THE HISTORY OF ENDOCRINE SURGERY

Richard B. Welbourn

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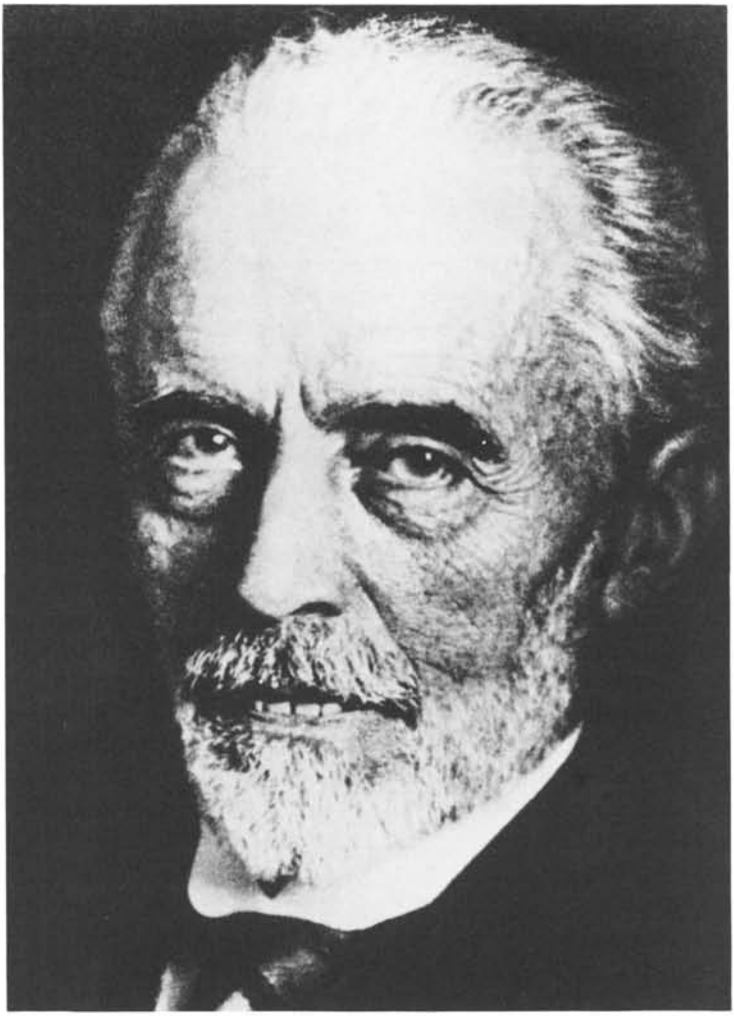
The History of Endocrine Surgery



Theodor E. Kocher. Courtesy of Theodor-Kocher-Institute, University of Bern, Switzerland.

THE HISTORY OF ENDOCRINE SURGERY

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In gratitude to my friends:
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and enabled me to write this book.

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Contents

Foreword

The history of medical science forms the very foundation of the body of knowledge which has evolved into our present understanding of medicine and pathologic processes. Too often today we become involved in current advances and new information and forget the basics reported in earlier years. If we constantly keep in mind the classic descriptions of disease and their importance in clinical practice, the management of patients with pathologic conditions would be simpler and the costs to the patient and those underwriting the expenses of health care most likely less. Although our knowledge of etiology, pathophysiology, pharmacology, and availability of modern technical capability might make the care of patients more effective and safer, these 'technical advances' are not always necessary in the overall care of disease states. As an example, in reviewing the classical contributions and publications of Parry, v. Basedow, Graves, Plummer, Kocher, Mayo, Dunhill, and v. Mikulicz, little further information would be needed to diagnose and treat patients with exophthalmic goiter. The same would be true for many other endocrine diseases as well as other diseases elsewhere in the body.

Richard Welbourn has done the physician community and especially those physicians interested in endocrinology a great service in bringing together in one publication the contributions of the giants of the past and the historical facts that, for the most part, remain pertinent in the practice of endocrinology today. The history of any subject is the basis of its culture and should not be forgotten since it remains the foundation of our current knowledge and is necessary for our present education, research, and clinical practice.

The History of Endocrine Surgery is an excellent recording of the contributions of each generation to the next one which follows.

Oliver H. Beahrs
Emeritus Professor of Surgery, Mayo Foundation
President, American College of Surgeons, 1988–89

Preface

"Only the man who is familiar with the art and science of the past is competent to aid in its progress in the future." So wrote Theodor Billroth of Vienna, one of the founders of modern surgery in the second half of the nineteenth century and a major contributor to the surgery of the thyroid.

By the middle of the twentieth century operations had been performed on all known endocrine glands, and those on the thyroid and the pituitary were practiced widely and well. Operations on other glands were undertaken rarely, and some of them were fraught with danger. The term "endocrine surgery" had hardly been heard. After the advent of cortisone, however, surgeons began to undertake endocrine surgical procedures more often and with greater safety than before. The endocrine glands had long been recognized as an integrated system, and now their surgery also came to be viewed as a whole. Thus endocrine surgery began to emerge as a new discipline within general surgery. On the other hand, the pituitary, which had once been within the domain of general surgeons, had already, for purely technical reasons, passed entirely into the hands of neurological and rhinological surgeons.

I became interested in the surgery of the endocrine glands in 1951 and 1952, while working at the Mayo Clinic, where cortisone had just been discovered and used therapeutically. The surgeons employed it with astonishing success to support patients undergoing adrenalectomy for Cushing's syndrome. Eventually endocrine surgery became my main concern. I knew that its history was fascinating and, when I retired in 1982, I began to study it systematically. The early surgical histories of some of the glands—the thyroid, the pituitary, and the parathyroids—and of surgical stress had been described already, but the full story of endocrine surgery had not been told. And so I came to write this book.

