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SPECIAL ARTICLE

A History of Pediatric Specialties

In the twelfth article in this series, Dr. Fisher provides a colorful description of the history of pediatric endocrinology and the central role played by Dr. Lawson Wilkins and other major leaders in the early development of this specialty in North America. Dr. Fisher describes the advances in this field in diagnosis, screening, prevention and treatment of endocrine disorders as well as advances in our understanding of the biology of endocrine problems in childhood. The care and study of children with diabetes was incorporated into pediatric endocrinology at a later stage and now is a central component of this specialty. This review also describes clearly the creation of societies, journals and education programs that have been central to the development of pediatric endocrinology as a major specialty of Pediatrics.

A Short History of Pediatric Endocrinology in North America

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ABSTRACT

Pediatric endocrinology evolved as a subspecialty from the era of biochemical and metabolic clinical investigation led by John Howland, Edwards Park, and James Gamble at Johns Hopkins; Allan Butler at Boston University and Harvard University; Daniel Darrow at Yale University; and Irving McQuarrie at the University of Rochester and the University of Minnesota during the early 20th century. The father of the new subspecialty was Lawson Wilkins, a private pediatric practitioner in Baltimore, Maryland, who was invited by Dr. Edwards Park to establish an endocrine clinic at the Harriet Lane Home at Johns Hopkins in 1935. Dr. Wilkins managed his practice and the clinic until 1946, when, at the age of 52, he accepted a full-time position at the University. Dr. Nathan Talbot was invited to develop a pediatric endocrine clinic at Massachusetts General Hospital by Allan Butler in 1942. These units and their associated subspecialty training programs during the 1950s and 1960s provided the large majority of the second-generation pediatric endocrinologists who went on to establish endocrine subspecialty programs in university medical centers in North America as well as Europe and South America. Diabetes as a clinical pediatric discipline evolved in parallel from the early clinics of Elliott Joslin and Priscilla White in Boston, M.C. Hardin and Robert Jackson at the University of Iowa, George Guest at the University of Cincinnati Children's Hospital, and Alex Hartman at the St. Louis Children's Hospital. The Lawson Wilkins Pediatric Endocrine Society was founded in 1971, and the Council on Diabetes and Youth was established within the American Diabetes Association in 1980. Medical and economic factors led to increasing integration of pediatric diabetes and general endocrine care and training, and diabetes care now is a major activity within the subspecialty of pediatric endocrinology. The growth of pediatric endocrinology in North America has paralleled the growth of academic medicine during the past half-century. In 2002, there were 72 training programs in North America: 65 in the United States and seven in Canada. The endocrinology sub-board of the American Board of Pediatrics was established in 1978 to certify training and competence in endocrinology, including diabetes. By 2002, the board had certified 927 pediatric endocrinologists. Pediatric endocrine subspecialists during the past half-century have contributed major advances in our understanding of the ontogeny of endocrine systems and the diagnosis and treatment of fetal-perinatal endocrine disorders; newborn screening for endocrine and metabolic disorders; the physiology and therapies for disorders of sexual differentiation and pubertal maturation; the development of anthropometric standards for childhood growth and development; the characterization and physiology of hormone systems, including receptors and hormone actions; the molecular genetics of a number of congenital endocrine disorders and heritable endocrine diseases; development of pediatric endocrine diagnostics and reference standards; the pathophysiology and management of autoimmune endocrine disease; and development of a growing armamentarium of therapeutic agents for treatment of endocrine and metabolic diseases. **(*Pediatr Res* 55: 716–726, 2004)**

Abbreviations

APS, American Pediatric Society
CAH, congenital adrenal hyperplasia
ESPE, European Society for Pediatric Endocrinology
JCE, The Journal of Clinical Endocrinology
LWPES, Lawson Wilkins Pediatric Endocrine Society
MGH, Massachusetts General Hospital

The history of endocrinology dates back to the 14th century, when surgery, burnt sponge, and seaweed were used for the treatment of goiter (1). The modern concepts of ductless glands and internal secretions developed during the latter half of the 19th century, when in 1889 Brown Sequard, a French neurologist and physiologist, described the use of animal testicular extracts for men with senile debility (2). The efficacy of this approach was not substantiated, but the concepts were established with the report by George Murray in 1891 of successful

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treatment of myxedematous patients with thyroid extract and with William Osler's report in 1896 of the treatment of Addison disease with adrenal extract (3, 4). Most of the endocrine hormones were isolated and characterized as the science and clinical approach to the glands of internal secretion evolved during the early 20th century (4–21) (Table 1).

