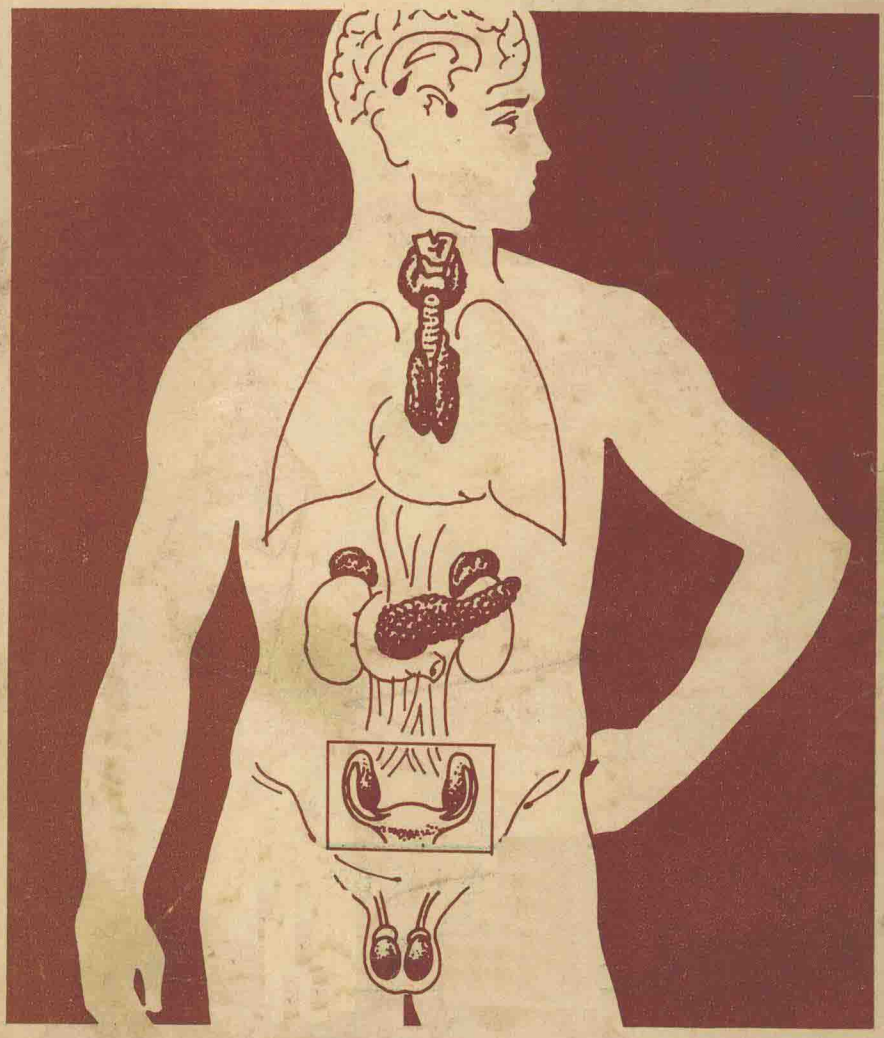
Surgical Endocrinology:
Clinical Syndromes



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Surgical Endocrinology
Clinical Syndromes

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Surgical Endocrinology

To Students of All Ages
Who Ask
"Why?"

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Foreword—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 (*London 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 (*London 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 pharmacologist 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 (1934-49) 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 (1936-38) 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. f. 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 Sandström published it in a little known Swedish journal (*Upsala Läkaref Förhandl.*, 15:441, 1880). The function of the parathyroid glands remained a matter of considerable speculation until the Austrian surgeon Felix Mandl excised a small tumor of the left inferior parathyroid gland in a patient with fibrous cystic osteitis in 1925, followed by considerable relief to the patient and great improvement of the concomitant osteoporosis (*Wien. klin. Wschr.*, 38:1343, 1925). Mandl, a young surgeon in Professor Hochenegg's clinic at the University of Vienna's Allgemeines Krankenhaus, reported his interesting story at the December 4, 1925 meeting of the Vienna Congress of Physicians. Mandl had first implanted a parathyroid gland freshly obtained at necropsy from a patient who died in the emergency admittance ward, which procedure was without effect. Mandl noted that the patient's excreted urine was rich in calcium and white in color. No tumor was palpable in the neck but at operation a definite tumor of the left inferior parathyroid gland was found and excised. The patient's chronic bone pain relented immediately and his fractures healed. There was an observed 80 percent decrease in calcium excretion in the urine, attending the excision. Professor v. Eiselsberg, a keen student of ductless glands (*Wien. klin. Wschr.*, 5:81, 1892), was the presiding officer but strangely had nothing to say relative to this remarkable achievement; nor did the five well-known Vienna surgeons and physicians who discussed Mandl's presentation appreciate its significance. In defense of his thesis on conclusion of the discussion Mandl indicated that Siegfried Hoffheinz (*Virch. Arch.*, 256:705, 1925), an assistant to Professor Otto Lubarsch of the Pathologic Institute in Berlin, had observed hypertrophy of the parathyroid glands in more than 50 percent of patients with generalized osteitis fibrosa that had come to autopsy.