The existing histories provided good introductions to the early literature, but most of my work involved reading many hundreds of original articles, the most important of which are listed after each chapter. When secondary sources only have been used (mainly textbooks, monographs, and review articles), they are cited as references. For various reasons I had to rely largely on these in writing about thyroid cancer and the parathyroids and about stress. I have also talked and corresponded with friends and colleagues in many countries and have referred to some of their interesting letters as personal communications. In addition I have visited many of the places where endocrine surgical history has been (and is being) made. In several places my accounts of events differ from those given elsewhere, but they are fully supported by the references that I have quoted.

The story of endocrine surgery is traced from its origins to about 1980. More recent work, most of which cannot yet be seen in perspective, is described in current textbooks and reviews. The emphasis is on endocrine surgery, but related branches of medicine, surgery, and science are discussed when appropriate. I have not included chapters on the gonads and the thymus, because I ran out of time and space for them here; I hope to relate their endocrine surgical histories elsewhere.

Thomas Carlyle, the nineteenth-century Scottish writer, correctly stated that history was the biography of great men, and I have included a biographical index and portraits of surgeons and others who have made important contributions. This index includes the basic information—who, when, what, and where—about all the men and women named in the text, so far as I have been able to discover it, and additional notes about some of the major contributors. The chronology shows the main events described in the different chapters in their temporal relationships, and also lists some relevant milestones in general medicine, surgery, and science, and a few in political and social history, to provide historical perspective.

I hope that historians, endocrine surgeons, endocrinologists, and many others will find as much pleasure and value in reading this history of endocrine surgery as I have found in its preparation.

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Richard Welbourn

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The following sources were used throughout the book:

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Other general sources are listed at the end of each chapter.

How to Use This Book

The reader will find that each paragraph in the text is followed by a lettered/numbered key in parentheses. The letter corresponds to the current chapter title. The number indicates which paragraph is being read in the chapter. There are many cross-references in the text and by quickly flipping through the pages the reader can locate the corresponding material. The same system has been applied to entries located in the Biographical and Subject Indices.

For quick reference, a key to the location of the lettered paragraphs is provided inside the back cover.

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The History of Endocrine Surgery

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1 (E)

Evolution of Endocrine Surgery

Endocrine surgery has been practiced for hundreds of years, but has only been recognized as such since the beginning of this century. It has undergone many successive, overlapping waves of change, varying in magnitude, speed, and duration, but three main phases of evolution can be recognized. In the first, surgery of the endocrine glands formed part of surgery in general. The second phase followed the emergence of endocrinology as a science in the early 1900s, when surgeons appreciated that they were operating on endocrine glands, often to relieve the effects of oversecretion. The third, or present, phase started in the 1950s, after the advent of cortisone, when surgeons began to view endocrine surgery as a whole instead of concentrating on separate glands. (E.1)

Most of the glands and tissues that form the endocrine system were recognized by the end of the nineteenth century. At first they were described and studied individually, like other organs, and only later grouped as ductless glands or as sources of internal secretions. The gonads were recognized in prehistoric times. The testes were probably noticed first because of their situation, but the ovaries were known to the Ancient Egyptians(1a). Galen, the Roman physician who dominated medicine for fifteen centuries, described the pituitary in the second century(2). The great Italian Renaissance anatomist, Andreas Vesalius of Padua, included a description of the thyroid in *De Humani Corporis Fabrica* in 1543(3). Thomas Wharton, physician to St. Thomas' Hospital, London, who courageously stayed in the city throughout the great (bubonic) plague of 1665, included the thyroid, the suprarenals, and the pancreas among the glands in his *Adenographia* of 1656 and 1659(4). (E.2)

DUCTLESS GLANDS

The functions of the endocrine glands remained unknown and the subject of much speculation for many years. In 1766 the Swiss scientist Albrecht von Haller of Berne(1b) described the thyroid, the thymus, and the spleen as glands without ducts that poured special substances into the circulation(5a). This process was first demonstrated experimentally by the great Parisian physiologist, Claude Bernard, who in 1855 described sugar, which entered the portal vein, as the "internal secretion" and bile as the "external secretion" of the liver. He went on to list the spleen, the adrenals, the thyroid, and the lymphatic glands as having internal secretions only(5b). (E.3)

The concept of internal secretion received support in other ways. The general effects of castration in both sexes had been recognized in ancient times, and John Hunter of London, the founder of surgical science, had noted in 1786 that the testes controlled the development of secondary sex characters in man and animals(6). Thomas Addison, physician to Guy's Hospital, London, provided evidence that absence or destruction of endocrine glands caused disease when, in 1855, he published his work "On the constitutional, and local effects of disease of the suprarenal capsules" (p. A.4). Theodor Kocher (Fig. E.1), Professor of Surgery at Berne, confirmed this principle in 1883, when he described the condition of "cachexia strumipriva" after total extirpation of the thyroid gland in man (p. T.40). Soon hypothyroidism from this and other causes was recognized, and thyroid extracts, which were sometimes effective, were prepared for replacement therapy. Thus, by the end of the nineteenth century there was clear evidence that the product of a ductless gland was physiologically active, that its absence caused disease, and that its replacement brought relief. In the 1890s a potent vasoconstrictor was extracted from the adrenal medulla by George Oliver, a general medical practitioner from Harrogate, England, and Edward Schäfer (later Sharpey-Schäfer), Professor of Physiology at University College, London. The active principle, "epinephrine" or "adrenalin," was isolated in 1897 and 1901—the first internal secretion to be identified (p. A.7). (E.4)

ENDOCRINOLOGY

At this time—the turn of the century—the physiological climate was dominated by Ivan Pavlov of St. Petersburg (now Leningrad), who believed in nervism—the view that the nervous system controlled most bodily activities(7a). Perhaps for this reason few people regarded the ductless glands seriously. However, in 1902 two other physiologists at University College, William Bayliss (Fig. E.2) and Ernest Starling (Fig. E.3), made a startling discovery, "breathtaking in its elegant simplicity" (7b). They found that acid in the gut stimulated secretion in the pancreas when both organs were denervated, that acid introduced directly into the circulation did not stimulate it, and that injection of an extract of jejunal mucosa mimicked the action of acid in the gut(8). They realized that these findings required the operation of a chemical reflex rather than a nervous one, and proposed the name "secretin" for the hypothetical "chemical messenger" involved. This represented a new class of substance, not adequately described as an internal secretion, and in 1905 Starling proposed the name "hormone" from a Greek word (ὁρμανειν) meaning to excite (7c). This was soon adopted generally. An "endocrine" (GK ἐνδον = within + κρίνειν = separate) function had been attributed to the Islets of Langerhans in 1893 by Édouard Laguesse of Lille, France(8A), and this term also came into general use within a few years. Thus a new principle in physiology was established, and the science of endocrinology was born. (E.5)