A few physicians who were interested in endocrinology in the United States convened at the 1916 meeting of the American Medical Association to formalize an association for endocrinology; the Association for the Study of Internal Secretions was formally incorporated in Delaware on January 13, 1918 (22). Meetings have been held yearly since 1916, except for 1943 and 1945 during World War II. Publication of the society journal, *Endocrinology*, began in 1917. Publication of a second clinical journal, *The Journal of Clinical Endocrinology* (JCE), began in 1941. In 1952, the society was renamed The Endocrine Society, and the JCE became *The Journal of Clinical Endocrinology and Metabolism*.

Pediatricians were not involved with the association during the formative years. The major pediatric association was the American Pediatric Society (APS), formed in 1888 (23, 24). The growth of pediatric academic centers and the increasing emphasis on clinical investigation led to the formation of the Eastern Society for Pediatric Research in 1929. This organization evolved into the Society for Pediatric Research in 1932 and provided a forum for the young investigator (23). Investigative pediatrics during the early part of the 20th century was largely focused on infectious diseases, nutritional disorders, and preventive pediatrics, but the availability of sophisticated biochemical methods between World Wars I and II led to major advances in understanding of salt and water metabolism, acid base balance, and carbohydrate and calcium metabolism associated with important advances in therapy of dehydration, hypoglycemia, diabetes, and rickets. Major contributors to these advances included John Howland and his associates William Marriott, Edwards Park, and James Gamble at the Harriet Lane Home; Allan Butler at Boston University and Harvard University; Daniel Darrow at Yale University; and Irvine McQuarrie at the University of Rochester and the University of Minnesota (23, 24). The Howland Award of the APS was established in 1952, and Drs. Park (1952), Gamble (1955), McQuarrie (1958), Darrow (1959), and Butler (1969) were early recipients, in large part for these contributions (24).

Table 1. *Isolation and characterization of hormones*

1900	Purification of epinephrine, J. Takamine, T.B. Aldrich
1915	Crystallization of thyroxin, E.C. Kendall
1923	Purification of insulin, F. Banting, C. Best, J.B. Collip
1925	Purification of PTH, J.B. Collip
1927	Synthesis of thyroxine, C.R. Harrington
1928	Isolation of posterior pituitary hormones, O. Kamm *et al.*
1923–1934	Isolation and characterization of ovarian and testicular hormones, E.A. Allen, W.M. Allen, S. Aschhein, A.F.J. Butenandt, G.W. Corner, E.A. Doisy, G.F. Marrian, L. Ruzicka, O.P. Wintersteiner
1927–1934	Isolation and characterization of the pituitary and chorionic gonadotropin, S. Aschheim, H.M. Evans, H.L. Fevold, F.L. Hisaw, E. Laquerer, G.F. Marrian, B. Zondek
1933	Isolation of pituitary prolactin, O. Riddle
1936–1938	Isolation and characterization of adrenal cortical hormones, T. Reichstein, J. von Euw, E.C. Kendall, A. Grollman
1944	Isolation of growth hormone, C.H. Li, H.M. Evans
1953–1954	The synthesis of oxytocin and vasopressin, V. du Vigneaud *et al.*

See references 1–18.

Pediatric endocrinology evolved as a subspecialty from the earlier era of biochemical and metabolic clinical investigation led by Howland, Park, Gamble, McQuarrie, Darrow, and Butler, facilitated by the evolution of subspecialty-focused academic pediatric centers, funding for research by government and private sources, and development of subspecialty-oriented national medical professional societies and journals promoting basic and clinical research. Basic and clinical endocrinology were further stimulated with the development of RIA by Berson and Yalow in 1956 (25). Highly sensitive and specific RIAs for the measurement of hormones in tissues and biologic fluids transformed endocrine research and practice. A second transformational stimulus was the development of PCR technology by Kary Mullis in 1983 while working at Cetus Corporation (26). PCR facilitated extension of endocrine research to the molecular genetic level. Drs. Yalow (1977) and Mullis (1993) were recipients of Nobel Prizes for this work; Dr. Berson died in 1972, before the Nobel committee awarded the prize.