Adolph Hanson (*Milit. Surg.*, 52:280, 1923), a general surgeon of Faribault, Minnesota was the first to isolate an active parathyroid extract with helpful advice from Arthur Hirschfelder, professor of pharmacology at the University of Minnesota. Two years later, James Collip isolated parathormone (*J. Biol. Chem.*, 63:395, 1925), the active secretory principle of the ductless parathyroid gland.

The Canadian orthopaedic surgeon Frederick Banting of Toronto read Moses Barron's account (*Surg. Gyn. Obstet.*, 30:350, 1920) describing atrophy of the acinar cell portion of the pancreas attending obstruction of the duct of Wirsung

by calculi. He then ligated the excretory ducts of the canine pancreas, producing atrophy of the trypsinogen-secreting area without injury to the cells of Langerhans located primarily in the tail of the pancreas (*J. Lab. Clin. Med.*, 7:251, 1921-22). These islets had been described in a Berlin Inaugural thesis by Paul Langerhans (1869) a medical student. By this means, Banting, with the assistance of Charles Best, also a medical student, isolated insulin, a useful agent in the control of diabetics and the only hope for juvenile diabetics.

In 1955 the University of Ohio surgeons Robert Zollinger and Edwin Ellison (*Ann. Surg.*, 142:709-29, 1955) described patients with gastric hypersecretion who proved to have pancreatic gastrinomas for whom total gastrectomy became the operation by choice. Their report has constituted the primary incentive and stimulus to the great forward thrust lent gastrin studies by Roderick Gregory and his associates in Liverpool (*J. Physiol.*, 169:18, 1963).

Since antiquity differences between male and female have been recognized as owing to dissimilarities in the sex glands. In his *Animal Oeconomy* (1786), John Hunter observed that in the male, the secondary sex organs, prostate, seminal vesicles and the penis depend upon the testes for maturation. Hunter used gross measurement and excision to establish the relationship. Microscopy was yet not in general use by biologists, and Hunter employed no magnification larger than a hand lens. In the "land-mouse" and the mole, the seminal vesicles are scarcely discernible in winter, said Hunter, but very large in summer, and the seminal vesicles vary in size according to the size of the testes. Hunter did not attempt castration of patients in the hope of diminishing urinary obstruction from prostatic hypertrophy.

A century after Hunter, Joseph Griffiths of Edinburgh (1890) reported that when a young bull was castrated, the prostate gland remained small. Griffiths extended Hunter's inquiry to the dog and cat, also studying the histologic changes attending castration. In a three-year-old dog, castrated a year earlier, Griffiths found the prostate small, firm, tough and fibrous, unlike the large soft gland of the normal male dog. A very similar situation attended castration of the male cat, especially when done at three weeks of age (*J. Anat. Physiol.*, 24:27, 1890).

Robert A. Moore reported the autopsy findings of a man 39 years of age who had undergone castration at 34 years in the hope of escaping the social stigma of being a homosexual. The prostate was considerably smaller than normal for his age, observed Moore, and the "seminal vesicles are exceedingly small" (*Am. J. Pathol.*, 12:620, 1936). There are few if any other published accounts of the condition of the prostate some years after castration in adult men.

Eunuchs, castrated as young boys before puberty, retain preadolescent soprano voices and have beardless faces. Eunuchs are free from enlargement of the prostate, common to aging men. Eunuchs were known in China 1100 years before Christ and were highly prized servants in households and government in the Orient and Eastern Mediterranean countries in antiquity. Oriental princes placed eunuchs in charge of the bedchamber and in the seraglios of their harems. Eunuchs are mentioned in both the Old and New Testaments.

Emasculation of young slave boys was common, for they commanded a considerably higher price than other boys in the slave market. They were sold as eunuchs for Moslem harems into the twentieth century. "A clean sweep" operation was usually done of scrotum, testes and penis.

In a succession of papers (1893-1904), J. William White of Philadelphia advocated excision of the testes as a solution for urinary retention occasioned by an enlarged prostate, a suggestion debated vigorously at the time. The mortality was surprisingly high, varying from 13 to 18 percent in the hands of its advocates, probably a reflection of application in terminal cases. Probably a third of White's patients upon whom orchiectomy was performed suffered from cancer of the prostate. Strangely enough, neither White nor any of his successors followed up with an account of the nature of the histology of prostatic tissue removed in patients undergoing orchiectomy for urinary retention (*Trans. Am. Surg. Assoc.*, 11:197, 209, 1893; *Ann. Surg.*, 40:788, 1904).