The science grew rapidly, soon assuming great importance, and many who contributed to it were awarded Nobel Prizes. The first was Kocher, in 1909, "for his works on the physiology, pathology and surgery of the thyroid gland." More endocrine tissues and many more hormones were identified in subsequent years and their functions and complex interrelationships explored. The Leydig cells of the testes, the Islets of Langerhans, the Kulchitsky cells in the gut, and the parathyroid glands, all of which had been described in the nineteenth century, were recognized as endocrine organs. Early functional studies led to the isolation of thyroxine from the thyroid in 1914 by Edward Kendall, a chemist at the Mayo Clinic (p. T.51), and the extraction of insulin from the pancreatic islets in 1921 by Frederick Banting, an orthopedic surgeon and physiologist from London, Ontario, and his colleagues in Toronto (p. G.13). Banting shared a Nobel Prize in 1923. (E.6)

As more was learned of the endocrine glands, the central role of the anterior pituitary in regulating growth and controlling other glands became clear. In 1931 Walter Langdon Brown of London, England, described it as "the leader in the endocrine orchestra" (9). The endocrine glands were thus seen not only to share a common mode of action, but to be functionally interdependent. The endocrine system provided an integrated mechanism for controlling bodily functions which complemented that of the nervous system. (E.7)

Already, however, there were indications that the separation of the two systems was artificial. In 1911 Walter Cannon, Professor of Physiology at Harvard University, Boston, had described how emotional nervous stimuli caused the secretion of a hormone, adrenaline, by the adrenal medulla, which was not only an endocrine gland but also part of the autonomic nervous system(10). Then, in 1921, Otto Loewi, a pharmacologist at Graz, Austria, established the chemical nature of nerve transmission(1c). In the 1930s secretory cells were observed in the hypothalamus, which is part of the brain, and this was later found to exert neurohumoral control over the anterior pituitary(1d). The hypothalamus was itself governed both by the hormonal products of its own stimuli (by feedback mechanisms) and by higher nervous centers(1e). Pierre Masson, a pathologist in Montreal, had suggested in 1914 that the Kulchitsky cells in the gut formed a diffuse endocrine organ, and later (in 1928) described them as being neural also (p. G.1). A few years later (in the 1930s) the Austrian pathologist, Friedrich Feyrter of Gdansk (Danzig), Poland(11), described a system of *helle Zellen* (clear cells), which were distributed widely in the tissues but were most prominent in the gastrointestinal tract and in the pancreas, and suggested that they might secrete hormones that acted locally. All these findings, which indicated that the nervous and endocrine systems were inseparable, were brought together and extended in the 1960s by Everson Pearse, a histochemist in London, who found that Masson's and Feyrter's cells shared important functional characteristics with cells in some of the major endocrine glands and in the hypothalamus. All were concerned with the handling of amines and the production of peptides, and were conveniently described by the acronym APUD (amine precursor uptake and decarboxylation)(12). More recently an enzyme (neuronspecific enolase), previously found only in neurons, was demonstrated in all these cells also(13). These and many other observations further confirmed the concept of a single neuroendocrine system, pervading all the tissues of the body, but most conspicuous in the gut and the brain. (E.8)

Knowledge about hormones progressed all this time, and thyroxine was synthesized by Charles Harington in London in 1927(1f). The pursuit of steroids in the adrenal cortex and gonads occupied the center of the chemical stage next and reached its climax with the isolation and synthesis of cortisone by Kendall and the Swiss chemist Tadeus Reichstein in the 1940s (p. A.41). In the late 1960s the emphasis changed again, and peptides came to the fore, largely as a result of three developments: the invention of radioimmunoassay (RIA) by Solomon Berson and Rosalyn Yalow of New York in 1959(1g), the application of immunocytochemistry, and the advent of Pearse's APUD concept. At the same time the regulatory peptides and amines of the neuroendocrine system were seen to function in three different ways, namely, endocrine (secreted into the circulation and acting at a distance), paracrine (secreted and acting locally), and neurocrine (secreted at synapses and acting as neurotransmitters)(14). (E.9)

ENDOCRINE DISEASE

The first disturbances of endocrine function to be recognized were those of deficient secretion, and Addison's disease and hypothyroidism were described before hormones were discovered. Hypopituitarism was recognized soon after (p. P.5). The idea that diseases might be associated with endocrine *hyper*function emerged more slowly. Hyperthyroidism in Graves' disease (p. T.88) and hyperpituitarism in acromegaly (p. P.4) were proposed in the nineteenth century, but were not generally accepted at first.

