SURGICAL ENDOCRINOLOGY

CLINICAL SYNDROMES

SECOND EDITION

STANLEY R. FRIESEN
NORMAN W. THOMPSON

Surgical Endocrinology

CLINICAL SYNDROMES *Second Edition*

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Surgical Endocrinology

CLINICAL SYNDROMES *Second Edition*

To the memory of
Owen H. Wangensteen
who anticipated the reunification of the neural and the endocrine influences that regulate function; he insisted on the preservation of these to maintain normal physiologic balance, but when homeostasis became decompensated he argued for their surgical correction.

Owen H. Wangensteen
1898–1981

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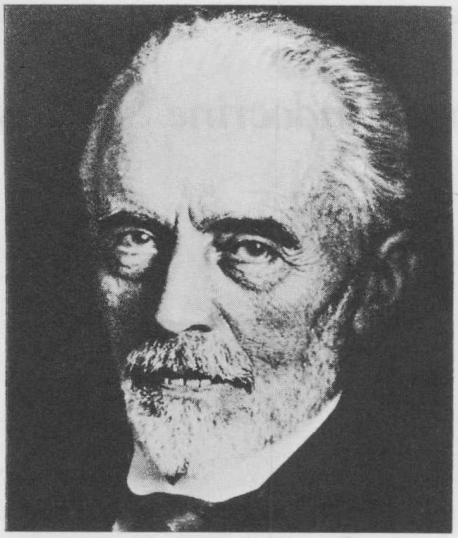
Foreword: The Evolution of Endocrine Surgery

Surgical endocrinology is the practice of endocrine surgery together with the basic science that sustains it. Surgical clinicians are concerned about patients and their needs, but scientific researchers support their work. Indeed, there is a symbiosis between surgical clinicians and scientific researchers and a sharing of problems, ideas, and discoveries.

The first edition of this book quickly became the standard work on surgical endocrinology, and it is not surprising that a second edition is now required. For this Dr. Stanley Friesen has enlisted Dr. Norman Thompson as coeditor. Both are my good friends and world leaders in the field. They have gathered a remarkable international team of contributors, some of them new for this edition, and all of whom write with the authority of experience and scholarship. Dr. Owen Wangensteen's foreword to the first edition, "A Look Back," described some aspects of the development of surgical endocrinology.[40] I am also looking backwards, but in a different way.

When I trained in surgery in the 1940s, I learned to operate on the thyroid gland and was occasionally fortunate to assist with the removal of rare endocrine tumors, such as pheochromocytomas. This, however, was all part of general surgery, and no one singled out the surgery of the endocrine glands as the special discipline that it has now become. I see its development as successive waves of change, differing in magnitude, speed, and duration, which may be grouped in three overlapping phases. The first phase started hundreds of years ago and lasted until the early part of this century, when the science of endocrinology was born. Its major component was the surgery of the thyroid gland, which evolved as part of surgery as a whole. Goiters have long attracted attention because they lie near the surface of the body, may become large and unsightly, and sometimes threaten life. For centuries surgeons have attempted to alleviate goiter effects, including the effects of toxic goiter, often at the earnest entreaty of their patients and, until a century ago, against their own better judgment. The results were sometimes remarkably good, but in general, thyroid operations were so hazardous, carrying an operative mortality of about 40%, that many leading surgeons would not attempt them. Indeed, they were proscribed by the French Academy of Medicine in 1850.[9] The second half of the 19th century, however, saw three major advances in surgery: anesthesia, antisepsis leading to asepsis, and effective control of bleeding. All these benefited thyroid surgery, and Spencer Wells' forceps, introduced in 1874,[41] had an immediate and particular impact because of the vascularity of the gland.

