine surgery [4b]. The first credible account of operations for goiter was written by Roger Frugardi (twelfth century) of Salerno in 1170 [6, 7a]. He described the use of setons (two threads passed through a goiter at right angles, tied over a pack, and tightened twice daily until they cut through to the surface) and ligation of a pedunculated goiter with a bootlace.

The first thyroidectomy of which there is a published account was performed by Pierre-Joseph Desault (1744–1795) in Paris in 1791 during the terror of the French Revolution [7b]. Thirty years later Johann Hedenus (1760–1836) of Dresden successfully removed six suffocating goiters, a feat not equaled for many years [8]. Ligation of the thyroid arteries, described in 1811 by William Blizard (1743–1835) in London, proved useful for a long time [9]. He intended it as preliminary to thyroidectomy, but it was often used alone, causing diminution in size or sloughing and separation of the goiter.

Despite these successes, the results of thyroid operations in general, like those of all major procedures, were poor, and many patients died from bleeding and infection. During the middle of the nineteenth century the operative mortality from thyroid operations was about 40% [10a], and many reputable surgeons refused to do them [11]. However, a revolution in surgery was at hand in the form of anesthesia, antisepsis, and hemostasis; and the results of all operations, including those on the thyroid, began to improve.

First, anesthesia, which was pioneered in the United States during the 1840s, made operations easier but not safer because bleeding and sepsis continued to kill [10b]. A thyroidectomy was performed under ether anesthesia by Nikolai Pirogoff (1810–

Fig. 1. Samuel Clark Harvey (1886–1953). (Reprinted with permission from his daughter, Miss E. Harvey.)

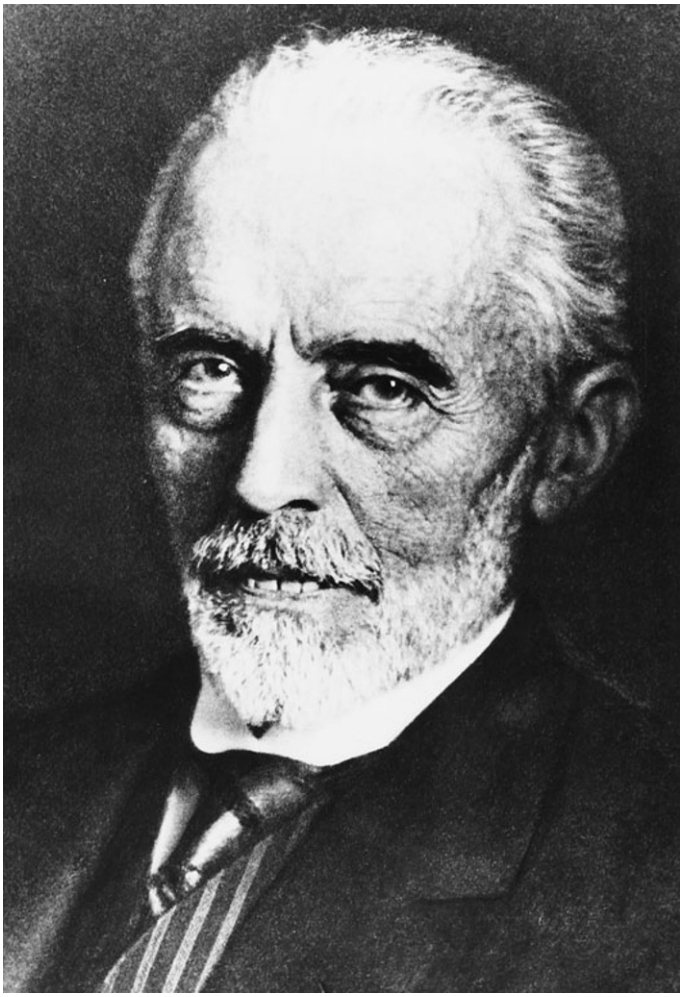

Fig. 2. Theodor Emil Kocher (1841–1917). (Reprinted with permission from Prof. M. Baggiolini, Director of Theodor Kocher Institute, Bern, Switzerland.)

1881) of St. Petersburg in 1849 [10c]. Antisepsis with carbolic acid, which came next, was introduced by Joseph Lister (1827–1912) in Glasgow in 1867 [7c]. It was adopted slowly, but wherever it was used the operative mortality fell [10d]. Steam sterilization and asepsis followed about 30 years later. The history of hemostasis, the third great advance, was recounted by Harvey in 1929 [12]. Prevention of bleeding at operation had been attempted in various ways for centuries, but the first really effective hemostatic forceps were described by Thomas Spencer Wells (1818–1897) in London in 1874 [13]. Forceps had a marked influence on surgery of the thyroid because it is such a vascular gland.

One of the first to use general anesthesia, antisepsis, and effective hemostasis together for thyroid operations was the great Swiss surgeon Theodor Kocher (1841–1917) (Fig. 2) of Bern [7d, 10e, 14]. He was appointed Professor of Surgery there in 1872 at the age of 31 and did more than any other surgeon, before or since, to develop the science and art of thyroid surgery. In 1909 he received a Nobel Prize, the first of several awarded to workers in endocrinology.* Switzerland was a major goitrous area, and Kocher undertook thousands of thyroidectomies. When he started his operative mortality was about 15%, but he reduced it progressively to less than 1% for simple goiter by the end of the century.