Once they had been, many syndromes of hormonal excess were described, and new ones continue to be recognized. (E.10)

The diagnosis of endocrine disease was made first on clinical grounds, on the basis of clinico-pathological correlations (e.g., signs of an adrenal or pituitary tumor with appropriate clinical features) and on nonspecific chemical measurements (e.g., blood sugar or calcium). Bioassays and chemical analyses of hormones followed, and finally RIA and related procedures. Static measurements often gave way to dynamic assays of the effects of stimulating and inhibitory factors. All these, together with routine biochemical screening, facilitated the recognition of endocrine disease. Anatomical definition of lesions depended mainly on x-rays and later on radioisotopic imaging. X-rays were discovered by Wilhelm Röntgen of Würzburg, Germany, in 1895(15a) and within six years were found to show enlargement of the sella turcica by a pituitary tumor (p. P.7). Each advance in radiological technique was applied, when appropriate, to the endocrine glands, and progressively better images were obtained. Isotopes of iodine, introduced in 1938, revolutionized the investigation of thyroid structure and function, and other isotopes were applied later to this and other glands (p. T.51). (E.11)

Treatment of endocrine lesions involved mainly the replacement of defective secretion, the reduction of excessive secretion, and the removal or destruction of tumors. Organotherapy, which was practiced for centuries before the advent of endocrinology(5c), involved feeding organs, tissue extracts, or body fluids to replace the functions of defective members, such as the heart, spleen, testes, blood, and semen. Although ineffective, it evolved imperceptibly into replacement therapy. Indeed, George Murray of Newcastle-upon-Tyne, who first treated myxedema successfully by the injection of thyroid extract (p. T.43), was told that he might as well inject an emulsion of the spinal cord for locomotor ataxia(1h). The specific secretions of most endocrine glands were, however, purified, and many of them synthesized, and they came to be used effectively for the treatment of deficiency syndromes. (E.12)

ENDOCRINE SURGERY

By the end of the nineteenth century endocrine glands were being excised increasingly for the treatment of glandular enlargement, hyperfunction, and neoplasia, and also for certain other diseases. Before hormonal replacement therapy was available, transplantation of endocrine tissues seemed a rational method of restoring defective function, but was rarely effective because its immunological principles were not understood. All these operations formed the basis of endocrine surgery. (E.13)

Up to the middle of the nineteenth century the scope of surgery in general was very limited(16a). Surgeons treated simple fractures, dislocations, and abscesses, and performed amputations with dexterity, but high mortality, for compound fractures and severe sepsis of the limbs. They ligated major arteries for aneurysms, which were common, and made heroic attempts to remove external tumors. Some specialized in the management of anal fistulae and bladder stones. Abdominal surgery was almost unknown, although pointing abscesses were drained, strangulated herniae were reduced, and lumbar colostomy was sometimes performed for colonic obstruction. A few bold operators opened the abdomen to divide obstructing bands and adhesions or even to ligate the abdominal aorta for aneurysm. (E.14)

Endocrine surgery began empirically with castration, which was practiced, especially in males, before the dawn of history as a social or religious, rather than a medical, procedure, and was sometimes self-inflicted(1i). In some countries it continued in these roles until modern times, especially to provide attendants for harems and castrati for choirs. Ovariotomy, the removal of ovarian cysts for general, not endocrinological, reasons, opened the door to abdominal surgery years before the introduction of anesthesia, antisepsis, and hemostasis. It was performed successfully by Ephraim McDowell, a country practitioner in Danville, Kentucky, in 1809, and was subsequently developed and popularized by others, notably Thomas Spencer Wells in London. Despite their best efforts, the operative mortality long remained at about 20 percent(16b). (E.15)

During this first phase the most important endocrine surgical procedures were operations for goiter, which has always been common in endemic areas. Goiters were usually obvious, often unsightly, and sometimes suffocating, and surgeons began to treat them at least 800 years ago when they threatened life. Roger Frugardi at the great Italian School of Salerno provided the first credible description of operations for goiter in general in about 1170 (p. T.8). Pierre-Joseph Desault of Paris is the first surgeon who is known to have published an account of an actual operation for the successful removal of a goiter, which he performed in 1791 during the French Revolution (p. T.12). His and some other results were remarkably good, but in general thyroid operations were so hazardous, carrying a mortality rate of about 40 percent from bleeding and sepsis, that many leading surgeons would not perform them (p. T.24). (E.16)

THE SURGICAL REVOLUTION

The second half of the nineteenth century, however, saw a revolution in surgery, equivalent to that in transport which followed the invention of the steam engine. Three separate developments in thirty years combined to bring this about: general anesthesia, antisepsis (followed by asepsis), and effective hemostasis. (E.17)

General anesthesia was introduced in the 1840s. Ether was used first by Crawford Long, a physician in Jefferson, Georgia, in 1842, and demonstrated by William Morton, a dentist, in Boston, Massachusetts, in 1846. Later that year it was used by Robert Liston in London for an amputation. Nitrous oxide was employed next, by Horace Wells, a dentist in Hartford, Connecticut, and chloroform by James Young Simpson, Professor of Obstetrics in Edinburgh (17a). Anesthesia was soon adopted widely and was used for removal of a goiter by Nikolai Pirogoff of St. Petersburg in 1849 (p. T.25). Its obvious benefit of abolishing the pain of operations enabled surgeons to perform their work without hurry, and one immediate result was that they undertook more operations. The problems of sepsis and bleeding, however, remained. Wounds were expected to suppurate before healing, and pus had been regarded as "laudable" since the time of Galen. More sinister infections caused death from secondary hemorrhage, erysipelas, septicemia, pyemia, and hospital gangrene. The last, a lethal infection of surgical wounds, was held in awe and increased to such an extent that some hospitals were threatened with closure (18a). (E.18)

Joseph Lister, Professor of Surgery in Glasgow, Scotland, published in 1867 the first remarkable account of antisepsis with carbolic acid, with which he saved the lives of patients with compound fractures (17b, 19) (Fig. E.4). By 1870, when he had moved to Edinburgh, he was using antisepsis for elective operations, his wounds healed by first intention, and sepsis had been almost eliminated. However, Lister's work was not appreciated for many years in Britain or America, and he was opposed vehemently, especially in London, where he had graduated, when he returned there in 1877. But on the continent of Europe antisepsis was soon adopted widely, with results similar to Lister's. Ernst von Bergmann of Berlin introduced steam sterilization in 1886 and *a*sepsis in 1891 (15b). (E.19)