The function of the thyroid was not yet known, and surgeons opened the door to its understanding. Theodor Kocher, who became professor of surgery at Berne in 1872 at the age of 31, did more than any other single surgeon before or since to develop the practice and science of thyroid surgery (Fig. 1). In this he towered above all others, even Professor



Professor Theodor Kocher

Theodor Billroth in Vienna, as the first phase of endocrine surgery closed and the second opened up. In 1909 he was awarded the Nobel Prize. Switzerland was a major goiter area, and Kocher did hundreds of thyroidectomies, reducing his operative mortality from that prevailing at the time to less than 0.5% at the end of his career.[43] Sometimes he undertook total thyroidectomies, but he was disturbed to learn from Professor J. L. Reverdin in Geneva that grave physical and mental disturbances might follow this operation. He reviewed personally 18 of the 34 patients whom he had thus treated, and 16 suffered from a condition which in children he likened to cretinism and named "cachexia strumipriva."[19] Others, including Reverdin, were struck by its similarity in adults to myxedema. The causes of these diseases were not known, but in 1883, at a meeting of the Clinical Society of London, Sir Felix Semon, an ear, nose, and throat surgeon, pointed out that all three were associated with absence or degeneration of the thyroid and suggested that this common factor was responsible for the clinical features. Semon was ridiculed, and the society did not publish his remarks. However, the *British Medical Journal* carried a full account.[36] He was soon proved right,[30] and in 1891, Professor George Murray of Newcastle-upon-Tyne prepared an extract from the thyroid glands of sheep and used it successfully to treat myxedema.[29,30] This was the first clear indication that the product of a ductless gland was physiologically active, that its absence caused disease, and that its administration brought relief.

By the end of the 19th century, there was circumstantial evidence that other ductless glands (the gonads and the adrenal medulla) secreted chemicals that entered the blood and exerted general physiologic activity, and in addition, epinephrine had been purified.[40] The gonads were removed empirically in both sexes to influence distant organs and tissues.[40] Operations for tumors in these and other glands (the pituitary and the adrenals) were also undertaken occasionally.

At this time, the prevailing climate of opinion in physiology was greatly influenced by Ivan Pavlov of St. Petersburg (now Leningrad), who believed in "nervism," the view that nervous reflexes controlled most bodily functions. Perhaps for this reason, and despite the evidence, few people regarded the ductless glands seriously. It remained for two physiologists in London, Dr. William Bayliss and Professor Ernest Starling, in 1902 to perform the crucial experiment and to draw the revolutionary conclusion, namely, that hormones in the blood

mediated *chemical* reflexes.[40] They had the genius to realize that this illustrated a new principle in physiology—and so the science of endocrinology was born.

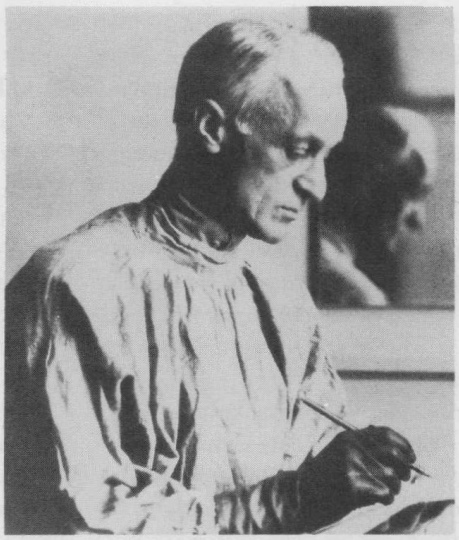
As the science grew, increasing numbers of endocrine tissues and hormones were identified. Endocrine diseases, owing to excessive or defective secretion of hormones, also were recognized, and surgeons became involved because a surgical operation often provided the only rational and effective means of treatment. This was the second phase in the development of endocrine surgery, which extended into the second half of the 20th century. Surgeons came to remove tumors of endocrine glands not only because of their neoplastic nature, but also, and more important, because of their secretions, thereby curing metabolic diseases. This established a new principle in surgery. Sometimes surgeons attempted the transplantation of glands to restore endocrine function, particularly in Addison's disease, diabetes, and hypothyroidism.[34]

During this phase, thyroid surgery, particularly operations for toxic goiter, became increasingly safe and effective as a result of developments in surgical strategy and technique[10,11] and the introduction first of iodine[25] and then of antithyroid drugs.[27] Finally, radioactive iodine not only facilitated measurement of thyroid function, but also proved a valuable adjunct or alternative to operations for toxic and malignant goiters.[13,15] Among the surgeons who contributed most were Sir Thomas Dunhill in Melbourne and London, Dr. William Halsted in Baltimore, Dr. Charles Mayo in Rochester, Dr. George Crile in Cleveland, Sir Cecil Joll in London, and Dr. Frank Lahey in Boston.