These background events and the training of an increasing number of academic pediatric endocrine subspecialists have fueled major advances in our understanding of fetal, neonatal, childhood, and adolescent endocrine systems physiology and led to our current concepts and approaches to recognition, nosology, and therapy of pediatric endocrine and metabolic disorders. Important advances have included development of the ontogeny of endocrine systems and the diagnosis and treatment of fetal-perinatal endocrine disorders; the physiology and therapies for disorders of sexual differentiation and pubertal maturation; newborn screening for endocrine and metabolic diseases; the development of anthropometric standards for childhood growth and development; characterization and physiology of hormone systems, including receptors and hormone actions; characterization of the molecular genetics of a number of congenital endocrine disorders and heritable endocrine diseases; development of pediatric endocrine diagnostics and reference standards; the pathophysiology and management of autoimmune endocrine disease; and the development of a growing armamentarium of therapeutic agents for treatment of endocrine and metabolic diseases.

FIRST-GENERATION PEDIATRIC ENDOCRINE PROGRAMS

Harriet Lane Home, Johns Hopkins. The father of the new pediatric endocrinology subspecialty was a private pediatric practitioner in Baltimore who had no formal clinical investigative training. Lawson Wilkins was born in 1894, the son of George L. Wilkins, a physician, and Harriet Schreiner Wilkins. His mother died in 1900, and his father remarried in 1905. Lawson graduated from the Johns Hopkins Medical School in 1918 while still abroad serving as an orderly in the Johns

Hopkins Hospital Unit in France during World War I. He completed an internship in internal medicine in New Haven, during which time he decided to go into pediatrics because he thought it was a branch of medicine then leading in the biochemical and metabolic approach (27). He accepted an internship at the Harriet Lane Home under direction of John Howland, and influenced by his father, a general practitioner in Baltimore, he began the private practice of pediatrics in 1922 and spent 25 y, until 1946, as a practicing pediatrician. He married Lucile Mahoulin in 1926 and fathered two children, George Lawson Wilkins II and Elizabeth.

As a house officer, Wilkins' demonstrated his organized approach to patient care. Impressed by the poor care of children with congenital syphilis and their lack of follow-up care, he started a dedicated clinic, organized the care, and obtained a special social worker to develop a follow-up system. As a result, Dr. Howland authorized the Clinic for Congenital Syphilis as the only special clinic in existence until 1927 (27). Wilkins's investigative approach was kindled by the observed emphasis on the laboratory during his house staff training, and very soon after entering private practice, he began his scientific studies. Because he had no laboratory training, he developed collaborations to provide laboratory support. His first paper with Benjamin Kramer in 1923 was a report on the potassium content of human serum. This was followed in 1927 by a collaboration with Emmett Holt, Orr, and Boone on studies of calcium and phosphorus metabolism in rickets. This led to a collaboration with biochemist Charles Bills, a postgraduate student in the School of Hygiene at Johns Hopkins, on a project to cure rickets with intramuscular injections of cod liver oil (27). He also conducted clinical studies, including during 1924–1927 a study of parenteral and oral vaccine therapy of dysentery. There were also therapeutic papers on immunization against diphtheria, scarlet fever, whooping cough, and measles and clinical papers on Hirschsprung's disease, lead poisoning, and meningitis. Dr. Wilkins had maintained an association with Edward Bridge in the epilepsy clinic at Johns Hopkins for some years and in 1937 published a triad of papers: On Epilepsy in Childhood: I. A Statistical Study of Clinical Types; II. The Incidence of Remissions; and III. Results with the Ketogenic Diet (27).

In 1935, Dr. Edwards Park, who replaced Dr. Howland as head of pediatrics at Johns Hopkins in 1927, offered Wilkins the directorship of the epilepsy clinic after Dr. Bridge moved to the University of Buffalo. Wilkins declined, saying that he would prefer to work in some less depressing field (27). Dr. Park believed that important advances were about to be made in endocrinology, and anxious to place Wilkins at the head of an important section of the department, he offered him the directorship of the endocrine clinic (27). As Wilkins stated, "It was Dr. Edwards Park who shepherded me back to the academic fold after 25 y in private practice—in 1935, when he asked me to establish a pediatric endocrine clinic at the Harriet Lane Home, I knew nothing about the subject and replied, 'Do you wish to make me a Charlatan?' It was just my sheer good luck and opportunism that new tools for studying endocrine disorders had been forged over the preceding years and that many endocrine interrelationships had recently been elucidated by animal experimentation" (28).