*Other Nobel Prize winners mentioned herein have (NP) after their names.

Gonads

During the eighteenth century the great surgical scientist John Hunter (1728–1793), of London, castrated cockerels, replaced their testicles in the abdomen, and found that the male secondary sex characters depended on the presence of viable testes. His main interest, however, was in the vital forces that allowed organs to be transplanted, and it was left to Arnold Berthold (1803–1861) of Göttingen, a century later, to confirm Hunter's findings and to conclude that the testes controlled development of the secondary sex characteristics through their influence on the blood [5]. These findings were pertinent to much other work on internal secretions undertaken during the second half of the nineteenth century but were strangely overlooked until 1910; they played no part in the general development of endocrinology until then [15].

Operations on the ovaries to drain or remove cysts were pioneered by Ephraim McDowell (1771–1830), a frontier practitioner in Danville, Kentucky (U.S.A.) in 1809. His work opened the door to abdominal surgery long before the advent of antisepsis [16]. Removal of normal ovaries for dysmenorrhea and neurosis was introduced by Robert Battey (1828–1895) of Augusta, Georgia (U.S.A.) in 1872 [5] but by 1895 had fallen into disrepute, when George Beatson (1849–1933) of Glasgow removed the ovaries from women with advanced breast cancer, with marked regression of the growth in one case. At about this time William White [1850–1916] of Philadelphia suggested castration to relieve benign prostatic obstruction, and the operation was soon practiced widely but with little benefit.

Somewhat earlier, in 1889, the distinguished Parisian scientist Charles-Édouard Brown-Séquard (1817–1894), then aged 72, made the extraordinary claim that he had rejuvenated himself with injections of canine testicular extract [5]. He apparently did not know of Hunter's and Berthold's work because had he done so he would surely have used it to support his claim. He went on to assert that bovine testicular extracts were even more effective and would relieve not only senile debility but locomotor ataxia, pulmonary tuberculosis, malignant ulcers, Addison's disease, and many other afflictions. This work, though ridiculed by many scientists, stimulated much interest in internal secretions. Many people accepted Brown-Séquard's work uncritically and claimed that they had confirmed his findings. This new treatment was named "organotherapy" and was exploited by physicians, quacks, and pharmaceutical firms worldwide. Clinical endocrinology, which was emerging at the same time, was long confused with it and therefore "suffered obstetric deformation at its very birth."

Later some surgeons undertook *surgical* organotherapy, and in France during the 1920s Serge Voronoff (1866–1951) of Paris transplanted apes' testicles into about 50 men of all ages, most of whom suffered from hypogonadism or senile debility [17]. Voronoff claimed that many of these men had been rejuvenated. His "before and after" photographs are unconvincing, but several other surgeons, including Max Thorek (1880–1960) in Chicago, followed suit. Organotherapy was a blind alley, but it persisted into the 1930s, when at last clinical endocrinology came into its own.

Thyroid Surgery: Phase 2

Despite the use of hemostats, fear of bleeding from the cut surface of the thyroid long deterred surgeons from incising it, and they undertook total lobectomy instead. If a unilateral operation failed to relieve suffocation, they removed the whole gland. The thyroid was not known to have any important function until 1883, when Kocher learned from Jacques-Louis Reverdin (1842–1929) of Geneva that total thyroidectomy might change people's personalities and physical features in distressing ways [5]. Kocher called back 18 patients on whom he had performed this operation and found that 16 were affected. (Eventually all were.) He named this condition "cachexia strumipriva" and was struck by its similarity to cretinism in children. Others noted its resemblance to myxedema in adults. No one knew the causes of these diseases, but Felix Semon (1848–1921), an ENT surgeon in London, pointed out that cretinism, myxedema, and cachexia were all associated with an absence or degeneration of the thyroid. He suggested that somehow this deficit caused the diseases, and research by many workers soon proved him right.

One of these investigators was Victor Horsley (1857–1916) of London, who studied the effects of thyroidectomy in animals [5]. His findings led him to suggest to George Murray (1865–1939) of Newcastle-upon-Tyne that he should inject thyroid extract to treat people with myxedema. Murray did so in 1891, two years after Brown-Séquard's report of organotherapy. He did not mention this work and had sound reasons for acting as he did. People were skeptical, but his first patient recovered and remained well for 30 years [18]. Others soon found that thyroid extract was effective by mouth as well.

Glandular Deficiency and Excess

The work on thyroid function did much during the 1890s to promote the idea that loss of internal secretions by ductless glands caused disease. Not only did thyroid deficiency cause cretinism and myxedema, but much evidence suggested that deficient secretion by the adrenal cortex and the pancreatic islets caused Addison's disease and diabetes mellitus, respectively. Bold surgeons used heterografts to treat these diseases, but transplanted animal tissues were ineffective [19]. After the success of thyroid extract, William Osler (1849–1919) in Baltimore prepared a weak adrenocortical extract and used it with clear benefit in one addisonian patient [5]. At this time also epinephrine (adrenaline) was isolated from the adrenal medulla [20]. All this work had been done before secretin, the "first hormone," was discovered in 1902.

