WILKINS

THE DIAGNOSIS AND TREATMENT OF ENDOCRINE DISORDERS IN CHILDHOOD AND ADOLESCENCE

WILKINS

THE DIAGNOSIS AND TREATMENT OF ENDOCRINE DISORDERS IN CHILDHOOD AND ADOLESCENCE

FOURTH EDITION

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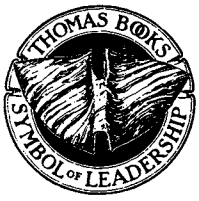

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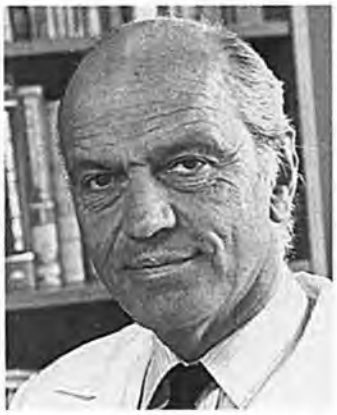

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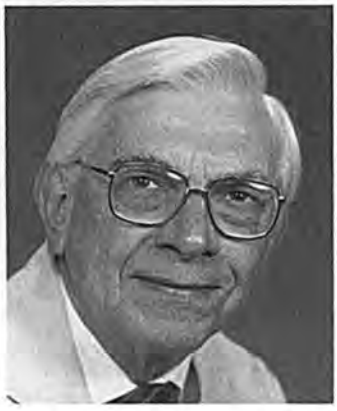

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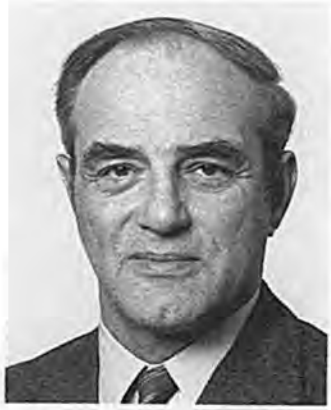

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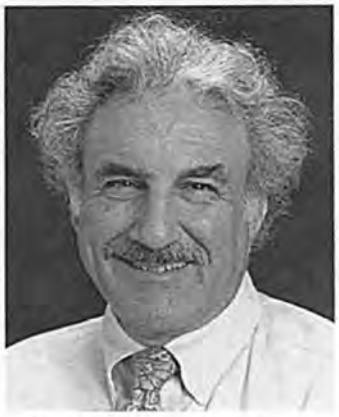

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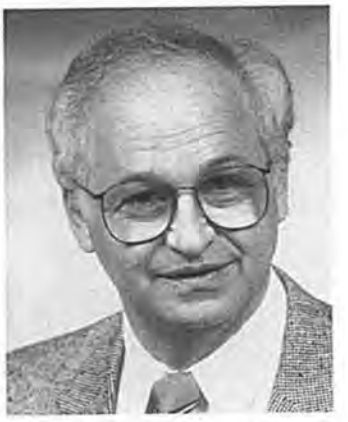

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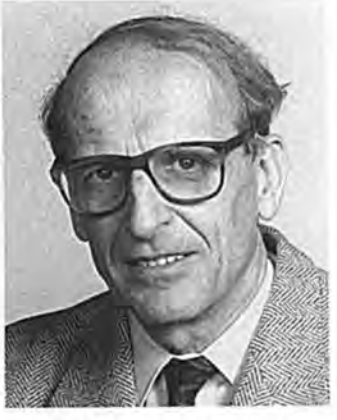

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LAWSON WILKINS

Lawson Wilkins was born 100 years ago in 1894 and died at the age of 69 in 1963. Thirty years have passed since then and 28 years since the publication of the Third Edition of this text (1965). Dr. Wilkins' demeanor, accomplishments, and the esteem in which he was held by peers and by his extended family of pediatric endocrine trainees are mostly unknown to recently trained pediatric endocrinologists. Since volumes could be written about each aspect of Dr. Wilkins' life, an abbreviated biography is inadequate. Nevertheless, the brief history of his life which is recorded in this, the Fourth Edition of his textbook, provides the opportunity to perpetuate the image of a man who should not be forgotten by professionals in the pediatric world.

Lawson Wilkins was born in 1894 in Baltimore. His father, Dr. George Wilkins, was probably the most highly respected family practitioner in the city. Historical accounts indicate that George Wilkins was intellectually curious, dedicated to his patients, and attentive to detail. His son exhibited the same characteristics. The death of his mother when Lawson was five years of age significantly strengthened the already close bond between father and son. Not surprisingly, the son followed in his father's footsteps.