For 11 y, Wilkins continued his practice and added research and teaching in pediatric endocrinology. He had a grant from the Commonwealth Fund to support his scientific work, but there was no salary included and he received no salary from the Johns Hopkins University (27). Dr. Park commented, "At first he concentrated on the study of children suffering from thyroid deficiency, where he knew he was on solid ground, and he used to take me into his laboratory to show me the exquisite graphic studies of his patients. The graphs, he told me, he worked out between midnite and 2AM. I can recall my astonishment that he had the energy to do this after his daily marathon" (27).

In 1938, Wilkins recruited Dr. Walter Fleischmann, a Viennese physiologist, to collaborate on studies of creatine and cholesterol metabolism in children with congenital hypothyroidism. Publications of results of these studies appeared in the first issue of the Endocrine Society's JCE in 1941 (29–32). Wilkins also developed an early interest in congenital adrenal hyperplasia (CAH), and in 1940 with Dr. Fleischmann and John Eager Howard, he published in the journal *Endocrinology* a case report entitled "Macrogenitosomia Praecox Associated with Hyperplasia of the Androgenic Tissue of the Adrenal and Death from Adrenocortical Insufficiency" (33). The patient, a boy 3.5 years of age, had been referred from Hollywood, Florida. He presented with the height and weight of a 6- to 8-y-old, precocious development of male sex organs, pigmentation of the skin and gums, hyponatremia, salt craving, and mental retardation. He died suddenly on hospital day 6. Autopsy findings included hyperplasia of the prenatal cells of the adrenal cortex with hypoplasia of normal cortical cells and bilateral tumor-like masses of aberrant adrenal cells in the testes. Assay for androgens using the castrate rat colchicine assay of Fleischman showed adult male values. The authors stated, "Our case is the first of which at autopsy a diffuse bilateral hyperplasia of the adrenals has been found in the male causing a condition analogous to pseudohermaphroditism in the female." This was the first report of CAH in a male child. The first case in a female child had been reported by Luigi De Crecchio from the University of Naples in 1865 (34). Knowing that the secretion of adrenal androgens was controlled by ACTH, Wilkins made several unsuccessful attempts to suppress ACTH in children with CAH by administering weak androgens. However, when synthetic cortisol became available, working with Drs. Roger Lewis and Robert Klein, his early clinical associates, he was able to show that adrenal androgen production in girls with CAH could be suppressed by chronic cortisol therapy (35).

Dr. Wilkins and Walter Fleischman published a paper in 1944 in the JCE describing the pathology and associated clinical symptoms of ovarian agenesis in three patients (36). The ovarian agenesis was associated with increased excretion of urinary gonadotropins measured by the uterine weight bioassay in immature rats, indicating normal pituitary function and suggesting a primary ovarian developmental defect. The authors reviewed these and 27 other patient reports in six earlier publications relating the clinical features to the existent theories of sexual differentiation. They concluded that "ovarian

agenesis is due to a defect of germ plasma causing failure of primordial germ cells to develop or persist in the genital ridge." This early interest in sexual differentiation led to clinical studies by Dr. Wilkins and his early trainees developing our current understanding of the pathophysiology of ovarian agenesis based on the discovery of the "Barr body" and the fetal castration studies in rabbits conducted by Dr. Alfred Jost (37–39).

Data that were developed in the endocrine clinic between 1935 and the late 1940s were collated in the form of photographs and drawings exemplifying disease processes for presentation and teaching at meetings of the American Academy of Pediatrics and for a poster session at the First International Congress of Pediatrics in Zurich in 1950. This was done in collaboration with Drs. W.C. Deamer of the University of California, W.A. Reilly of the University of Arkansas, H.P.G. Seckel of The University of Chicago, and Richard Wagner of Tufts University in Boston (40). This extensive display, providing examples of each of the commonly diagnosed pediatric endocrine disorders with diagnostic criteria and pathophysiologic information, was collated and developed as the first edition of his classic textbook *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence* in 1950 (40).