People were not yet ready for the idea that ductless glands might secrete excessively, but surgeons had already begun to operate for three diseases, which are now known to arise in this way: toxic goiter, acromegaly, and adrenal virilism. However, they operated because the patients had tumors, not because they suffered from endocrine disease.

Toxic goiter had been described posthumously by Caleb Parry (1755–1822) of Bath, England, in 1825 and later by Robert Graves (1795–1853) in Dublin and Carl von Basedow (1799–1854) in Merseburg, Germany [21a]. During the next 60 years several patients, operated on because they had goiters but who had clearly been thyrotoxic, were cured of their symptoms by operations that included the use of setons, arterial ligation, and thyroidectomy. No one seemed to appreciate the significance of this result until 1884, when Ludwig Rehn (1849–1930) of Frankfurt-am-Main reported three patients who were cured of their toxic symptoms incidentally when their goiters were removed for the relief of dyspnea [5]. He proposed quite reasonably that overactivity of the thyroid was responsible for the condition; but this idea remained controversial for a long time.

At about the same time, acromegaly was described by Pierre Marie (1853–1929) in Paris. In keeping with the prevailing climate of opinion, he regarded it as a manifestation of pituitary insufficiency [21b]. Soon after, in 1889, Horsley, a pioneer of neurosurgery who had also worked experimentally on the thyroid, operated transcranially for a pituitary tumor to relieve headaches [22]. A few years later Frank Paul (1851–1941) of Liverpool treated an acromegalic patient similarly [23].

Adrenal tumors sometimes presented as abdominal swellings. In 1855 Thomas Addison (1793–1860) of London had described a disease, which was later named after him, in which tuberculous

and other lesions destroyed the adrenal cortices [21c]. No other adrenal syndromes were then recognized. It is hardly surprising therefore that Knowsley Thornton (1845–1904), of London, thought that a large abdominal mass in a woman with severe hirsutism arose from the kidney or the spleen [24]. He removed it successfully and found that it weighed at least 20 pounds (9 kg) and that it was a carcinoma of the adrenal cortex. Convalescence was stormy, but the patient recovered [25], only to die 2 years later from recurrence [26]. Thornton was well prepared for this feat, as he had worked with Lister, who had taught him antisepsis, and with Wells, from whom he would have learned how to operate on the abdomen and to control bleeding. However, he did not relate the hirsutism to the adrenal cortex.

Endocrinology and Endocrine Surgery

By the turn of the century, then, knowledge was accumulating about the role of ductless glands in disease. The concept of glandular insufficiency was widely accepted, and that of excessive secretion had been proposed. Surgery of the thyroid for relief of goiter had been developed remarkably and its role in causing glandular deficiency established. The possibility that *excessive* secretion by the thyroid could cause disease was being actively investigated.

Most *normal* bodily functions, however, were thought to be under the control of the nervous system, a view strongly supported by Russian physiologist Ivan Pavlov (1849–1936) (NP) [27a] of St. Petersburg. A new concept, however, was soon provided by two younger physiologists, William Bayliss (1860–1924) and Ernest Starling (1866–1927) in London. They knew that acid in the small intestine stimulated the secretion of pancreatic juice, presumably by nervous reflex action. In 1902 with simple, elegant experiments they discovered that pancreatic secretion resulted from a *chemical* reflex, activated by a blood-borne agent or body derived from the jejunal mucosa, which they named "secretin" [27b]. In 1905 Starling proposed the name "hormone," from a Greek word meaning "to excite," for this new class of substances that provided stimulation via the bloodstream [5]. The term "internal secretion" was no longer adequate to describe them. Hormones were soon accepted generally, and a new principle in physiology was established. The science of endocrinology was launched, but clinical endocrinology still had far to go.

With the new century the novel science developed rapidly, and surgeons contributed much to it. More and more endocrine glands and hormones were recognized, and several diseases caused by hormonal excess were discovered. These diseases in particular provided challenges and opportunities for surgeons. Endocrine surgery entered a new and exciting phase in which operations to cure disease, by removing overactive endocrine glands and tumors, were developed and refined. Sometimes surgeons rose to the opportunities provided by first encounters with new diseases, and often they made disciplined attacks on successive difficulties until their long-sought goals were achieved. Many surgeons became expert in the science and surgery of individual glands, notably the thyroid, pituitary, adrenals, and parathyroids; and they worked closely with colleagues in other disciplines for their diagnosis, treatment, and research. In some cases new medicines or other therapeutic measures made surgery safer; in others they augmented it; and sometimes they replaced it. As fast as surgery retreated on one front, it advanced on another; and different forms of therapy joined in a cooperative game of leap-frog. Some of the landmarks are described here in the approximate order in which they first figured large on the historical horizon.

Toxic Goiter

Toxic goiter provided the first challenge. Soon after Rehn's paper, Kocher began to operate for toxicity, rather than for goiter; and within 20 years he had treated some 250 patients. He removed one lobe, as he did for simple goiter, but the operative mortality was much higher (3.5%). Moreover, one-fourth of the patients were not cured and required second operations [28]. Kocher turned to preliminary ligation of the thyroid arteries, as Blizard had done for simple goiter, to render the operation safer. He found that the improvement was so marked he could then excise the goiter without risk, or that he need not do so at all. Surgeons in North America who visited Europe followed suit.