After receiving a baccalaureate degree from The Johns Hopkins University in 1914, Lawson Wilkins began medical school there. Along with many other medical students, he volunteered in 1917 to go to Europe and serve as an orderly in a medical unit during World War I. After the war, he was accepted as an intern in internal medicine at Yale for a year. He then returned to Baltimore to serve a pediatric internship at The Johns Hopkins Hospital, where the influence of Drs. Blackfan, Park, Kramer, and other giants of pediatric medicine of that period further whetted his keen intellectual appetite.

It was most likely his desire to follow in his father's footsteps that prompted him to become a primary care physician (pediatrics) in Baltimore

in the early 1920s. Until the time he accepted a full-time academic position in 1946, Wilkins practiced general pediatrics for 25 years with intense intellectual curiosity and great compassion for his patients. This author has on several occasions met adults in Baltimore who remembered Dr. Wilkins fondly as their pediatrician. These individuals had no idea that Dr. Wilkins had made major contributions to medicine as an endocrinologist and a geneticist.

In 1935, Dr. Edward Parks who was instrumental in the development of various subspecialties in pediatrics, invited Lawson Wilkins to establish an endocrine clinic in the Harriet Lane Home of The Johns Hopkins Hospital. Dr. Wilkins was reluctant, since endocrinology at that time was the trade of quacks and charlatans. He accepted the part time position, however, and with Drs. Fuller Albright, John Eager Howard, George Thorn, Robert Williams, and a few others, he transformed endocrinology into a respectable subspecialty.

Wilkins focused on the problems in pediatric endocrinology — particularly problems of growth and genetics — while his confreres attended to the accumulation of knowledge about endocrinology in adults. Although he was intensely interested in the metabolism and control of carbohydrate and fat metabolism, he assiduously avoided a clinical interest in diabetes. Interestingly, he never considered diabetes a disease of the endocrine system, although he believed hypoglycemia was.

Once Wilkins re-entered academic medicine he contributed in the fields of clinical investigation and patient care. He was the author of hundreds of papers, and in the period from 1935 to 1948 he studied all auxological aspects of growth in both normal children and those with various endocrine disorders. The picture of Wilkins demonstrates him plotting on one of the hundreds of charts with he composed — often late at night. He was a master at using auxology as a diagnostic tool and extended his investigation by accumulating valid data in studies which he established to determine the effect of testosterone and other hormones on nitrogen, calcium, and cholesterol metabolism, as well as growth.

He encouraged Bongiovanni, Migeon, and Eberlein to establish a laboratory in conjunction with his endocrine clinic, as these individuals shared his interest in adrenal steroid metabolism and the pathophysiology produced by deficiencies of various enzymes involved in cortisol synthesis. From these studies, he and his trainees, Crigler, Klein, Gardner, Migeon, and Rosenberg, successfully determined the appropriate treatment for patients with congenital virilizing adrenal hyperplasia.

He always took the opportunity to apply in his studies the work of those doing related studies in other areas. His elucidation of normal and abnormal sexual differentiation in the human best exemplifies this phenomenon. Wilkins applied what Alfred Jost had learned from animal experiments about sexual differentiation, and proved that the anatomy of the reproductive system in gonadal agenesis and pseudohermaphroditism could be explained by the presence or absence of androgens and Mullerian Inhibition Factor. He extended these studies into the field of genetics and cytogenetics, and he was among the first to apply the cytological techniques of Dr. Murray

Barr to identify the inactivated X chromosome (Barr bodies) observed in the nuclei of patients with Klinefelter syndrome and in female pseudohermaphrodites. These diagnostic aids facilitated the diagnosis and therapy of patients with abnormalities of sexual development. His fascination with this field prompted him to invite John Money to join his group to study the psychological aberrations of endocrine disturbances and the effect of therapy thereon. It was Money working with Wilkins from which the important discipline of psychoneuroendocrinology began.

Wilkins loved to teach students, residents, and others. To do this he continually took photographs and made drawings of patients and their internal organs when these were surgically exposed. He followed patients closely, and his repeated photographs of them made it possible to teach about these entities on a longitudinal basis.