In 1946, Dr. Francis Schwentker, who succeeded Dr. Parks as head of pediatrics at Johns Hopkins, offered Dr. Wilkins a full-time position in the department. Wilkins was then age 52 and despondent over the death of his only son in an automobile accident in 1944, and he decided to vacate his private practice for a full-time academic career even though it meant a considerable reduction in income (27). The full-time position had no fixed duties outside his clinic, and he was free to pursue those things he most liked to do: read, study, enter the laboratory, and think (27). In 1942, he had been promoted from assistant to associate professor and in 1957 became full professor. Lucile, his wife of 33 y, died in 1959, and Wilkins decided to retire in 1960. He met and married Catrina Anderson Francis and enjoyed the last 21/2 years before he died of a heart attack in 1963. Robert Blizzard, then heading pediatric endocrinology at Ohio State University, and Claude Migeon replaced him as co-directors of the Hopkins pediatric endocrine division.

Wilkins's many honors included the Borden Award of the American Academy of Pediatrics (1953), the Francis Amory Prize of the American Academy of Arts and Sciences (1955), the Modern Medicine Award (1955), the Koch Award of the Endocrine Society (1961), and the Howland Award of the APS (1963). He served as president of the Endocrine Society (1955–1956) and president of the APS (1961–1962) and was an Honorary Member of the Royal Society of Medicine in England and several other foreign societies. Figure 1 is a photograph of Dr. Wilkins and his wife Lucille taken in 1954 at a dinner honoring Dr. Wilkins by a group of his early trainees.

Massachusetts General Hospital, Boston. In 1942, a specialized pediatric endocrine clinic was established at the Massachusetts General Hospital (MGH) under direction of Dr. Nathan Talbot. This clinic evolved from the view of Dr. Fuller Albright in the adult endocrine division at MGH that there was a growing opportunity in pediatric endocrinology (Dr. John Crawford, personal communication, April 2001). In the late 1930s, Albright began a collaboration with Allan Butler, then a protégé of James Gamble at the Children's Hospital, studying vitamin D–resistant rickets, pseudohypoparathyroidism, and

Figure 1. Dr. Wilkins and his wife Lucille at a 1964 dinner honoring Dr. Wilkins by a group of his early trainees. From left to right: Lytt Gardner, Walter Eberlein, John Crigler and his wife, Claude Migeon, Lawson Wilkins, Judson Van Wyk, Mrs. Lucille Wilkins, Alfred Bongiovanni, Melvin Grumbach, Mrs. Robert Klein, Thomas Shepard, and Robert Klein. Photograph courtesy of Robert M. Blizzard.

congenital adrenal hyperplasia. As a result of the collaboration, Albright began a campaign to bring Butler to MGH, and in 1942, Butler was brought to head pediatrics at what was at that time termed the Children's Medical Department. Butler brought with him Nathan Talbot to lead the Adolescent Endocrine Clinic, explanted from Children's Hospital with the agreement that this specialized endocrine unit was sufficient for the needs of the area and would not be replicated (Dr. John Crawford, personal communication, April 2001).

The early endocrine associates of Dr. Talbot at the MGH included Edna Sobel, John Crawford, and Janet McArthur. Dr. Talbot, like Dr. Wilkins, was interested in most areas of pediatric endocrinology but focused with his first associates on the use of testosterone to accelerate growth of prepubertal children and studies of steroid hormone metabolism in children. The second textbook of pediatric endocrinology, *Functional Endocrinology from Birth Through Adolescence*, was published by Dr. Talbot and his associates in 1952 (41). This text reflected the more metabolic orientation of James Gamble and Walter Cannon, whereas Wilkins's textbook had a more hormonal focus.

SECOND GENERATION OF PEDIATRIC ENDOCRINOLOGISTS

These pediatric endocrine units and their associated subspecialty training programs during the 1950s and 1960s provided the large majority of the second generation of pediatric endocrinologists who went on to establish subspecialty programs in university medical centers in North America, as well as Europe and South America. The trainees in the Wilkins program between 1948 and 1960 numbered 24 United States associates and 17 visiting fellows from Argentina, Canada, Denmark, England, France, Greece, Israel, Lebanon, Mexico, Switzerland, and Yugoslavia. Second-generation trainees in Boston during the same period numbered some 30 individuals, including several fellows from Canada, England, France, Iceland, India, Iran, Israel, Mexico, Norway, Switzerland, and Turkey.