Control of bleeding in surgical operations had always been a problem for lack of suitable instruments, and hemorrhage was a common cause of death. The simplest devices were manual pressure with sponges and the application of chemical styptics or the cautery. Ligatures of thread, silk, or catgut were applied to vessels with the aid of tenacula and aneurysm needles. Divided arteries were grasped with torsion forceps and twisted. Traditionally, ligatures were left long, hanging out of the wounds until they separated. It was some time after the advent of antisepsis before it was appreciated that short ligatures, especially of sterilized catgut, and the small portions of tissue that they strangulated could be left safely in the depths of a wound. Self-retaining artery forceps of several types were devised early in the nineteenth century, and those of Johann Dieffenbach of Berlin, and of Liston were well known (16c, 20). All, however, were clumsy and had little influence on surgical technique. To compound the problem of hemorrhage, the practice of "therapeutic" blood-letting for many diseases continued well into the nineteenth century (p. T.18) (17c). It was often employed during and after operations for various complications, even when hemorrhage had been copious(18b). Well before the end of the century, however, some pioneers were transfusing blood, and Theodor Billroth, Professor of Surgery in Vienna, was doing so by 1877(21). (E.20)

All these considerations applied to ovariotomy and operations for goiter. Management of the pedicle was a special problem in the former(16b), and hemorrhage a hazard in the latter, because the thyroid is such a vascular organ(18b). The breakthrough in hemostasis was made by Spencer Wells, who devised simple self-retaining artery forceps, with one catch, which he used first in about 1872 and reported in 1874 (22) (Fig. E.5). Wells' forceps were improved by the addition of a ratchet and by being made lighter, and were modified in many other ways by him and by others. Artery forceps transformed surgical technique and greatly reduced operative bleeding and its attendant mortality(18c). (E.21)

A last, small part of the surgical revolution was the introduction of cocaine for local infiltration anesthesia by William Halsted, then of New York, in the 1880s (23). Cocaine and its analogues have been used extensively in operations for goiter. Unwittingly, Halsted and his colleagues became addicted, with tragic consequences. (E.22)

In the last quarter of the nineteenth century most of Europe enjoyed relative peace and stability, while travel and communication became easier and faster than ever before(24). Many branches of science and medicine burgeoned, and great improvements in hospital design and in the nature and quality of nursing were emerging. All these factors combined to create an environment in which the surgical revolution could flourish. Anesthesia, antisepsis, and hemostasis not only rendered existing procedures much safer, but enlarged the scope of surgery in general, allowing the body cavities and joints to be opened with relative impunity. At the same time outstanding surgeons were ready to grasp the new opportunities and to meet the challenges provided by surgery as a whole. For many years, however, the dexterous surgeon could work effectively under primitive conditions, as in patients' own homes, and with few assistants (p. T.27). (E.23)

Progress in thyroid surgery was phenomenal, particularly in Central Europe in the hands of Billroth and Kocher, in Vienna and Berne, respectively (p. T.29). By the end of the century Kocher's operative mortality for simple goiter was 0.2 percent and, as this first phase of endocrine surgery drew to a close, he did more than any other one surgeon before or since to develop the practice and science of thyroid surgery. The operative mortality for ovariotomy was halved(16b). In the 1890s orchiectomy was proposed for prostatic enlargement by William White of Philadelphia and was undertaken by many surgeons (p. C.5). Oophorectomy was performed for advanced breast cancer by George Beatson of Glasgow (p. C.2). (E.24)

At the close of the century also surgeons began to tackle lesions in two other endocrine glands. Adrenal tumors were not then diagnosed until they were found at operation or at autopsy, but progress in abdominal surgery allowed some to be excised, and in 1889 Knowsley Thornton, a junior colleague of Spencer Wells in London, removed one successfully (p. A.10). The same year Victor Horsley, also of London, who was already active in thyroid research (p. T.42) and a pioneer of neurosurgery, operated for the relief of pressure caused by a pituitary tumor (p. P.8). At about the same time the first ineffective attempts at transplantation of endocrine glands were made—for hypothyroidism in 1890 (p. T.43) and for Addison's disease in 1897 (p. A.64). Both were continued until reliable replacement therapy was available—thyroxine in the 1940s and cortisone a decade later. (E.25)

SECOND PHASE OF ENDOCRINE SURGERY

As endocrinology developed and syndromes of hormonal excess were recognized, surgeons became increasingly involved because of the success of surgical operations for their relief. This opened the second phase of endocrine surgery, which extended into the latter half of this century. Endocrine glands were removed not only because they were neoplastic, but also because, whether tumorous or hyperplastic, they secreted excessive quantities of hormones. In this way metabolic diseases were cured by surgical operations, and a new principle in surgery was established. Some achievements resulted from surgeons and their colleagues rising to the opportunities provided by first encounters with newly recognized diseases, while others were the outcome of disciplined attacks upon successive difficulties until the long-sought goals were achieved. Sometimes individuals contributed most, sometimes groups and institutions. (E.26)

The second phase of endocrine surgery afforded several examples of first encounters with syndromes, which surgeons tackled, eventually with success. These included hyperparathyroidism by Felix Mandl in Vienna in 1925 (p. P.10), pheochromocytoma by César Roux in Lausanne, Switzerland, and Charles Mayo in 1926, and hyperinsulinism by William Mayo (Charles' elder brother and colleague) in 1927 (p. G.16) and Roscoe Graham in Toronto in 1929 (p. G.17). On the other hand, prolonged efforts by many people were required before operations for toxic goiter or pituitary tumors could be approached with confidence. Thyroidectomy for hyperthyroidism began to emerge in the nineteenth century (p. T.99), but only became safe and effective as the result of four important developments in the twentieth. First, in 1908 Thomas Dunhill of Melbourne led the way in resecting sufficient thyroid tissue to cure the disease (p. T.101). Second, in 1922 C. Mayo and Henry Plummer, at the Mayo Clinic, started to use iodine preoperatively (p. T.106). Third, the introduction of radioiodine in 1942 provided a valuable adjunct or alternative to operations (p. T.109). Last, in 1943, Edwin Astwood of Boston introduced antithyroid drugs, and the next year Oliver Cope, Francis Moore, and Howard Means, also of Boston, reported the use of thiouracil preoperatively (p. T.113). Many surgeons have tackled the pituitary since Horsley's transcranial operations. In his day few of them were ready to undertake neurosurgical procedures, and general surgeons, ear, nose, and throat (ENT) surgeons, and neurosurgeons in Europe and the United States turned to an extracranial, transsphenoidal approach. Hermann Schloffer of Innsbruck, Austria, was the first to operate thus, in 1907 (p. P.9), but pride of place belongs to Harvey Cushing of Baltimore and Boston, who founded the first school of neurosurgery and whose brilliant work spanned thirty years (Fig. E.6). During this second phase no one else contributed so much to the surgery of the pituitary or any other endocrine gland. His work culminated in 1932 with the bold hypothesis that a basophil adenoma of the pituitary was the causative lesion in the fatal disease that now bears his name (p. P.32). (E.27)