Other endocrine syndromes that surgeons tackled, eventually with success, included adrenal virilism, by Mr. Knowsley Thornton in London as early as 1889, before the syndrome had been recognized,[37] and Dr. Emil Bovin in Stockholm in 1909[3]; hyperparathyroidism by Dr. Felix Mandl in Vienna in 1925,[23] Dr. Isaac Olch in St. Louis in 1929,[2] and Drs. Edward Churchill and Oliver Cope in Boston in 1932[5]; pheochromocytoma by Professor César Roux in Lausanne[28] and Dr. Charles Mayo in Rochester[24] in 1926; hyperinsulinism by Dr. William Mayo in 1927[42] and Dr. Roscoe Graham in Toronto in 1929[17]; Cushing's syndrome in 1951 (which I will return to later); Conn's syndrome by Dr. William Baum[4] and Dr. Reed Nesbitt[31] in Ann Arbor in 1955; and the ulcerogenic syndrome by Dr. Robert Zollinger and Dr. Edwin Ellison in Columbus[44] in the same year.

Some of these achievements resulted from surgeons and their colleagues rising to the opportunities provided by single encounters with newly recognized diseases, while others were the outcome of disciplined attacks on successive difficulties until the long-sought goals were achieved. Sometimes individuals contributed most; sometimes groups and institutions. A long line of individuals has tackled surgery of the pituitary since 1889, when Sir Victor Horsley of London first operated transcranially on a pituitary tumor to relieve pressure.[16] At this time, few surgeons were ready to undertake neurosurgical operations, and from 1907 onward, general surgeons, ear, nose, and throat surgeons, and neurosurgeons in Europe and the United States turned to an extracranial transsphenoidal approach. The first to operate thus was Professor Hermann Schloffer of Innsbruck in 1907.[35] Pride of place, however, belongs to Dr. Harvey Cushing of Baltimore and Boston, who founded the first school of neurosurgery and whose brilliant work spanned 30 years (Fig. 2). During this period, no one else contributed so much to surgery of the pituitary or any other endocrine gland.[7] 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.[8]

In cooperative work among groups of clinicians and basic scientists, the Mayo Clinic staff has contributed more than any other to the development of branches of endocrinology and endocrine surgery during this second phase. Contributions included, from the early 1900s onward, the surgery of toxic goiter and, in 1914, the isolation of thyroxine; the first study of an insulinoma; remarkable results in the treatment of adrenocortical tumors in the 1930s and 1940s[39]; and the isolation of cortisone by Dr. Edward Kendall. This drug became available to surgeons in 1949, and the effect of its use to cover adrenalectomy for Cushing's syndrome by Dr. James Priestley, Dr. Waltman Walters, and their colleagues, published in

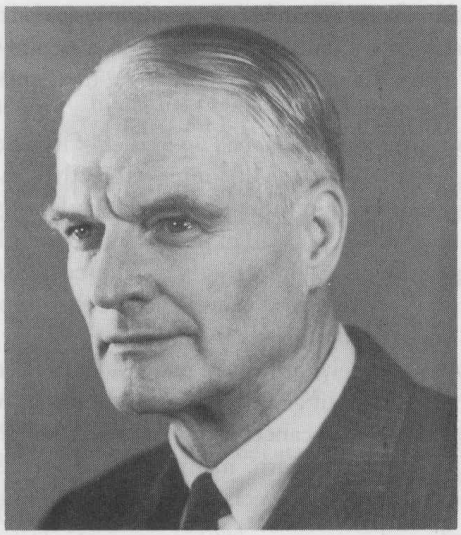


Dr. Harvey Cushing

1951, was revolutionary.[33] In the 1950s and 1960s, Priestley and other colleagues, following Dr. Charles Mayo's lead in 1926, also led the world in the surgical treatment of pheochromocytomas.[32]