The First Edition of his textbook entitled "The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence" was derived from his collection of photographs and drawings which exemplified disease processes. In the late 1940s he utilized posters of these photographs and drawings at the annual meetings of the American Academy of Pediatrics to teach pediatric endocrinology to the pediatricians attending these meetings. The teaching process was so successful that he elected to publish these materials as the First Edition of his text in 1950. Seven years later, in 1957, he came forth with the Second Edition which was equally well received. The Third Edition was completed to a significant degree when Wilkins died in 1963. Drs. Migeon and Blizzard completed the text, and the Third Edition was published in 1965. These texts were accepted as the bible of pediatric endocrinology for many years.

A major factor contributing to the success of these books was the Atlas which was at the end of most chapters. The pictures in these Atlases are perpetuated to some extent in this, the Fourth Edition of Wilkins' text, which you are holding in your hands.

He was equally noted for training fellows who avidly sought fellowships with him so they in turn could become pediatric endocrinologists. Forty-one fellows who subsequently became academicians in the United States or abroad were listed in the acknowledgement sections of the second and third editions, and his legacy has become so widespread that a current listing would be impossible!

Lawson Wilkins was more than a scientific giant. He was a man of great magnetism and personality. Few who knew him could forget his bass voice which he put to good use singing ballads and occasional bawdy songs long into the night. He loved to sail his boat on Chesapeake Bay and tell jokes, which he masterfully embellished. He adored and was adored by Lucile Mahool, his wife of many years who died in 1959.

At a meeting in Baltimore of the Lawson Wilkins Pediatric Endocrine Society in the mid 1960s, Dr. John Eager Howard related the following about Wilkins: "When I first met him, I was even more impressed by the vitality of the man than by his scientific studies. In response to my knock on the door, the rafters fairly reverberated to the booming voice that urged me to come in. His whispers in a conference could cause consternation,

for his 'That fellow is putting out pure hogwash' could be heard all over the room. But I should hasten to say that his comments were rarely uncomplimentary, for an immense generosity toward others was one of his most endearing qualities." In accord with Dr. Howard's observation, his fellows, including Blizzard and Migeon, found Dr. Wilkins to be a paradox in that he was gruff but gentle. And while he always dominated the situation, he never exhibited dominating behavior toward individuals.

We in pediatric endocrinology and genetics are indeed blessed to have had such a man lead us. It is respect, admiration and adoration of him that has prompted us to continue his textbook and publish the Fourth Edition.

ROBERT M. BLIZZARD, M.D.

This book is dedicated to
our parents,
our wives and our children,
our teachers and our students,
and our patients.

The Editors

FOREWORD

The First Edition of Lawson Wilkins' book "The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence" was published in 1950. It was the first textbook on pediatric endocrinology and had a major impact on the development of this new pediatric subspecialty. The Second Edition, again written by Wilkins appeared in 1957, and the Third Edition was published together with his associates Robert Blizzard and Claude Migeon in 1965. A long time has passed since then. The younger pediatric endocrinologists of today are aware of Lawson Wilkins as a historical figure, but no longer know and use his textbook. The present publication of the long awaited Fourth Edition, published on the centennial of Dr. Wilkins' birth, and edited by Michael S. Kappy, Robert M. Blizzard, and Claude J. Migeon, therefore, is a major event in pediatric endocrinology.

Lawson Wilkins, the sole editor of the first two editions, can truly be regarded as the father of pediatric endocrinology. He was a practicing general pediatrician before he established the endocrine clinic at the Harriet Lane Home in Johns Hopkins Hospital. The 1940s were the founding days of pediatric subspecialty clinics.

Wilkins dedicated his first book "to my father George L. Wilkins, Edwards A. Park and F. Albright, the family physician, the pediatrician and the endocrinologist who have been my principal inspirations." The motivation and personal attitude expressed in this dedication is exemplary and still valid for all of us.

In Wilkins' First and Second Editions of his books most of the fundamental clinical knowledge of today already was present. This and the illustrations at the end of each chapter, which was called an Atlas, and which contained photographs, charts and figures of individual patients, made the books clinically immensely useful. But most of today's laboratory tests were lacking. When these editions were published it was not possible to estimate the blood level of hormones. For the estimation of urinary hormones there existed a few color reactions such as the Zimmermann reaction for 17-ketosteroids and a few expensive time consuming bioassays in mice. The books took into account bone age determinations only to a limited degree, as these were not yet fully developed and did not take into account the differences between sexes. It only was shortly thereafter that the first edition of the Atlas of Greulich and Pyle was published. The study of chromosomes for clinical diagnosis had not been described, and the fact that Turner and Klinefelter syndromes are chromosomal aberrations was not yet known.