When groups of clinicians and basic scientists cooperate, the crucial contributions come sometimes from one person or discipline and sometimes from another. A striking example is provided by the Mayo Clinic, whose staff contributed more than any other group to the development of many branches of endocrinology and endocrine surgery at this time. These included the surgery of toxic goiter, the isolation of thyroxine, the first study of an insulinoma, remarkable results in the treatment of adrenocortical tumors by Waltman Walters in the 1930s and 1940s (p. A.33), and the isolation of cortisone. The effect of its use to cover adrenalectomy for Cushing's syndrome by James Priestley, Walters, and their colleagues, published in 1951, was revolutionary (p. A.54). In the 1950s and 1960s Priestley and others, following C. Mayo's lead, also led the world in the surgical treatment of pheochromocytomas (p. A.121). (E.28)

In this second phase, two world wars influenced the development of endocrine surgery in rather different ways. Up to the outbreak of the Great War (1914–18) surgery was truly international, and surgeons visited each others' clinics and attended international congresses. Europe was the center of activity, and Berlin, Vienna, London, Berne, and Paris held the main attractions. American surgeons who later contributed to endocrine surgery and who visited Europe included Halsted, Cushing, C. Mayo, and George Crile of Cleveland, Ohio. Typical of the international congresses was that held in London in 1913, when the Royal College of Surgeons of England awarded honorary fellowships to many distinguished surgeons from abroad (Fig. E.7), including Crile, a pioneer of surgery for toxic goiter; Cushing, who was aged only 44; Anton von Eiselsberg from Vienna, who had contributed to thyroid and pituitary surgery; and W. Mayo. Kocher, who had received an honorary fellowship previously, was present also. (E.29)

The first casualty of the war was communication, and the international congress due to be held in Munich in 1917 was cancelled. Kocher's last visitors' book in Berne contains about 100 signatures each year up to 1914, but a total of only 21 from then until his death in 1917. In Europe medicine and surgery were concentrated on the problems of war; much was learned about the management of wounds, and orthopedic and plastic surgery advanced, while endocrine surgery stood still. Horsley, who had contributed much, died on active service in Mesopotamia in 1916. One fortunate gain for Europe was that Dunhill, who served with the Australian forces in Europe, was persuaded to move from Melbourne to London in 1920. America suffered much less disturbance, and endocrine surgery, particularly of the thyroid and the pituitary, continued to advance. (E.30)

After the war Europe recovered slowly, but the rise of the Nazis in Germany in the 1930s resulted in the flight of many gifted Jewish scientists and surgeons to other countries. Oscar Hirsch, a pioneer in the surgery of the pituitary (p. P.12) and of exophthalmos (p. T.124), and Felix Mandl left Vienna in 1938, the year of the Anschluss. Happily, they were able to continue their work elsewhere, Hirsch in the United States and Mandl in Palestine. (E.31)

World War II (1939–45) saw the start of a second surgical revolution, equivalent perhaps to that caused by the jet engine in transport. Three factors contributed. Blood transfusion, which had been practiced on a small scale, was organized nationally and in the armed forces in Britain, and later in America and elsewhere. Specialized techniques in anesthesia, particularly intubation and the use of positive pressure, were taught widely in the forces and, together with relaxants, transformed anesthetic practice. Penicillin, the first antibiotic, discovered in England before the war, was developed by government support in the United States and used extensively in the latter part of the war, and other antibiotics soon followed. These advances made all operations safer, including those on the endocrine glands, and also opened up new fields, especially surgery of the heart. Surgeons were no longer self-sufficient, and skilled teams of doctors, technicians, and nurses were formed to support them in their work. All became involved with much more then operative technique, and sought, as Kocher and Cushing had done before, to understand and control the disturbances of bodily function that not only accompany disease, but are induced by operation. (E.32)

Again, medicine and surgery were less disturbed in North America than in Europe, Asia, and elsewhere, and after the war the United States became the center of activity, generously welcoming large numbers of visiting workers from abroad. Within a few years, however, research and practice in all branches of medicine, including endocrine surgery, became international once again, and men and women moved freely about the world, exchanging ideas and experience. (E.33)

MODERN ENDOCRINE SURGERY

Another advance of the 1940s resulted from an extraordinary report that German air pilots were receiving adrenal cortical extracts to prevent hypoxia. Naturally the U.S. government was persuaded to support work in this field, and cortisone was developed and released for use in 1948(25). Its arrival had an explosive effect on endocrine surgery. Adrenalectomy was rendered safe almost overnight (p. A.54), and total hypophysectomy became practicable (p. P.45). The scope of endocrine surgery for cancer of the breast and prostate was enlarged (work for which Charles Huggins of Chicago was awarded a Nobel Prize in 1966) (p. C.7), and the adrenal cortex became a focus of work on the endocrine response to stress. Furthermore, cortisone rendered adrenal transplantation for Addison's disease superfluous and facilitated effective transplantation of other organs. At the same time steroid therapy for rheumatoid arthritis and other diseases posed new surgical problems. All this brought the surgery of the endocrine system together in the 1950s, and surgeons then began to appreciate it as a whole. This was the start of the third and present phase of its evolution. One of the first surgeons to view endocrine surgery in this way was Oliver Cope of Boston, a founder of modern endocrine surgery (Fig. E.8). Starting early in the 1930s and continuing for over forty years, he made important contributions to the surgery of the thyroid, the parathyroids, and the adrenals, and stimulated others to do the same (26). (E.34)