The advent of cortisone had an explosive effect on endocrine surgery. It not only rendered adrenalectomy safe almost overnight, but also made total hypophysectomy practicable,[21] enlarged the scope of endocrine surgery for cancer of the breast and prostate,[18] and became the pivot of our understanding of the endocrine response to stress. At the same time, steroid therapy for general diseases confronted surgeons with new problems. I was privileged to be working at the Mayo Clinic in 1951 and 1952, at which time many of us rode, exhilarated, on the crest of the cortisone wave, which integrated surgery of the endocrine system, showing us the subject as a whole rather than the surgery of individual glands. This was the start of the third and present phase of surgical endocrinology. The first surgeon to view, practice, and advance endocrine surgery as a whole, even before this, was Dr. Oliver Cope of Harvard Medical School and Massachusetts General Hospital[6] (Fig. 3). From the early 1930s, for over 40 years, he made important contributions to the surgery of three glands: the thyroid, the parathyroids, and the adrenals. More than any other, Cope deserves recognition as the father of modern surgical endocrinology.

During the 1950s and 1960s, steroids were the focus of endocrine research. Their study increased understanding of the normal and abnormal functions of the adrenal cortex and the gonads; medicine as a whole prospered. From the late 1960s, however, with the introduction of radioimmunoassay for measurement of peptides in the blood, immunocytochemistry for their recognition and localization in tissues, and the advent of Professor Everson Pearse's APUD hypothesis (amine precursor uptake and decarboxylation system), the emphasis changed and peptides came to the fore. Also from the late 1960s, the new concept emerged that bodily functions were controlled not by nerves and hormones separately, or even closely linked, but by a single neuroendocrine system. Syndromes of peptide excess, such as hyperparathyroidism, hyperinsulinism, hypergastrinemia, and pituitary hyperfunction, were diagnosed much earlier and studied more precisely than before. Furthermore, new peptides, whose origin was unknown, were recognized; endocrine or paracrine cells, particularly in the gut, with no known secretions, were found; and many peptides were seen to originate both in the brain and in the alimentary tract. At the same time, new syndromes resulting from peptide overproduction were described, particularly from tumors of the pitu-



Dr. Oliver Cope

itary (Chap. 22) and endocrine pancreas. The latter included the Verner-Morrison (WDHA, VIPoma; 1958),[38] glucagonoma (1966),[22] and somatostatinoma (1977)[20,12] syndromes. Although surgeons contributed to the treatment of all these, other therapeutic measures, such as H2 blockers for gastrinomas, chemotherapy for VIPomas, and long-acting somatostatin analogues for many tumors came to play important roles.

Since the 1950s, in this third phase, increasing numbers of surgeons have worked to establish surgical endocrinology as a major discipline within general surgery and surgical science. Some have followed Professor Oleg Nikolaiev at the Institute of Endocrinology in Moscow, who started to practice endocrine surgery exclusively in 1964. He and his colleagues have treated very large numbers of patients but have missed the great opportunities available for clinical research. Many of us, however, emulating Kocher, Cushing, and Cope, have developed the science of surgical endocrinology, creating dynamic and creative interfaces with other disciplines in clinical practice, teaching, and research. All this and more is reflected in this book.

The unity of endocrine surgery is expressed not only in practice, but also in publications, associations, and teaching. The first small book on endocrine surgery was published by Dr. James D. Hardy of Jackson, Mississippi, then at the University of Tennessee, in 1952.[14] A whole issue of the *American Journal of Surgery* was devoted to the subject in 1960,[1] and a larger book was published in 1963.[26] Many more publications, including both editions of this work, have followed. Postgraduate courses in endocrine surgery have been popular since about 1970, and associations of endocrine surgeons have been formed nationally and internationally since the early 1970s. A journal of endocrine surgery is now published in Japan.

Surgical endocrinology started as a trickle and has now become a flood. Where will it run next? In the immediate future the main stream is likely to follow its present course. But what of the pituitary and the gonads, which were formerly but are no longer the concern of many general surgeons? Specialist internists encompass the whole of medical endocrinology, and surgical endocrinologists must find ways of establishing the integrity of all endocrine surgery, if not by reentering fields that they have left, then at least by associating with others. Advances in pituitary surgery owe most to developments in neurosurgery and microsurgery, as practiced by neurosurgeons and ear, nose, and throat surgeons. Cannot endocrine surgeons also, like vascular and plastic surgeons, master microsurgical techniques? Adrenal surgery was at one time claimed for urologists, but endocrine surgeons have reclaimed most

of it. Are urologists to take or keep testicular surgery, or are endocrine surgeons to play a part, particularly when endocrine function is involved? The surgery of the ovaries is practiced by gynecologists in many countries, but need it be their preserve when endocrine function is in question?