First, William Halsted (1852–1922), from Baltimore, used Kocher's methods and obtained similar results [10f, 28]. Charles Mayo (1865–1939), from the Mayo Clinic in Rochester, Minnesota, went next. He was the first to use the term "hyperthyroidism" [29] and was later called "the father of American thyroid surgery" [30].

Most surgeons were now reluctant to remove more than one lobe of the thyroid for fear of causing hypothyroidism. In 1905, however, Frank Hartley (1856–1913) of New York approached the problem in a new way and proposed that cure of this disease depended on removal of sufficient thyroid tissue [31]. He claimed that by removing all of one lobe and often part of the second at the same time he had provided relief for more than 90% of his patients. Partial resection of thyroid lobes, instead of total lobectomy, had been pioneered for simple goiter some 20 years before by the Polish surgeon Johann von Mikulicz (1850–1905) of Cracow [32]. He had had the courage to cut into the gland and to leave a portion at the back of each lobe, when both had to be resected, to avoid hypothyroidism and injury to the recurrent laryngeal nerves. This operation had not been adopted widely, and Kocher found it unusually difficult [33]. Hartley had worked with Halsted, employing cocaine for local anesthesia. Both had become addicted, and Hartley died before he could contribute more [34].

Kocher, Halsted, and William Mayo (1861–1939), Charles' brother, all accepted Hartley's policy in theory [28]; but an Australian surgeon, Thomas Dunhill of Melbourne, did the most to develop it [34]. From 1909 onward this great pioneer, working on his own, removed the whole of the larger lobe and often half of the second lobe at one operation. In 1912 he reported 380 patients; only four had died (1.05%), and few required more operations [35]. Dunhill continued this work in London after World War I [36]. Other surgeons, including Charles Mayo, soon adopted this practice of removing more than one lobe [37] and gradually changed to bilateral subtotal resection, of the Mikulicz type, usually at a single operation [38].

Iodine provided the next great therapeutic advance for toxic goiter. It had been used on its own quite effectively for some years to treat both simple and toxic goiters. In 1923 Henry Plummer (1874–1936), an internist, and Walter Boothby (1880–1953), a clinical physiologist, at the Mayo Clinic, reported using Lugol's iodine preoperatively in 600 patients with toxic goiter. The number who died in hospital, awaiting operation, fell by two-thirds, and the operative mortality fell from 3.5% to 1.0% [39].

Charles Mayo and his colleagues almost abandoned thyroid artery ligation with "all its attendant suffering, morbidity, and expense" [40]. During the 1930s preoperative iodine therapy became the standard procedure worldwide, and the overall results improved [36, 38].

Then during the 1940s in the middle of World War II, two more developments transformed the situation within a few years. Radioiodine was introduced therapeutically in Boston and at Berkley in 1942 [41, 42] and antithyroid drugs in Boston the next year [43]. In 1944 Oliver Cope (1902–1994) and his resident Francis Moore (b. 1913) used thiouracil preoperatively [44]. Other antithyroid drugs followed, and adrenergic β-blockade was introduced in 1965 [45]. Soon these drugs and radioiodine, together with thyroidectomy, were used as alternative or complementary methods of treatment [4c], and the therapeutic problems of toxic goiter, at least at specialist centers, were virtually solved [46].

Pituitary

The pituitary provided the next challenge [4d]. At the beginning of the twentieth century few surgeons were ready for Horsley's transcranial operations; and general surgeons, ENT surgeons, and neurosurgeons turned to a transsphenoidal approach. The first method, introduced in 1907 by Hermann Schloffer (1868–1937), a general surgeon in Innsbrück, involved crude mobilization of the nose, and many patients died from meningitis [22]. Kocher and others in Europe and America made refinements, but pride of place goes to the great neurosurgeon Harvey Cushing (Fig. 3) [47, 48], who had close links with Yale. He graduated with his B.A. from there but pursued his main life's work in Baltimore and Boston, where he developed neurosurgery as an independent specialty. After retirement he returned to Yale as Stirling Professor of Neurology until his death in 1939.

Cushing approached the pituitary through the mouth, the nose, and the sphenoidal sinus [22], although he and others (including Harvey) continued to develop and use transcranial operations, when appropriate [49]; and they still operated to relieve the pressure effects of tumors. Some acromegalic patients obtained partial relief from their disease after operation, and soon this fact helped people to realize that acromegaly was a form of hyperpituitarism [50]. Growth hormone was not discovered until the 1920s, and another 10 years elapsed before pituitary operations were often undertaken to relieve endocrine disease.

Adrenals

Adrenal surgery came next [4e]. Syndromes of adrenocortical excess, which had not been recognized before, were described from the early 1900s. They included the adrenogenital syndrome [51], which Thornton had seen and failed to diagnose, and an "obese" form, which was later recognized as a variety of Cushing syndrome [52]. The adrenal lesions were either single tumors (usually malignant) or bilateral hyperplasia, both of which surgeons tackled. Sometimes they were remarkably successful, but often the patients died in acute adrenocortical failure, as they did with Addison's disease [53].