Congenital adrenal hyperplasia was fully described in its classical form, but of course not yet in its variations. The high familial incidence was mentioned, and also that the disorder does not occur in more than one generation. It is noted that this is in contrast to other disorders in which there is a marked hereditary tendency. This remark indicates that thinking in terms of genetics was far less developed in that time than today.

Pediatric endocrinology subsequently has come a long way. The effect and regulation of the classical hormones are well known. They can be measured in blood and urine. Hormones and regulatory factors are produced by all tissues, and have not only classical endocrine effects but also autocrine and paracrine effects. Genetics has become a most important field to understand endocrine disorders. Cytogenetics and molecular genetics continuously reveal the finer aspect of genetic regulation. The descriptional aspects of growth and pubertal development have made tremendous progress, and more and more of the regulation of growth and puberty is understood. All these new aspects, as well as technical aspects such as imaging technics, are fully covered in the present new edition. By necessity the number of authors and of pages has increased. Fortunately the organization of the book into text and illustration (Atlas) components has been retained. In this way the theoretical aspects and the practical clinical aspects of endocrine disorders are fully retained. In summary the book covers much wider aspects of pediatric endocrinology and neighboring fields than any other book in pediatric endocrinology and still keeps the original flavor of the clinical teacher Lawson Wilkins.

Because Lawson Wilkins had the greatest impact on my training as a clinician and clinical investigator, I add a personal note regarding Lawson. He along with Guido Fanconi stimulated my interests in endocrinology, metabolism, genetics, and growth. Both were superb clinicians and forceful and enthusiastic teachers.

Their scientific contributions were not the results of systematic laboratory research in the framework of a sophisticated research program, but the offshoots of very careful clinical observations combined with a deep interest in the patient and his problems. They used charts to follow the courses of diseases and the growth of patients. They recognized important disease aspects not noted by others, were able to add new insights into many diseases, and offered challenging new speculations.

Lawson and I met for the first time in 1950 at the International Congress of Pediatrics in Zurich. Guido Fanconi was president, and I was a local pediatric resident. Lawson was 56 years old and had just published a note on the first patient successfully treated for congenital adrenal hyperplasia with cortisone. His textbook was not yet published, but its illustrations were on exhibition at the congress. Both the exhibit and the man were great successes. He stood in front of his exhibit each day for several hours to answer questions. It was there that I asked him to see a young baby in our hospital, who had ambiguous genitalia because of the salt losing form of congenital adrenal hyperplasia. He examined the baby and spent about three hours with me explaining his new concepts of pathogenesis and treatment of this disorder. That baby was the first patient in our hospital, and

probably the first patient in Switzerland to be treated with cortisone.

In the summer of 1951 I visited Lawson in Baltimore. That year John Crigler and Lytt Gardner were his fellows, and Claude Migeon had just arrived as a foreign fellow from France. I previously had studied Lawson's new book carefully and had a long list of questions which he answered with patience and enthusiasm. It was for me a short, pleasant and most intensive private training course.

Between 1951 and 1963 I again met him several times and especially recall a Ciba Foundation colloquium in London in 1954. I was unable to grasp the steroid pathways presented by one of the speakers and asked for the slide to copy after the session. To my surprise, Lawson wanted to do the same, and we sat together in the empty dark meeting room copying the projected slide. In his deep voice he commented bluntly how damned difficult it was for a clinician to understand the steroid specialists.

Friends and myself founded in Zurich in 1962 the European Society of Pediatric Endocrinology. Regarding Lawson Wilkins as our spiritual father, we sent him a copy of the photograph of our group with the signatures of each. Lawson was very pleased and sent me, in return, the photograph of the 1963 reunion of his former and present fellows with all their names and present situations noted in his handwriting. This was shortly before his death. Although few of us ever saw him again, he is remembered fondly and with great respect by all pediatric endocrinologists who had the pleasure to learn from him.

ANDREA PRADER, M.D.

PREFACE TO THE FOURTH EDITION

For many pediatric endocrinologists, Lawson Wilkins' text was considered the leading authoritative work in the field. Certainly, the wealth of clinical information and case studies, coupled with exhaustive presentations of the state of the art at the time, contributed greatly to our education for decades. The tremendous advances in our knowledge necessitated a new edition. In the almost thirty years since the last (third) edition of this text in 1965, immunology and the biologies (cellular and molecular) have significantly increased our understanding of the pathophysiology of endocrine disorders and have added greatly to our therapeutic armamentarium.