Wilkins's associates who went on to establish pediatric endocrine training programs in the United States during the 1950s are listed in Table 2. Visiting foreign fellows who returned home to develop programs during the 1950s were Henning Andersen from Copenhagen, Denmark; Constantine Papadatos from Athens, Greece; and Jean Bertrand from Lyon, France. Trainees in Dr. Talbot's program during the 1940s and 1950s are listed in Table 3.

Several second-generation pediatric endocrine programs were established during the 1950s by pediatric academic faculty with nonformal training backgrounds. Dr. Vincent Kelley, a biochemist and professor of pediatrics at the University of Utah, developed an endocrine section that he directed from approximately 1950 through 1958, when he was recruited from Utah by Dr. Robert Aldrich to develop a formal endocrinology program at the University of Washington in Seattle. Dr. Thomas Shepard, who had moved to Seattle from Johns Hopkins in 1955, co-directed the program from 1959 to 1961, when he moved to Florida. Dr. Kelley headed this program until his retirement in 1970. He published a three-volume textbook in 1974: *Metabolic, Endocrine and Genetic Disorders in Children* (Table 4).

Dr. Donald E. Pickering was recruited to the University of California in San Francisco in 1950 as an assistant professor subspecializing in endocrinology after training with Dr. Robert Cooke and work with Dr. Gertrude Van Wagonen at Yale University. Dr. Delbert Fisher was a research associate with Dr. Pickering as a student and pediatric house officer studying a primate model for congenital hypothyroidism. Dr. Pickering was recruited to the University of Oregon to develop a pediatric endocrine program in 1956. He moved his monkey colony to Oregon and developed and initially headed the National Institutes of Health Primate Center in Beaverton. Dr. Fisher returned from military service to complete his endocrine fellowship at the University of Oregon, after which in 1960 he was recruited to head pediatric endocrinology at the University of Arkansas Medical School. He moved back to California in 1968 to develop the pediatric endocrine division at the Harbor-UCLA Medical Center. Dr. William Odell was recruited from the National Institutes of Health to head adult endocrinology, and the combined adult and pediatric endocrine divisions at Harbor-UCLA pioneered development and introduction of endocrine hormone RIAs in collaboration with the Nichols Institute. With Dr. Rosalind Yalow, they hosted the first Endocrine Society Radioimmunoassay Workshop in 1971 (42).

Dr. Robert Ulstrom was recruited by Dr. John Anderson to develop a formal pediatric endocrine division at the University of Minnesota in 1956. He had trained with Dr. Irvine McQuar-

Table 2. *Lawson Wilkins program associates who established United States pediatric endocrine training programs during the 1950s*

Robert Klein	University of Pittsburgh	1950
Lytt I. Gardner	SUNY, Syracuse, NY	1953
John F. Crigler, Jr.	Boston Children's Hospital, Boston, MA	1955
Alfred M. Bongiovanni	Children's Hospital of Philadelphia, PA	1954
George W. Clayton	Texas Children's Hospital, Baylor University	1954
Melvin M. Grumbach*	Babies Hospital, Columbia University, New York, NY	1955
Judson J. Van Wyk	University of North Carolina, Chapel Hill, NC	1955
Thomas Shepard III	University of Washington, Seattle, WA	1955
Robert M. Blizzard	Ohio State University, Columbus, OH	1957
David Mosier	UCLA School of Medicine	1957
Gerald Holman	University of Kansas	1959

* Dr. Grumbach moved to the University of California San Francisco in 1966.

Table 3. *Graduates from the Massachusetts General Hospital Pediatric Endocrine Program during the 1940s and 1950s*

Edna Sobel	Boris Senior
Charles Lowe	Margaret MacGillivray
John Crawford	Juan Sotos
Lytt Gardner	Lester Soyka
Leslie Corsa	Mary Arnold
Walter Eberlein	Donald Hillman
Stanley Ulick	Gerald Kerrigan
Dorothy Villee	William Bergstrom
Edgar Schoen	Lewis Holmes
Charles Reed	Marcus Vest*
	Zvi Laron*

* Dr. Vest was a foreign fellow from Switzerland; Dr. Laron was from Israel.