The search for potent cortical extracts with which to treat these patients began during the 1890s and continued into the 1930s and 1940s. It was led at the Mayo Clinic by Edward Kendall (1886–1972) (NP), who had earlier discovered thyroxine, and in Zürich by Tadeus Reichstein (b. 1897) (NP). Kendall's extract was potent, and with its help his surgical colleague Waltman Walters (1895–1988) removed these cortical tumors more successfully than anyone else [54].

Fig. 3. Harvey Williams Cushing (1869–1939). (Reprinted with permission from Yale University Library.)

Adrenocortical syndromes had been recognized long before the hormones were discovered, whereas the adrenal medullary hormone epinephrine was discovered many years before any pathologic role was found for it [20]. The clinical features of a pheochromocytoma had been described some years before that, but it was a long time before the hormone, the tumor, and these clinical manifestations were seen to be related. Surgical removal of a pheochromocytoma was always fatal until 1926, when César Roux (1857–1934) in Lausanne and Charles Mayo each removed such tumors successfully but without diagnosing them before operation. The quest for safe surgical treatment of these tumors was not completed for another 50 years [55].

Parathyroids

Parathyroid surgery began abruptly in Vienna in 1925 [4f]. Parathyroid deficiency was known, especially as a complication of thyroidectomy, and treatment was attempted with allografts long before hyperparathyroidism was recognized [56]. Friedrich von Recklinghausen (1833–1910), a pathologist in Strasbourg, described osteitis fibrosa cystica in 1891 [57]. Within a few years

parathyroid tumors were found in patients with this condition, but they were generally thought to be secondary to the bone disease. In 1915, however, the Viennese pathologist Friedrich Schlagenhaufer (1866–1930) proposed that they were primary and should be removed [57]. Ten years later, in 1925, a man suffering from this disease fractured his femur and came under the care of Felix Mandl (1892–1957) in Vienna. Mandl suspected parathyroid insufficiency and treated the patient first with thyroid and parathyroid extracts and then by transplantation of human parathyroid glands. Only when these measures failed did he explore the neck, at which time he found a parathyroid tumor and removed it, with remarkable benefit [58]. Hence one operation in one patient seemed to establish a causative role for the parathyroid lesions of von Recklinghausen's disease.

The next year (1926) in Boston, Edward Churchill (1895–1972) independently explored the neck of a patient with hyperparathyroidism that had been suspected on metabolic grounds, but he failed to find a tumor [57]. Unfortunately, the disease in Mandl's patient recurred 7 years after operation, by which time about 20 more successful operations had been done in Europe and America. Four of them were performed by James Walton (1881–1955) in London, who reported the first series of patients [59]. By then (the 1930s), parathyroid surgery was well under way and has advanced greatly since.

Manifestations of hyperparathyroidism other than osteitis fibrosa cystica led to earlier diagnosis and successful treatment of the disease [57]. First, during the 1930s, urinary calculi were recognized as a common manifestation. Then during the 1940s, 1950s, and 1960s, peptic ulceration and acute pancreatitis led to the recognition of a few more cases. Finally, from the late 1960s onward, increasing numbers of asymptomatic patients were diagnosed when a high blood calcium concentration was found on routine biochemical screening [60]. Today the number of operations for hyperparathyroidism are second only to those for thyroid disease in endocrine surgical units.

Single parathyroid adenomas were usually found initially, but from the late 1930s onward hyperplasia of all four (or occasionally more) glands has been commonly recognized, accounting for some 15% of cases by 1980 [61]. During the early days postoperative tetany was common, especially when bone disease was severe, and killed some patients until potent preparations of vitamin D and its analogs were introduced. Renal damage and hypertension also caused serious problems and accounted for some late postoperative deaths [4f].

Surgical technique improved with experience and this, combined with early diagnosis, resulted in the cure of nearly all patients by one operation in the best centers [61].

Insulin and Insulinomas

Next, also during the 1920s, insulin and insulinomas were discovered [4g, 27c]. Diabetes mellitus had long been thought to result from deficiency of a secretion from the islets of Langerhans, and in France Édouard Laguesse (1861–1927) of Lille had described these groups of cells as "endocrine" during the 1890s [62]. However, the antidiabetic factor was not found until 1921, when Frederick Banting (1892–1941) (NP), an orthopedic surgeon, John MacLeod (1876–1935) (NP), and their colleagues in Toronto prepared a potent extract of insulin from the islets of dogs [27d]. This work quickly transformed the lives of diabetics worldwide.

A few years later a patient went to the Mayo Clinic with symptoms and signs like those caused by an overdose of insulin. A pancreatic islet cell tumor secreting insulin was suspected, and William Mayo operated. He found an incurable islet cell carcinoma that contained insulin [27e]. Then in Toronto in 1929, Roscoe Graham (1890–1948) removed an insulinoma and cured the patient [27f]. Although many thousands of such tumors have been treated successfully since, they remain rare lesions.