In the last edition, receptor physiology was unknown and "end-organ resistance" was defined as a pseudoendocrinopathy that did not respond to the administration of a hormone known to be associated with an observed clinical picture.

The routine measurement of circulating hormones was unavailable in 1965; the concept of autoimmune endocrinopathy was in its infancy; the IGF/IGF binding system was unknown, as was an understanding of autocrine systems. There were no recombinant DNA-derived hormones such as insulin, growth hormone and IGF-I, and the therapeutic use of cadaver-derived human growth hormone had only been reported seven years previously. Genetic linkages, HLA and other, and gene defects were unknown, and screening for congenital hypothyroidism or congenital adrenal hyperplasia or for insulin dependent diabetes mellitus was not yet practiced.

The difficulty in producing a single authored book as Dr. Wilkins did is enormous, considering the logarithmic growth of knowledge in pediatric endocrinology over the past 30 years, and the editors quickly abandoned the idea. Instead, we invited experts in their respective endocrine specialties to contribute to this edition. Editorial polishing and a single graphic artist helped recreate the flavor of Wilkins' original editions. The authors included many clinical descriptions taken from their practices, and it is our hope that the text will be helpful to pediatricians, pediatric endocrinologists, housestaff and students.

Finally the editors would like to quote Edward Curtis who spent decades gathering material for his monumental study of the Indians of North America:

> *In bringing to a close this result of thirty years of research the writer wishes also to record an expression of his gratitude to those other friends who offered every encouragement during the formative period of the work and who never lost faith*

in its ultimate fruition. Mere thanks seem hollow in comparison with such loyal cooperation; but great is the satisfaction the writer enjoys when he can at last say to all those whose faith has been unbounded, "It is finished."

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We also gratefully acknowledge the extended time and effort required by the authors to bring this book to its completion in a manner that we believe Lawson Wilkins would appreciate.

THE EDITORS

For myself, I gratefully acknowledge the time and effort of my colleagues at the University of Virginia, Dr. Alan D. Rogol, Dr. William L. Clarke, and Dr. James R. Kerrigan, who often freed me from other responsibilities so I could dedicate the time required to assist the other editors in editing this text, and the time and dedication of Ms. Mary Westervelt, Ms. Pamela Breeder, Ms. Juanita Bishop, Ms. Melanie Bishop, and Ms. Fotini Bezirianidis Vavelidis, executive secretary and research assistants who made editing this text a pleasure.

Of course, I wish to recognize Lawson Wilkins as the person who influenced me most in my professional life as teacher, scientist, preceptor, and friend. Dr. Lee Forrest Hill (1895-1980) who was my pediatric teacher, preceptor and friend, and who introduced me to Lawson, receives almost equal recognition. He taught me to think like an investigator, to always treat the patient and not just the disease, and to be exhilarated by teaching others. To the fellows who trained under my supervision at Johns Hopkins and the University of Virginia, I also extend my gratitude for having taught me, directly and indirectly, much more than I taught them. Finally, I recognize and appreciate the encouragement and support which my beloved wife, who is now deceased, gave to me over 42 years of married life. Hopefully she is aware that this book finally was completed.

ROBERT M. BLIZZARD

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MICHAEL S. KAPPY

I would like to acknowledge all those who contributed to my development as a person, a physician, a scientist and a teacher, particularly:

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Dr. Sotirios Briskas, pediatrician, whose eulogy of research was a major influence;

Dr. Lawson Wilkins, the first pediatric endocrinologist, who was a teacher, father figure, and a friend;

Dr. Leo T. Samuels, steroid biochemist, who helped me recognize the importance of basic sciences in medical research;

Dr. Barbara R. Migeon, my wife, who introduced me to the role of genetics in biomedical research;

and my children, whose love has been and remains most precious.

I am also most grateful to my colleagues and to the pediatric endocrine fellows who trained at Johns Hopkins for their contribution to my accomplishments and for their kind support. The dedicated secretarial help of Mrs. Doris Barrington and Kathy Whitehurst is gratefully acknowledged.

CLAUDE J. MIGEON

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Chapter 1

ORGANIZATION AND FUNCTION OF THE ENDOCRINE SYSTEM

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I. INTRODUCTION

Endocrinology is the science of cellular communication: it is the discipline that explores the manner in which one cell influences the function of another cell and, at times, itself. The essential components of a (inter)cellular communication system are (1) a secretory cell, which produces (2) a transmitter or messenger molecule which travels (3) in a fluid compartment to (4) a target cell (LeRoith et al, 1986). There are four major systems of intercellular communication: nervous, neuroendocrine, endocrine and immune (Bateman et al, 1989). These are highly integrated and significantly interrelated since each influences and controls certain functions of its sister systems and is, in turn, regulated and directed by the system it has affected. The intimate functional relationship between the nervous, immunologic and (neuro)endocrine systems also reflects their close evolutionary origins.