Table 4. *Pediatric endocrine textbooks*

Wilkins L	*The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, Charles C Thomas, Springfield * 4th Ed edited by M. Kappy, R. Blizzard, C. Migeon	1st Ed 1950 2nd Ed 1957 3rd Ed 1965 4th Ed 1994
Talbot NB, Sobel EH, McArthur JW, Crawford JD	*Functional Endocrinology from Birth through Adolescence*, Harvard University Press, Cambridge	Pub 1952
Hubble D	*Pediatric Endocrinology* Blackwell Scientific, Oxford Pub 1969	1st Ed 1969 2nd Ed 1975
Gardner LI	*Endocrine and Genetic Diseases of Childhood*, WB Saunders, Philadelphia	1st Ed 1969 2nd Ed 1975
Kelley VC	*Metabolic, Endocrine, and Genetic Disorders of Children*, Harper and Row, New York	Pub 1974
Bacon GE, Spencer ML, Hopwood NJ, Kelch RP	*A Practical Approach to Pediatric Endocrinology*, Year Book Medical Publishers, Chicago	1st Ed 1975 2nd Ed 1982
Brook CGD	*Clinical Paediatric Endocrinology*, Blackwell Scientific, Oxford, Cambridge	1st Ed 1981 2nd Ed 1989 3rd Ed 1995 4th Ed 2001
Job JC, Pierson M	*Pediatric Endocrinology*, John Wiley, New York	Pub 1981
Collu R, Ducharme JR, Guyda HJ	*Pediatric Endocrinology*, Raven Press, New York	1st Ed 1981 2nd Ed 1989
Kaplan S	*Clinical Pediatric Endocrinology*, WB Saunders, Philadelphia	1st Ed 1982 2nd Ed 1990
Bertrand J, Rappaport R, Sizonenko PC	*Pediatric Endocrinology*, Williams & Wilkins, Baltimore	1st Ed 1982 2nd Ed 1993
Lifshitz F	*Pediatric Endocrinology*, Marcel Dekker, New York	1st Ed 1985 2nd Ed 1990 3rd Ed 1996 4th Ed 2003
Sperling MA	*Pediatric Endocrinology**, WB Saunders, Philadelphia	1st Ed 1996 2nd Ed 2002

* Successor to Kaplan S.

rie at the University of Minnesota and served as a junior faculty member before moving in 1953 to UCLA. Dr. Anderson used the lure of a fully equipped laboratory suitable for steroid research to attract Dr. Ulstrom from UCLA to replace Dr. McQuarrie, who was retiring at age 65. Dr. Eleanor Colle and Dr. Elsa Paulsen were fellows with Dr. McQuarrie and completed training with Dr. Ulstrom.

Dr. Maria New completed a fellowship in biochemistry and renal function with Dr. Norman Kretchmer and another in steroid biochemistry with Dr. Ralph Peterson at the New York Hospital, Cornell Medical Center. She was appointed head of the new pediatric endocrinology division at Cornell in 1964. Her productive collaboration with Dr. Petersen continued for some 15 y.

The second-generation pediatric endocrinologists had many advantages over the first-generation pioneers. They were generally accepted as trained subspecialists in academic centers committed to subspecialty organization and were recruited to full-time positions, usually with laboratory space and often with start-up funding. National Institutes of Health funding now was available, and clinical investigation was encouraged. Fellowship training was recognized and sought by pediatric trainees, and funding for trainees became available from local budgets, National Institutes of Health, and private foundations. Research was encouraged, and endocrine and other subspecialty section platforms for research presentations were rapidly incorporated into the Society for Pediatric Research and the APS meeting formats.