Cushing's Syndrome

The next major event in clinical endocrinology was Cushing's bold suggestion in 1932 that a basophil adenoma of the pituitary was the essential lesion in a disease he named "pituitary basophilism" [4h, 63] but which most people refer to as Cushing's syndrome. The clinical features were the same as those caused by some adrenocortical tumors. Regardless of whether the primary lesion was in the pituitary, it transpired eventually that the symptoms and signs were caused by excessive secretion by the adrenal cortex [64]. Bilateral adrenalectomy seemed a rational form of treatment, but removal of too little tissue had no effect and removal of too much was fatal. Even subtotal adrenalectomy by Walters, using Kendall's potent extract, killed 30% of the patients [65].

Work on adrenocortical extracts continued, led by Kendall and Reichstein. The essential components proved to be steroids, the most active of which was compound E [66a]. In 1941 shortly before America's entry into World War II, it was reported at a meeting at Yale University that the use of adrenocortical extracts prevented hypoxia in German air pilots flying at high altitudes [66b]. These rumors were untrue, but the U.S. government believed them and made work on compound E its top priority in medical research to further the war effort. One major outcome was the large-scale production of compound E, renamed cortisone, which became available for clinical use after the war in 1948 [66c].

James Priestley (1903–1979), at the Mayo Clinic, first employed cortisone to cover adrenalectomy for Cushing's syndrome in 1949, and this operation became safe and effective at once. His first 18 patients survived the operation, and nearly all were relieved of their disease [65], although some required additional operations to remove more adrenal tissue [67]. Surgeons elsewhere followed this procedure with similar results [68], but *total* adrenalectomy with permanent replacement therapy soon became the procedure of choice [69].

The 1950s

Several more developments during the 1950s provided new challenges and opportunities for surgeons. Cortisone enabled Charles Huggins (b. 1901) (NP) of Chicago to extend the scope of endocrine surgery for cancer of the breast and prostate [70].

Four new endocrine syndromes were described: malignant carcinoid syndrome in 1954 [27g], primary aldosteronism (Conn's syndrome) [71] and Zollinger-Ellison syndrome (gastrinoma) in 1955 [27h], and Verner-Morrison (vipoma) syndrome in 1958 [27i]. Other rare syndromes, associated with islet cell tumors, were described later [27j].

Carcinoma of the thyroid had previously had a poor prognosis,

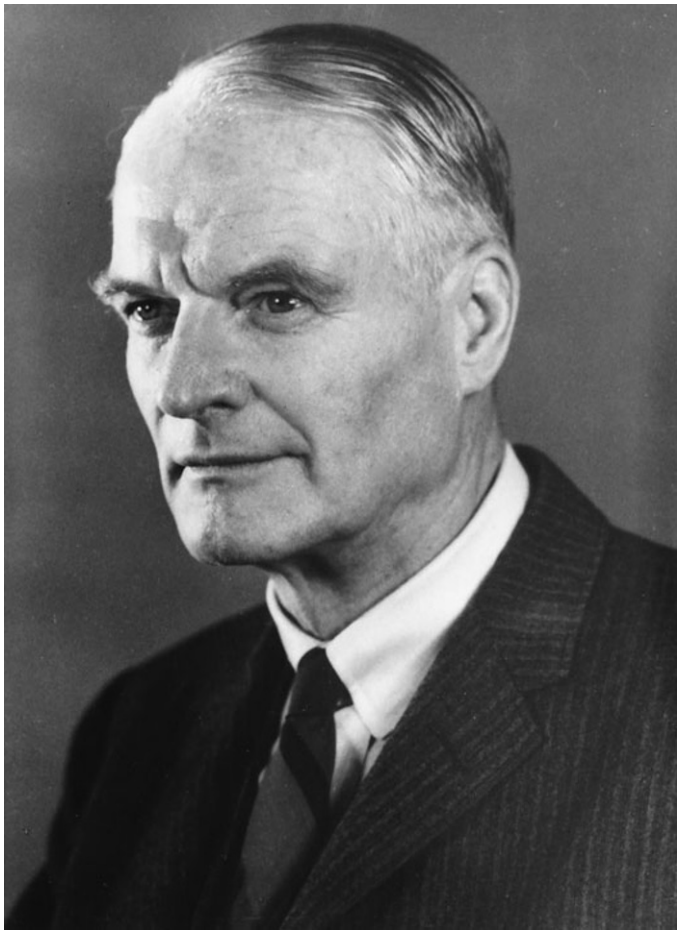

Fig. 4. Oliver Cope (1902–1994). (Reprinted with permission of Richard B. Welbourn.)

with only about 25% of patients surviving 5 years. During the 1950s several pathologic types were distinguished clearly; appropriate forms of therapy, including radical surgery, radioiodine, and thyroid extract, were defined; and results began to improve [4i, 72].

Endocrine Surgery

Since the 1930s some internists have seen the endocrine system as a whole and have specialized in clinical endocrinology, formed societies, published journals, and written books about their subject. During the 1950s a few surgeons in several countries who saw surgery of the endocrine system as a whole also thought that the unifying concept and understanding provided by endocrinology must go hand in hand with first class surgical technique. This goal could be reached only if they treated large numbers of patients, and so they began to practice endocrine surgery as a subspecialty within general surgery. One of the first of this group was Oliver Cope (Fig. 4) of Boston, who had made major contributions to thyroid, parathyroid, and adrenal surgery. Thus 40 years ago the modern era of endocrine surgery began [4a, 73, 74].