The mammalian multicellular endocrine system has evolved from plants and unicellular organisms (LeRoith et al, 1986; Roth et al, 1982; Roth et al, 1983). Thus, somatostatin-like material is present in flowering plants and bacilli, a growth hormone releasing factor-like agent is found in *Vibrio cholerae* (Rappaport and Grant, 1974), and a gonadotropin releasing hormone homologous to the vertebrate molecule is present in yeast. Insulin-like material and insulin receptors are detectable in insects and protozoa, and peptides similar to adrenocorticotropin, beta endorphin, human chorionic gonadotropin, calcitonin, thyrotropin and relaxin have been identified in unicellular organisms and in plants. Glucocorticoids and sex steroid hormones are synthesized by yeast. It is likely that such molecules function as intracellular messengers in microorganisms, and that their communicative function has been preserved and expanded as complex multicellular and multisystem organisms evolved into their present forms.

The classical concept of the blood-borne (endocrine) hormone is only one manner of intercellular communication (Figure 1.1). *Endocrine*

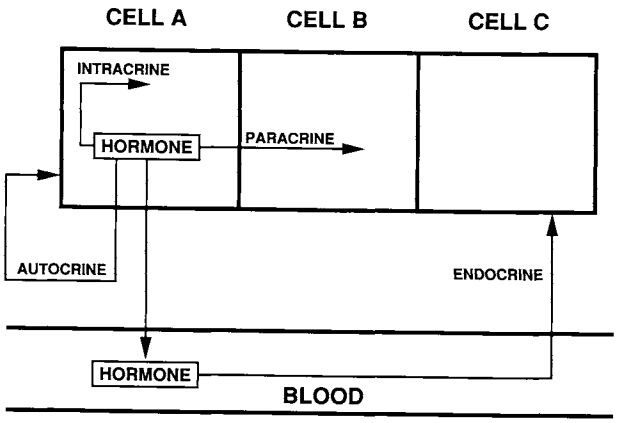

FIGURE 1.1 — Mechanisms of cellular communication: Endocrine, paracrine, autocrine and "intracrine."

communication connotes the secretion of a product by a gland into the circulation for action at a distant target cell. However, there is also *paracrine* communication by which a cell releases a messenger molecule which traverses the interstitial space to influence the action of an adjacent cell and *autocrine* communication in which the messenger affects the function of the cell which releases it. The concept of an *intracrine* form of intracellular communication in which a "hormone" is synthesized and acts within a cell without leaving and reentering has been postulated, bringing these concepts full cycle, analogous to the functioning of a unicellular organism (O'Malley, 1989). Similarly, the concept of a chemically identifiable hormone has changed as we have learned that the same molecule may serve as a hormone when secreted into the blood stream, as a neurotransmitter or neuromodulator when released from an axon in the central (CNS) or peripheral nervous system, or as a paracrine or autocrine effector when secreted elsewhere. Thus, many of the intestinal paracrine messengers regulating gut function act within the CNS as neurotransmitters, while classical neurotransmitters such as dopamine, norepinephrine and epinephrine also serve as hormones when synthesized and secreted by the adrenal medulla. The ubiquity of messenger molecules is illustrated by the ability of individual hypothalamic neuropeptides such as somatostatin to serve endocrine, para-