White's innovation preceded that of George T. Beatson (1896) of Glasgow, who performed excision of the ovaries in females for advanced cancer of the breast (*Lancet*, 2:104, 162, 1896), an operation that has been revived in recent decades and found often to be an effective palliative hormonal attack upon the problem of late breast cancer. Over the past three decades, orchiectomy has been endorsed by Charles Huggins (*Cancer Res.*, 1:293, 1941) as a therapeutic measure for cancer of the prostate. Whether castration will cause regression of benign prostatic hypertrophy in older men and animals is not definitely known. For cancer of the prostate current conventional professional advice is administration of agents to suppress plasma testosterone or orchiectomy. A few reserve all treatment until the appearance of metastases causing symptoms.

The interest and concern of physiologists, biochemists, and endocrinologists in more recent years in the function of ductless glands has added significantly to progress in this once very obscure field. The significant observations of the physicians Graves and Addison, and the surgeons Banting, Mandl, Hanson, Zollinger and Ellison have been illuminated by methodical studies in the hands of basic biological scientists and chemists.

The Galveston symposium of 1974 on gastrointestinal hormones (University of Texas Press, 1975) under the able supervision of the surgeon James C. Thompson served to point up the growing complexity of the problem of gastrointestinal hormones. The few hormones of that tract recognized 20 years ago have multiplied, indicating definitely that the field today is primarily one for the biochemist, chemist, endocrinologist, pharmacologist and physiologist.

The observant physician and surgeon of the Graves, Addison, Banting, Mandl and Hanson types will still continue to identify syndromes yet unrecognized, but their identification and clarification will need the attention of erudite representatives of the disciplines just enumerated. Definition of the nature of hormonal imbalances will serve to indicate the optimal mode of management.

The important contributions of three American scientists, Rosalyn Yalow, Roger Guillemin and Andrew Schally, working in diverse medical disciplines on broad aspects of endocrinology, fully justified their being named Nobel Laureates in October, 1977. Their significant work has opened new vistas for chemical identification of hormones, suggesting new methods for the control and management of neuroendocrine disorders. For decades, the hypophysis and the hypothalamus have been looked upon as the leaders of the hormonal symphony. Today, neuroendocrine secreting cells are known to be widely dispersed over the cerebral cortex and in the mucosa of the upper gastrointestinal canal. An abnormal secretion of somatostatin, secreted by both brain cells and mucosal cells of the upper gastrointestinal canal, may be a responsible inhibi-

tory factor in many disorders, perhaps including peptic ulcer and mental disorders. Neuroendocrinology is offering renewed and promising challenges and a fertile field for investigators as well as clinicians, opening new vistas and lighting the way to important advances in practical medicine.

The recent startling progress in endocrinology suggests that it may not be out of place to ask whether the tools and contributions of endocrinologists may not come in time to supplant the surgeon's knife in dealing with some endocrine disorders.

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Preface

Within the last two decades there has been such a massive proliferation of basic and clinical information relating to the rapidly expanding dimensions of the neuroendocrine system that it seems necessary to examine the directions and the diversities of these discoveries in order to bring them into focus. There has been a virtual "explosion" of newfound endocrine cells, newly identified humoral products and newly described syndromes. The increasing variety of clinical presentations of these syndromes which result from hypersecretion of neuroendocrine tumors and hyperplasias demand early diagnostic recognition and require sophisticated surgical management. Some of the original observations concerning the systemic effects of hyperfunctioning tumors have been made by surgeons who are the appropriate ones to whom treatment is usually entrusted. Intelligent surgical treatment is based on accurate diagnosis and a conceptual understanding of the pathophysiology of such syndromes. Accordingly, this book is directed specifically to these three goals: The unification of basic and clinical concepts, the simplification of diagnostic criteria, and the presentation of therapeutic options in surgical management. To accomplish these aims the material is presented with a functional approach in which diagnostic and management flowcharts, as well as diagrams of the pathophysiology for each syndrome are employed; there is, in addition, editorial bridging of basic and clinical observations for increased understanding of the many syndromes that involve surgical management.

The neuroendocrine cells from which hypersecreting dysplasias arise and from which circulating hormones are elaborated have presumably always existed, having survived countless centuries of evolutionary influences, but the recent detection and identification of them has been an exciting scientific accomplishment, as judged by the profusion of published articles about them. The sheer numbers of these publications, however noteworthy, would suggest that some revelations would be remembered and others would go unnoticed or forgotten, just as the sparks of a volcanic eruption remain vivid in our memory while the ashes are lost to the winds. This book is a presentation of many of the illuminating "sparks" and some of the overlooked "debris" as a compilation of usable knowledge for general and specialty surgeons about this dynamic neuroendocrine system, in health and disease.