The tide of events at this time brought all aspects of endocrine surgery together in other ways as well. During the 1950s and 1960s several distinct, familial syndromes were described in which hyperplastic or neoplastic lesions, often malignant, developed in two or more endocrine glands in susceptible members of affected families. They were named multiple endocrine adenoma, adenopathy, or neoplasia (MEA or MEN) [4j, 75]. There were two main types and several subdivisions. The main lesions were parathyroid hyperplasia, islet cell and pituitary tumors, medullary thyroid carcinoma, and pheochromocytoma in various combinations. These disorders made demands on surgeons who understood the whole endocrine system and were prepared to tackle more than one gland.

Then in 1959 Solomon Berson (1918–1972) and Rosalyn Yalow (b. 1929) (NP) in New York introduced the radioimmunoassay [76]. Within a few years the emphasis in endocrinology changed from steroids to amines and peptides; and endocrinologists became interested in the neuroendocrine system, which elaborates these hormones. This idea was extended by Everson Pearse (b. 1916) of London, when he discovered that many neuroendocrine tissues, including some epithelial cells in the gut and elsewhere, and their tumors shared basic histochemical characteristics that reflected the ways in which they handled amines and synthesized peptides. He used the acronym APUD to describe their features, and neuroendocrine tumors were, for a time, called apudomas [77]. For the first time many diverse lesions, including MEA/MEN and paraendocrine tumors, which had previously seemed unrelated and disorganized, came together in a rational way.

For the past 20 years developments in molecular biology and genetics have transformed endocrinology and medicine as a whole and today are making an impact on endocrine surgery. One important result is that by detecting DNA markers those individuals within some MEN families who are at risk of developing tumors can be screened, identified, and treated in good time [78]. More developments will follow.

The principles of endocrine surgery were established by Kocher, Cushing, Cope, and other masters. Every effort is made to diagnose syndromes early, before they cause serious trouble, and to recognize and locate lesions while they are still small. Surgeons, in consultation with colleagues, select the most appropriate forms of therapy. An operation may be needed, but nonoperative procedures, such as drugs, hormones, radiotherapy, and invasive radiology, are sometimes better alternatives and are often essential adjuncts before, during, and after operation. Before operation the specialized team is assembled and arrangements are made for any investigations, such as blood tests, imaging, or biopsies, that may be required during the procedure. Operations are planned beforehand, but surgeons must be prepared to change course if they meet the unexpected. Tumors or hyperplastic lesions are usually excised, but transplantation of endocrine tissues, especially the pancreatic islets [79] and the parathyroids [80], is still practiced after 100 years and probably has more to offer in the future.

Pituitary Surgery

The application of these principles may be illustrated by the way in which pituitary lesions are approached, particularly in patients with Cushing's syndrome. At first most operations on the pituitary were undertaken when large tumors caused trouble locally, especially after the syndrome had been controlled by adrenalectomy [81, 82]. Then for some years, if an obvious tumor was seen on radiographs, many neurosurgeons operated to stop it growing and

hopefully to cure the syndrome [83]. When some years later it became clear that these tumors *were* the causative lesions in most patients, many surgeons began to operate expectantly, usually with success, to remove tiny microadenomas [22]. In 1927 Cushing had seen a small adenoma at autopsy in an acromegalic patient and had suggested "taking the next obvious step" of removing it while the fossa was still small [50], but he did not pursue the idea. In fact, he abandoned transsphenoidal hypophysectomy for non-secreting tumors in 1930 in favor of transcranial operations because he could not deal adequately with large suprasellar lesions from below [22].

In Europe, however, some surgeons continued to operate from below, when appropriate; and during the late 1950s Lennart Gisselsson (1914–1962), a Swedish ENT surgeon in Örebro, began to use the operating microscope through a paranasal, trans*ethmo*sphenoidal route [22]. Pituitary microsurgery was taken up by other ENT surgeons in Denmark and England, and more than 500 such operations were reported in 1965 [22]. This same year Jules Hardy, a neurosurgeon in Montreal, began to operate with the microscope by Cushing's transsphenoidal route, and his technique was adopted generally by neurosurgeons [22]. His technique is now the preferred method in most centers for treating all but the largest pituitary tumors. In many cases irradiation, hormones, and drugs provide effective alternative and adjunctive forms of therapy [84].

Today pituitary surgery, which was originally practiced by general surgeons, such as Schloffer and Kocher and later Harvey, has passed entirely into the hands of neurosurgeons and ENT surgeons for purely technical reasons. Transcranial operations are rarely needed now, but they of course require the services of neurosurgeons. The transsphenoidal approach, which is required most often, demands a surgeon who can use the operating microscope, and many surgeons in other fields have mastered this technique. The pituitary is an endocrine gland, and its surgery is endocrine surgery. Perhaps general endocrine surgeons, who handle all the other endocrine glands, will before long enter the field of pituitary surgery, as general surgeons did 90 years ago and as Samuel Harvey did by the transcranial route much more recently.