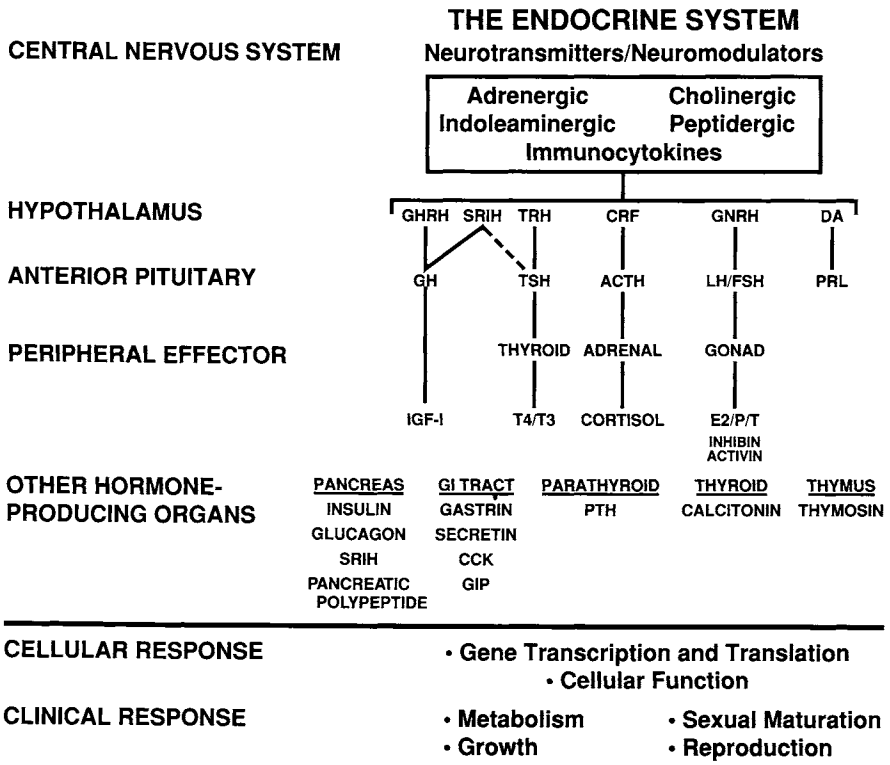

FIGURE 1.2 — The endocrine system: Regulation and response.

crine and neurotransmitter function in the CNS and in peripheral organs.

The complexity of the intercellular communication system expands many fold if one considers not only the transmitting messenger substances which can be modified, but their serum carrier proteins, membranous, cytoplasmic and nuclear receptors and the cascade of intracytoplasmic and intranuclear events that occur before a hormone mediated cellular action is executed.

An outline of the components of the endocrine system is presented in Figure 1.2 and Table 1.1.

A. Cellular Communication

1. Endocrine

The "classically" defined endocrine glands are the anterior and posterior pituitary, thyroid, parathyroid, adrenal cortex, adrenal medulla, ovary, testis, and pancreas. To this list must be added the brain, thymus (thymopoietin), gastrointestinal tract (gastrin, gut-glucagon, and many others), kidney (erythropoietin), and possibly other structures which secrete substances into the circulation for action at distant sites. The protein/peptide and steroid/thyroid/vitamin D hormones circulate either free or bound to carrier proteins (*vide infra*) until they encounter the target cell. At the target cell, protein and peptide hormones bind primarily to receptors located on the outer plasma membrane while steroid, thyroid and vitamin D hormones bind to cytoplasmic and/or nuclear receptors. Ultimately hormones affect cellular action by influencing ion transport, enzyme function (protein kinases) and gene function, transcription and/or translation, either indirectly through a series of intramembranous and intracytoplasmic reactions or by binding of the hormone-receptor complex directly to DNA control (promoter) regions on the gene.

2. Paracrine

Paracrine communication involves the diffusion of cell products from one cell to an adjacent target cell through the extracellular space

Table 1.1 — Protein Hormones of the Endocrine System

Hormone	*Amino Acids*	*Precursor*	*Gene Site*	
			Hormone	*Receptor*
Hypothalamic neurohormones				
TRH	3	242		
GnRH	10	91	8p21-q11.2	
CRH	41	196	8q13	
GHRH	40/44	10B	20	
SRIH	14/28	116	3q28	
Neurohypophyseal				
ADH	9		20	
Oxytocin	9		20	
Anterior pituitary				
TSHα (LHα, HCGα, FSHα)	96	120/92	6q12-21	
TSHβ	110	137/117	1p22	22q11-13
LHβ	115	121	19p13.37	
FSHβ	115		11p13	
ACTH	39	239	2p25	
β-LPH	91			
β-End	31			
GH	191/176	217	17q22-24	5p12-13.1
PRL	199		6p22.2-q21.3	
Pancreatic Islet				
Insulin	51	110/86	11p15.5	
Glucagon	29	180/160	2q36-37	
PP	36	95/69		
Thyroid				
Calcitonin	32		11p15.4	
(CGRP)	37			
Parathyroid				
PTH	84	115/90	11p15	
(PTH-like)			12p11.3-12.1	
Atrial				
ANF	28	152/126	1p36.2	
Gonadal				
Inhibin-α	134	366	2q	
Inhibin-βA	116	426	7	
Inhibin-βB	115	407	2p	
MDIF	536	560/544	19p	
Gastrointestinal				
Gastrin	17/34	101		
CCK	33	115/95		
Secretin	28			
VIP	28		6q26-27	
PHI	27			
GIP	42	153		
Bombesin	14			
GRP	27	148/125	18q21	
Motilin	22			
Neurotensin	13			
Growth Factors				
IGF-I	70		12q22-24.1	15q25-26
		IA 153		
		IB 195		
IGF-II	67	180/156	11p15.5	6q25-27
EGF	53	1217	4q25-27	7p11-13
TGF-α	50	160	4p11-13	
TGF-β1	112	390	19q13.1-13.3	
TGF-β2	112	412	1q41	
TGF-β3	112	412	14q24	
PDGFα	110	211	7p22-q21	5q31-32
β	109		22q12.3-qter	
FGFα	140		4	
β	146		5	
NGFα	232			
β	118	327	1p22.1	
γ	232			