It has been my good fortune to observe at firsthand this rediscovery of the neuroendocrine system. My initial work with A. G. E. Pearse, during a sabbatical leave, concerned the role of the pyloric ganglion cells in the pathogenesis of congenital pyloric stenosis. At that time some of the histochemical charac-

teristics of these myenteric cells were observed which would later become applicable to the developing APUD concept. Although other investigators considered these neural cells as the possible source of gastrin, it remained for James E. McGuigan to positively identify the gastrin cell to be within the mucosa. Shortly thereafter, I again had the opportunity to work with Pearse as the APUD concept was being formulated and was on the scene when a host of new endocrine cells in the gastrointestinal mucosa were found and described. The cytochemical similarities of these mucosal endocrine cells to the myenteric neural cells were confirmed and now, after more studies, the functional interrelationships of the autonomic nervous system and the diffuse endocrine system are firmly established, even to the extent that some of the same hormones have been found in both gastrointestinal and neural (brain) tissues. In the meantime, I had briefly observed Gregory and Tracy's monumental work on the isolation and identification of the gastrin polypeptides in hog antral mucosa and later, in human islet cell tumors. Many of the above milestone discoveries were prompted by the exciting clinical observations of Zollinger and Ellison that pancreatic islet cell tumors might be an unexpected source, other than the gastric antrum, of the ulcerogenic secretogogue, gastrin. At the present time it is the accumulation of *basic* scientific discoveries which is making the more recently described *clinical* syndromes understandable.

It is hoped that in this book the fusion of the discoveries in the basic sciences with the observations in the clinical sciences will clarify even the most complex endocrine syndromes. Only through a clear understanding of the basic concepts is it possible to sort out the extremely bizarre clinical presentations of some of the hyperfunctioning endocrine disorders. This is particularly relevant when we consider the wide spectrum of endocrinopathies, from the simple sporadic syndrome through a kaleidoscopic array of polyhormonal, pluriglandular, familial and "ectopic" phenomena.

I have observed that when physicians and surgeons have had occasion to talk and think about these so-called "rare endocrine syndromes" it frequently becomes apparent that the syndrome is not so rare after all. More often than not, such a possible "case" is suddenly recalled to memory, having been missed in diagnosis because of a lack of awareness of the syndrome or simply of lack of time to have read appropriate articles widely dispersed in many journals. More and more patients are now recognized as having endocrinopathies involving the gastrointestinal tract, and these are usually properly diagnosed and treated, but unexplainable clinical pictures are still occasionally observed, and these await future clarification. It is expected that this book, with its up-to-the-minute information, contributed by recognized authorities in their fields, will familiarize those physicians and surgeons who are already knowledgeable about most endocrinopathies with the most recent concepts of the pathophysiology, diagnosis and management of old and new syndromes. It should also provide a source of understanding for busy clinicians who care for patients of all ages who might have endocrine abnormalities.

There are a number of features which perhaps are unique to this book. In an attempt to unify conceptual and practical considerations, some of the basic information in the first part of the book is reintroduced in the clinical chapters, particularly in the editorial commentaries. Diagrams illustrating the pathophysiology of each syndrome, many of which are entitled mnemonically,

further clarify the clinical presentations. There are, among the clinical chapters, practical applications of clinical concepts by means of management flowcharts which illustrate points of consideration and decision, from the presenting clinical situation to the final diagnosis of each syndrome. This book also departs from the traditional format of subjects by organ systems to a more functional grouping of syndromes based upon the type of hormone elaborated, such as those caused by secretion of the ubiquitous fast-acting *amines*, or of the newer but slower acting *polypeptides* and/or the familiar chronic-acting *steroids*. A composite table of useful information, matching syndromes with their humoral agents, biologic actions and diagnostic features is centrally placed in the book for ready reference to the key characteristics of each syndrome.

Certainly, as new information continues to develop, the present methods of diagnosis and treatment will necessarily be refined, but the fundamental concepts which are presented here are not likely to change. These modern-day concepts will continue to be applicable even to the newer approaches of target-cell modification and tumor therapy.

It is difficult to acknowledge fully the deep appreciation I have for the contributing authors, already exceedingly busy with ongoing work, who gave again of their time and expertise for this new book. I sincerely thank them and their associates and secretaries. The editors of J. B. Lippincott Publishing Company have been more than helpful and supportive. I am also grateful to Dr. Robert Bolinger, my long-time friend and editorial consultant on this book, for his abundant help and advice, and to my secretary, Mrs. Caroline Weaver, for her superb assistance from the inception of this book to its completion. The unselfish understanding of my wife, Beth, through many hours is more than I deserve and I thank her for that.

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