Conclusion

Harvey was a good general surgeon, and good surgeons are more than good technicians. They understand what they do and, together with colleagues, provide total care for their patients before, during, and after operation. Surgery today is much more complex than it was in Harvey's time, and no one is able to master such a large field of work as he did. More surgeons therefore specialize to satisfy their patients' needs.

The idea of endocrine surgery spread slowly at first. Through example, teaching, writing, and the formation of associations of endocrine surgeons the numbers grew, and now hundreds of surgeons practice it worldwide as a special discipline within general surgery. Many combine it with other appropriate branches, especially gastrointestinal and breast surgery, but a few practice it exclusively. In 1995 the International Association of Endocrine Surgeons, founded in 1979, circulated the first (incomplete) list of some 130 units that provide clinical services in endocrine surgery, many of them with facilities for education and research. In the specialized centers the standards are high, and the results are excellent and improving all the time. Further advances will surely come from new ideas, fresh discoveries, and their general application to clinical surgery.

Résumé

La chirurgie endocrinienne consiste en l'exérèse de tissus malades ou l'excision de glandes normales associée parfois à une réimplantation. L'histoire de la chirurgie endocrinienne a commencé, dans la préhistoire, par la castration de l'homme pour des raisons sociales et, au 12è siècle, sont décrites des interventions sur la thyroïde. Jusqu'à la fin du 19è siècle, la plupart des interventions étaient effectuées pour pallier les effets secondaires des hypertrophies de la thyroïde, des ovaires, de l'hypophyse, des surrénales ; avec l'avènement de l'anesthésie, de l'antisepsie et de l'hémostase modernes, la chirurgie pour goitres non toxiques non bénins de la thyroïde s'est développée. L'insuffisance thyroïdienne postopératoire après thyroïdectomie totale a conduit au développement de l'opothérapie substitutive. Le goitre toxique était parfois soigné par une thyroïdectomie partielle. Après la découverte des hormones, au début de notre siècle, les connaissances en endocrinologie se sont accrues et de nombreux syndromes d'hyperproduction hormonale ont été décrits. Les chirurgiens ont commencé à opérer pour les traiter. La qualité du traitement chirurgical s'est amélioré avec le temps, grâce à un perfectionnement de la technique chirurgicale, surtout en ce qui concerne la chirurgie sur la thyroïde, la parathyroïde et l'hypophyse ; il s'est amélioré également grâce à l'amélioration du diagnostic et de la localisation des tumeurs, grâce à un travail en équipe et enfin grâce à l'utilisation des hormones, des médicaments et de la radiothérapie comme alternative ou traitement complémentaire avant, pendant ou après la chirurgie. D'autres progrès notables ont été enregistrés après résection de thyroïde du fait de l'utilisation d'iode et de médicaments antithyroïdiens avant la chirurgie pour goitre toxique. L'utilisation des corticostéroïdes rend la surrénalectomie sûre dans le traitement des cancers du sein, de la prostate et du syndrome de Cushing. Le nombre de chirurgiens pratiquant la chirurgie endocrinienne a augmenté au cours des 40 dernières années et constitue une spécialisation en chirurgie générale. Les résultats se sont beaucoup améliorés avec le temps.

Resumen

La cirugía endocrina incluye la resección de glándulas endocrinas enfermas o, en algunos casos, normales y ocasionalmente el trasplante de tejidos endocrinos. La castración masculina fue realizada por razones sociales en tiempos prehistóricos, y las operaciones tiroideas fueron descritas en el siglo XII. Hasta finales del siglo XIX la mayoria de las operaciones fueron emprendidas con el propósito de aliviar los efectos del crecimiento patológico de la tiroides, los ovarios, la hipófisis y las suprarrenales, y con el advenimiento de la anestesia, la antisepsia y la hemostasia efectiva, se perfeccionó la tiroidectomia para bocio benigno no tóxico. La insuficiencia tiroidea siguió a la tiroidectomía total, por lo cual se desarrolló la terapia de suplencia tiroidea. El bocio tóxico en algunos casos fue tratado mediante tiroidectomia parcial. Luego del descubrimiento de las hormonas, a principios de este siglo, se incrementó el conocimiento de la endocrinología y muchos síndromes de exceso hormonal vinieron

a ser descritos, y los cirujanos comenzaron a operar para controlarlos. Los resultados mejoraron con la maestría en la técnica quirúrgica, especialmente en cuanto a las operaciones sobre la tiroides, las paratiroides y la hipófisis, y también con el desarrollo de métodos para el diagnóstico de síndromes y la localización de las lesiones, con el trabajo en equipo y con el uso de hormonas, drogas y radioterapia como alternativas o modalidades terapéuticas adicionales durante y luego de la operación. Notables avances siguieron a la adecuada resección de tejido tiroideo y al uso de yodo y de drogas antitiroideas precediendo la operación por bocio tóxico. El uso de la cortisona hizo segura la adrenalectomía en el manejo del cáncer de seno y de la próstata y del síndrome de Cushing. Durante los últimos 40 años, un creciente número de cirujanos se ha especializado en cirugía endocrina, como una disciplina dentro del marco de la cirugia general, y los resultados terapéuticos han mejorado significativamente.

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