Many more lesions and syndromes have been recognized and treated effectively, often by surgeons, in this third period. They include Conn's (p. A.81) and the Zollinger-Ellison syndromes (p. G.29), medullary thyroid cancer (p. T.130), renal (p. H.9) and paraendocrine tumors (p. M.20), and multiple endocrine adenopathy (p. M.2). Endocrine surgeons, concerned with the whole endocrine system, were ready to meet these challenges. (E.35)

Pituitary surgery developed remarkably during this same period. Since the late 1960s tumors previously thought to be inactive have been found to secrete hormones and to cause specific syndromes (p. P.90). Surgical treatment, formerly designed to relieve pressure, was undertaken increasingly for endocrinological reasons. Transsphenoidal operations, which had been abandoned by most neurosurgeons in about 1930 in favor of the transcranial approach, were preserved, mainly by ENT surgeons in Europe. From the late 1950s Lennart Gisselsson in Örebro, Sweden, and then others refined them by the adoption of microsurgical methods. Jules Hardy, a neurosurgeon in Montreal, independently used the operating microscope in 1965 (p. P.70–73). Others soon followed him and now operate regularly and successfully on microadenomas, which reveal themselves clinically and biochemically but which cannot be detected anatomically. (E.36)

Transplantation of thyroid and adrenal homografts had been superseded by effective replacement therapy, but autografts of parathyroid and adrenocortical tissue were used in some situations, the former with success (p. PT.37), the latter less reliably (p. A.58). Homografts of whole pancreatic tissue and of islets, performed under immunological control for the relief of severe diabetes, were studied experimentally and hold promise for the future (p. G.58). (E.37)

The idea of the unity of endocrine surgery received further impetus in the 1970s, when tumors of Pearse's APUD cells were grouped as "apudomas"

(Fig. E.9). The word was coined in 1969 by Kálmán Kovács, Ilona Szijj, and their colleagues at Szeged, Hungary, who applied it to a paraendocrine, ACTH-secreting medullary carcinoma(27). Now for the first time many diverse peptide- and amine-secreting lesions, including paraendocrine tumors and most of the multiple endocrine adenopathies, which had previously seemed unrelated and disorganized in their behavior, came together in an orderly manner and were seen as products of the diffuse neuroendocrine system, sharing common, basic secretory characteristics(28). This concept clarified the nature and properties of apudomas, and prepared surgeons for all eventualities in the diagnosis, implications, therapy, and prognosis of patients harboring these lesions(14). (E.38)

Tangible expressions of the newly emerging discipline of endocrine surgery came from several quarters from the early 1950s. Books and journals devoted to the subject were published(29, 30, 31, 32). Postgraduate courses in endocrine surgery became popular in about 1970, and associations of endocrine surgeons were formed nationally and internationally in the 1970s and 1980s. (E.39)

Endocrine surgery grew steadily in stature as more and more leading surgeons entered the field. Today, as always, cooperation between surgeons and members of other disciplines produces the best research and provides optimal patient care. The most appropriate form of therapy for each patient often depends on the facilities available locally, and surgeons share in making therapeutic decisions. Surgical operations, well performed, often have most to offer, and increasing numbers of surgeons with the requisite skills are ready to undertake them. The stories of individual glands and topics in endocrine surgery are told in the following chapters in the approximate order in which they first appeared prominently on the historical horizon. (E.40)

GENERAL SOURCES

Shepherd, 1965. *See* Ref. 16.
Cope, 1978. *See* Ref. 26.

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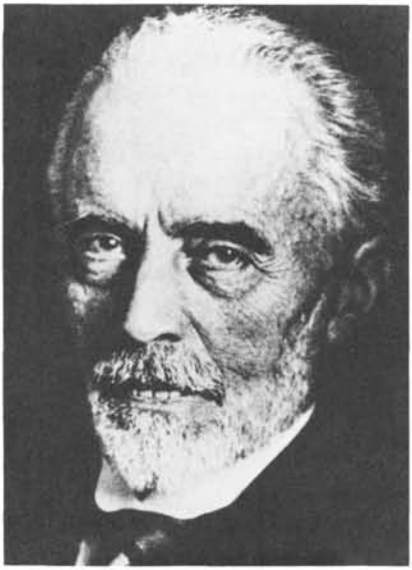


E.1.

E.2.

E.3.

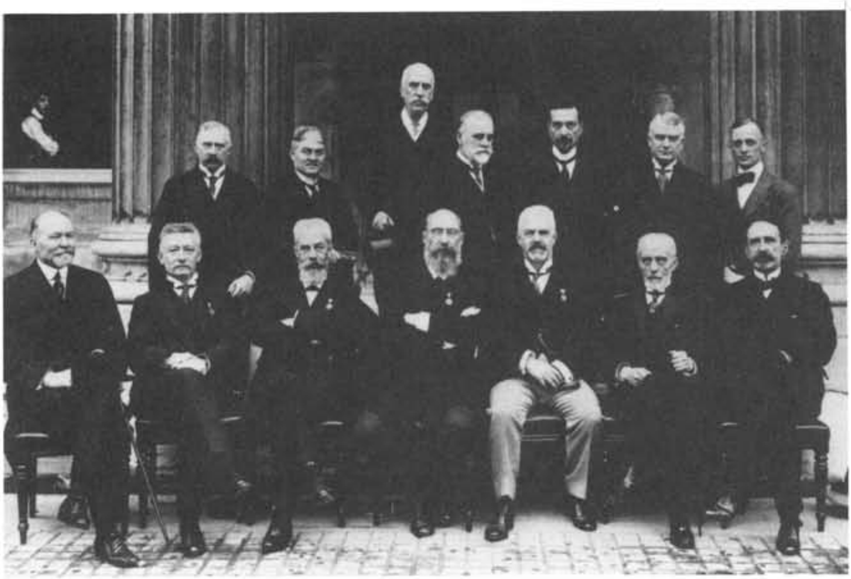
E.4.