The future of surgical endocrinology is wrapped up in that of its parent disciplines, surgery and endocrinology. Two centuries ago, John Hunter wrote that the last part of surgery, namely, an operation, was a reflection on the healing art. Early surgery was like an armed savage who took by force that which a civilized man would obtain by strategy. This is no description of modern surgery, for many endocrine surgical procedures, in the hands of masters, are elegant works of art. It does mean, however, that an operation is not always the best solution to a problem and that another therapeutic measure may sometimes supplant it more effectively and safely. Conversely, a medical remedy, such as carbimazole, may prove most valuable not as an alternative, but as a means of rendering an operation safer. And in years to come, the surgical therapy of cancer will probably be of historical interest only. While these are lessons for surgeons to learn, many internists, some of whom are antagonistic to surgery on principle, need to appreciate the overwhelming advantages of operations.

This book makes fascinating reading and provides a happy blend of laboratory work, clinical research, and practical surgery. It is the greatest major current contribution to surgical endocrinology and illustrates how fast the subject is advancing. I commend it warmly to all endocrine surgeons, established or in training, to endocrinologists, and to those of other disciplines whose work is related to endocrine surgery and who wish to learn what an intriguing and important subject surgical endocrinology has become.

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Foreword to the First Edition: A Look Back

This splendid and impressive monograph on the neuroendocrine system by Stanley Friesen and his active coworkers and collaborators in the broadly erupting field of neuroendocrinology is indeed timely and will be welcomed by all segments of the profession. The endocrine system, with long if not deep historical roots in many medical disciplines, has been emerging for decades as a special field of study and investigation. Over the past two decades progress in the field has been phenomenal, leading to histologic and chemical identification of responsible hormonal secreting cells, a truly remarkable achievement.

Dr. Friesen, distinguished surgeon of the alimentary tract, has schooled himself on the hormonal activities of cells in many organs and glands and is well qualified to undertake the difficult task of integrating and correlating many recent new observations and discoveries for the clinician. His observation that complete gastrectomy in the patient with a malignant pancreatic gastrinoma will sometimes ablate metastases was a bold and enlightening innovation (*Surgery* 62: 609, 1967). Over long years, Friesen has followed the work of the London pathologist and histochemist A. G. E. Pearse, with whom he collaborated on genetic aspects of the Zollinger-Ellison syndrome (*Ann. Surg.* 176: 370, 1972).

It would take the experience of an accomplished molecular biologist to do justice to a worthy and critical appraisal of the many exciting and significant developments in the broad sweep of this rapidly expanding discipline, a competence to which this surgeon cannot lay the feeblest claim. Even so, Dr. Friesen very generously maintained that I could come up with something appropriate for the occasion.

In the third edition of his two-volume work on the Innere Sekretion (1916), Artur Biedl of Prague listed more than 350 pages of references, definitely suggesting that endocrinology has a long historical background.

Robert Graves, a brilliant Dublin physician, described the clinical syndrome of exophthalmic goiter that has come to be known as Graves' disease with such accuracy that the modern reader would recognize the entity readily from his account (*Lond. Med. Surg. J.* 7: 516, 1835). Thomas Addison of Guy's Hospital, a colleague of Richard Bright, lived for his students; Addison described atrophy of the cortical portion of the adrenals, subsequently known as Addison's disease (*Lond. Med. Gaz.* 43: 517, 1855). His demonstration that atrophy and disease of the capsular portion of the adrenals in patients resulted in anemia and death led Charles Brown-Séquard to excise both adrenals in dogs and other animals; the effect was uniformly lethal (*C.R. Acad. Sci. (Paris)* 43: 422, 1856). The London physiologists George Oliver and Edward Sharpey-Schäfer demonstrated the presence of a substance in the medulla of the adrenal that elevated blood pressure in dogs, which they called adrenalin (*J. Physiol.* 18: 230, 1895). This finding was reaffirmed by the Johns Hopkins pharma-

cologist John Abel, which agent he labeled epinephrine (*Johns Hopkins Hosp. Bull.* 8: 151, 1897). In a series of papers, the chemist Edward Kendall and colleagues at the Mayo Clinic (1934–1949) isolated cortisone from the cortical portion of the adrenal, providing an effective therapeutic answer to the treatment of Addison's disease.