(Sporn and Todara, 1980). Examples of such intercellular communication occur within the pancreatic islets and the gonads. In the islets of Langerhans the A (glucagon), B (insulin), D (somatostatin) and F (pancreatic polypeptide) cells influence the secretion of hormones from adjacent cells. Somatostatin inhibits glucagon and insulin release, glucagon stimulates insulin secretion, and insulin enhances glucagon secretion. However, within the perfused rat pancreatic islet the order of cellular microperfusion is B→ A→ D cell, so that the stimulatory and inhibitory effect of the pancreatic hormones may be both direct (paracrine) and blood borne (endocrine) (Samols et al, 1988). In the testis insulin-like growth factor-I (IGF-I) secreted by Sertoli cells increases binding of luteinizing hormone (LH) to Leydig cells and enhances the effect of LH upon steroidogenesis (Saez, 1989). Testosterone and peptides derived from proopiomelanocortin secreted by Leydig cells have paracrine regulatory effects on Sertoli cell function, and this cell in turn affects Leydig cell number, morphology and activity. Inhibin, a peptide product of the testicular Sertoli and ovarian granulosa cells, inhibits pituitary secretion of follicle stimulating hormone. It also blocks the stimulatory effect of this gonadotropin on aromatase activity of the granulosa cell. Inhibin is a dimer of α and β subunits. There are two forms (A and B) of the β subunit of inhibin. Transforming growth factor is structurally similar to the β subunit of inhibin, and antagonizes the effect of inhibin on granulosa cell function (Saez, 1989). Activins and Mullerian duct inhibiting factor are also related structurally to inhibin. Insulin-like growth factors are secreted by mesenchymal cells in many tissues; they can bind to adjacent cells and stimulate DNA synthesis by those cells. Indeed, the paracrine (and autocrine) effects of the IGFs may be far more important in regulating cell growth and function than are their endocrine effects. Thus, there are complex interrelationships among a number of intragonadal effector molecules and circulating hormones that coordinate gonadal function.

3. Autocrine

In autocrine communication a cell secretes a factor for which it has receptors and to which it displays a biological response. Many of the growth factors (*vide infra*) appear to function in this manner, particularly the transforming growth factors which may be implicated in neoplastic proliferation (Sporn and Todara, 1980). That the mechanisms of cellular communication are not mutually exclusive is exemplified by IGF-I, for it acts as an endocrine effector when secreted by the liver into the systemic circulation, as a paracrine transmitter in its effects on testicular Sertoli and ovarian granulosa cell function and probably in both paracrine and autocrine manners to stimulate growth of fibroblasts.

4. Exocrine

Although the exocrine and endocrine systems are considered to be separate, they share many cytological and functional similarities. Intercellular messenger molecules such as prolactin, triiodothyronine and several growth factors may be found in exocrine secretions such as breast milk, and insulin and somatostatin are present in the secretion of intestinal cells although the functions of these agents are unknown.

II. MECHANISMS OF CELLULAR COMMUNICATION

A. Protein/Peptide Hormones

1. Biosynthesis

Protein/peptide hormones are derived from larger precursor molecules which may yield two or more products after transcription, translation and processing (Habner, 1981). The synthesis of protein/peptide hormones may be divided into nuclear and cytoplasmic phases (Figure 1.3a, 1.3b). Protein hormone biosynthesis begins with the transcription of DNA to RNA and proceeds through translation of RNA to protein precursors (prepro- and prohormones) and to the "maturing" of these precursors into the circulating effector form. The structural genes for proteins are flanked by one of several promoter (recognition) sequences on the 5' end that bind