E.1. Theodor E. Kocher. Courtesy of Theodor-Kocher-Institute, University of Bern, Switzerland. **E.2.** William M. Bayliss. Courtesy of The Royal Society. **E.3.** Ernest H. Starling. Courtesy of The Royal Society. **E.4.** Joseph Lister, by Walter William Ouless. Courtesy of the President and Council of the Royal College of Surgeons of England.

E.5.

E.6.

E.7.



E.5. Thomas Spencer Wells, by Rudolph Lehmann. Courtesy of the President and Council of the Royal College of Surgeons of England. **E.6.** Harvey W. Cushing. Courtesy of Yale Medical Historical Library, New Haven, Connecticut. **E.7.** Honorary Fellows of the Royal College of Surgeons of England (1913): *left to right:* (*back*) J. Nicolaysen, *G. W. Crile,* F. D. Bird, F. J. Shepherd, R. Bastianelli, *W. J. Mayo, H. W. Cushing;* (*front*) J. B. Murphy, W. Körte, H. Hartmann, E. Fuchs, *A. von Eiselsberg, T. E. Kocher,* T. Tuffier (endocrine surgeons italicized). Courtesy of Southampton General Hospital, Hants.

E.8.

E.9.

E.8. Oliver Cope. Courtesy of Oliver Cope, M.D., Harvard Medical School, Boston, Massachusetts. **E.9.** A. G. Everson Pearse. Courtesy of Professor A.G.E. Pearse, Royal Postgraduate Medical School, London.

2 (T)

The Thyroid

The thyroid gland lies near the surface of the body and gives rise to goiters, which are often large and unsightly, sometimes obstruct the trachea and esophagus, and may threaten life. For these reasons surgeons have long attempted to provide relief, and operations on the thyroid gland have evolved through the centuries as part and parcel of surgery as a whole. Until about 100 years ago operations were undertaken with trepidation under primitive conditions and often themselves proved fatal. Today they are routine, safe procedures with little morbidity. (T.1)

FROM ANTIQUITY TO THE MID-NINETEENTH CENTURY

Goiter and the Thyroid

Goiters (L guttur = throat) are very common in many parts of the world and were recognized long before the thyroid itself. They were formerly confused with other swellings of the neck, especially enlargement of the lymph nodes, and the terms "bronchocele" (Gk *βρόγχος* = trachea and bronchus + *κήλη* = tumor), "struma" (L = swollen gland), and "guttur" itself were often used interchangeably to describe them all. (T.2)

Goiters are said to have been known in China in 2,700 B.C.(1a). They were never endemic on the shores of the Mediterranean and, according to Franz Merke of Basle, in his authoritative *History of Goitre and Cretinism*, were not mentioned in Egyptian papyri(2a) or in Hippocratic or other ancient Greek writings(2b). They were noted by nonmedical Roman authors in the first three centuries A.D. in mountainous regions(2c, 2d), and Juvenal asked, "Who is still astonished at a goiter in the Alps?"(2e).

Many years passed before a physician wrote of goiter, the first probably being Paul of Aegina in the seventh century, who described an aneurysmatic bronchocele (2f). The next was Abul Kasim (Albucasis) of Cordoba, Spain (eleventh century), who referred to an "elephant of the throat," frequent in women and incurable (2g, 3). In the twelfth century physicians at the great Italian School of Salerno gave reliable accounts of goiter and distinguished it from scrofula (tuberculous lymph nodes) (2h). A century later medical and nonmedical writers wrote of goiters in particular regions, and Marco Polo described them in Turkestan (2h). (T.3)

Goiters have been depicted in art for centuries, mainly in regions where they are endemic, including South America and Mexico. Pottery at Berne in Switzerland and a Greco-Buddhist frieze at Gandhara in India in the second and third centuries show them clearly (2j). Goiters were portrayed as ordinary features in many works of art in Europe from the twelfth century onwards (2j), and Michelangelo depicted himself with an imaginary one, which had developed while he was painting the ceiling of the Sistine Chapel (2k)! Illustrations of goiters in medical literature first appeared in "wound men" in the fourteenth century (2l) and later achieved a high artistic level (2m). (T.4)

The normal thyroid was not recognized until the Renaissance. Galen is said to have described it much earlier, but Merke considers that he was describing the tonsils (2n) and credits the Italians with its first descriptions. In about 1500 Leonardo da Vinci drew the thyroid as a globular, bilobate structure, which he regarded as two glands, filling up empty spaces in the neck, but his drawings remained unknown for three centuries (2o). In 1543 Andreas Vesalius of Padua described and illustrated in *De Fabrica* two "glandulae laryngis" which, he thought, lubricated the larynx (p. E.2) (2p). Bartholomaeus Eustachius of Rome, who also discovered the adrenals (p. A.2), described a single "glandulam thyroideam" (L = shield-shaped) with an isthmus connecting its lobes, but his work was not published until the eighteenth century (2q). Julius Casserius, also of Padua, recognized the gland, shaped like a horseshoe, and regarded it as a lubricating and space-filling organ, which also made the neck pleasing to the eye (2r). Eventually, in 1619, Fabricius ab Aquapendente, another Paduan, recognized that goiters arose from the glandulae laryngis (2s). Thomas Wharton of London described the gland in his *Adenographia* in 1656 (p. E.2), named it "glandula thyroidoeis," and found that one specimen weighed six drachms (26 grams) (2t). He ascribed various functions to it, including those proposed by Casserius, also remarking that it contributed to the beauty of the throat, particularly in women. Many anatomical details were described subsequently, and in 1750 microscopy revealed vesicles in the gland (1b). Frederick Ruysch of Leyden suggested that the thyroid poured a peculiar fluid into the veins, and in the late eighteenth century Caleb Hillier Parry of Bath, who also described exophthalmic goiter, suspected that it provided a vascu-