The skeleton of the Irish giant Charles Byrne, one of the most exciting exhibits at London's Hunterian Museum, has always captivated the interest of visitors. To lessen the risk of detection of the stealth of the body, John Hunter, unfortunately, found it necessary to destroy all the soft tissues, thus removing the many striking features of soft tissues of tongue, hands, and feet of gigantism that Pierre Marie described so vividly under the title Acromegaly (*Rev. Méd.* 6: 297, 1886), a condition not inherited, but owing to abnormal secretory influences occasioned by enlargement of the pituitary body. The otologist Oskar Hirsch (1911), Harvey Cushing (1912), and the Vienna pathologist Jacob Erdheim (1916) added much to the understanding and management of some of the manifestations of acromegaly. For several decades up until quite recently it has often been said that the pituitary gland is the master gland in the hormonal symphony, a statement that recently has been seriously challenged by Roger Guillemin and other modern-day endocrinologists.

Claude Bernard (1849) noted in his doctoral thesis that cane sugar ingested by rabbits and dogs did not appear in the urine; when injected intravenously, in similar amounts, however, sugar appeared regularly in the urine. This occurrence suggested to Bernard the glycogenic function of the liver constituting the first demonstration of the presence of an internal secretion, the name by which Bernard characterized the phenomenon.

Bayliss and Starling discovered the role of HCl in releasing from the upper jejunal mucosa a chemical reflex that stimulated the flow of pancreatic juice (*J. Physiol.* 28: 325, 1902). In an ingenious experiment, Starling destroyed the mesenteric nervous connections to an isolated upper jejunal loop, leaving the isolated segment suspended only by its blood vessels. On the spot, Starling correctly concluded that stimulation of pancreatic secretion from the denervated loop was a chemical reflex, an inference he was able to validate by rubbing sand and dilute HCl into the mucosa of another jejunal loop; upon filtering the solution and injection into a jugular vein, a strong pancreatic secretion was elicited. Bayliss and Starling subsequently labeled the chemical reflex a hormone.

In an obituary note on Ernest H. Starling, C. J. Martin of London related (*Br. Med. J.* 1: 900, 1927) that he was present in the laboratory when Starling performed the telling experiment just described. This observation lent a new concept to the regulation of the secretion of the digestive glands. Prior thereto, the prevailing opinion of workers in the field, including Pavlov and his coworker Popielski and the Belgian physiologists Wertheimer and LePage, was a peripheral neural reflex. When Pavlov repeated and verified the Starling experiment, his interest in the physiology of the digestive tract waned; after some years he devoted the remainder of a long professional life to the study of conditioned reflexes.

Shortly after Bayliss and Starling's demonstration of a messenger in the mucosa of the upper jejunum which, on contact with HCl, released a hormone that stimulated secretion of pancreatic juice, Edkins demonstrated the presence of a hormone in the antral mucosa which he called gastrin (*J. Physiol.* 34: 133, 1906). Its presence was doubted by many physiologists for many years, until the London surgeon Heneage Ogilvie (1936–1938) verified its existence by comparing the effects of antral excision and antral exclusion in gastric resection for duodenal ulcer (*Edinb. Med. J.* 43: 61, 1936; *Lancet* 2: 295, 1938). Leaving a segment of the antrum attached to the duodenum, Ogilvie observed, invited neostomal ulcer at the site of the gastrojejunal anastomosis, an occurrence that could have been foreseen in the heightened secretion of HCl in dogs fed meat after such an operation, a finding observed by Hans Smidt of Jena (*Arch. Klin. Chir.* 130: 307, 1924). Today the role of Edkins' gastrin in stimulating gastric secretion is a major concern of gastric physiologists and clinicians.

Ivar Sandström, a Swedish medical student, described the parathyroid glands. He sent his paper initially to Rudolph Virchow, who declined its publication in his Archiv, whereupon