The Endocrine Society grew rapidly during the second half of the 20th century, reflecting the advancement of science and medicine, the organization of medical subspecialties, and formal certification of training and expertise in the clinical subspecialty. Growth of the Endocrine Society was associated with the formation of a number of subspecialty societies within the endocrine field, in some cases with associated journals. These included the American Thyroid Association in 1923, the American Diabetes Association in 1940, the American Fertility Society in 1944, the Society of Gynecologic Investigation in 1953, the Society for the Study of Reproduction in 1967, the International Society for Neuroendocrinology in 1972, the American Society for Andrology in 1975, and the American Society for Bone and Mineral Research in 1977. Pediatric endocrinologists became members of many of these societies. Two additional Endocrine Society journals, *Endocrine Reviews* and *Molecular Endocrinology*, were introduced in 1980 and 1987, respectively (43). Pediatric endocrine textbooks also began to proliferate (Table 4). Dr. Wilkins published the second edition of his textbook in 1957. The third edition was incomplete at the time of his death and was completed by Claude Migeon and Robert Blizzard for publication in 1965. A fourth edition, edited by Michael Kappy, Robert Blizzard, and Claude Migeon, was published in 1994 (Table 4). In the preface for the 1243 pages of the fourth edition, the authors quoted Edward Curtis, who spent several decades compiling material for a study of the Indians of North America: "—great

is the satisfaction the writer enjoys when he can at last say to all those whose faith has been unbounded, 'It is finished.'"

ESTABLISHMENT OF THE LAWSON WILKINS PEDIATRIC ENDOCRINE SOCIETY

Robert Blizzard and Claude Migeon organized biennial reunions for the Hopkins Endocrine Alumni in 1965, 1967, 1969, and 1971. These meetings were open to others who were interested in pediatric endocrinology, and attendance rose from 35 to 100 between 1965 and 1971. Organization of the meetings had become onerous, so on April 15, 1971, a group of some 40 pediatric endocrinologists at least 10 y out of training met in Baltimore to establish a formal endocrine society. The Lawson Wilkins Pediatric Endocrine Society (LWPES) was chosen as the name. On April 30, in Atlantic City, Claude Migeon was elected president, William Cleveland was elected vice president, Delbert Fisher was elected secretary, and Ira Rosenthal was elected treasurer. A membership committee, chaired by John Crigler, and a constitution and bylaws committee, chaired by Alvin Hayles, were formed. Dr. Hayles was a self-taught pediatric endocrinologist who developed the Division of Pediatric Endocrinology at the Mayo Clinic and was a founding member and first chairman of the subspecialty board of pediatric endocrinology.

During the following 12 mo, a membership of 160 individuals, including 77 founding members, were recruited, and on May 23, 1972, a Constitution and Bylaws were approved, officers and directors were elected, and committee members chosen. The first official meeting of the new society organized by Dr. Marvin Cornblath was held in San Francisco in May 1973. Meetings have been held yearly since 1973 in conjunction with the annual meeting of the Pediatric Academic Societies. Membership of the LWPES by 2002 has grown to 840 active members, 113 emeritus members, 42 corresponding members, and eight honorary members. Past presidents of the society are listed in Table 5.

Since 1950, several pediatric endocrinologists have served as presidents of the Endocrine Society, including Lawson Wilkins (1956–1957), Melvin Grumbach (1981–1982), Delbert Fisher (1983–1984), and Maria New (1991–1992). Lawson Wilkins (1961), Judson Van Wyk (1989), Melvin Grumbach jointly with Selna Kaplan (1992), and Maria New (2003) have been recipients of the Fred Conrad Koch Award of the Endocrine Society; and Melvin Grumbach (1980), Maria New (1988), Claude Migeon (1992), Robert Blizzard (1994), and Delbert Fisher (1998) have been recipients of the Robert H. Williams Distinguished Leadership Award of the Endocrine Society. Alfred Bongiovanni (1956) and Perrin White (1991) have received the Ernst Oppenheimer Award and Walter Miller (1988) the Edwin Astwood Award of the Endocrine Society. Alvin Hayles (1979) and Delbert Fisher (1989) have served as president of the American Thyroid Association. Lawson Wilkins (1963), Melvin Grumbach (1997), and Delbert Fisher (2001) have been recipients of the Howland Award of the American Pediatric Society.

Table 5. *Past presidents of The Lawson Wilkins Pediatric Endocrine Society*

1972–1973	Claude J. Migeon	1988–1989	Allen W. Root
1973–1974	William W. Cleveland	1989–1990	Douglas Frasier
1974–1975	Robert M. Blizzard	1990–1991	Louis E. Underwood
1975–1976	Melvin M. Grumbach	1991–1992	Raymond L. Hintz
1976–1977	Judson J. Van Wyk	1992–1993	Jo Anne Brasel
1977–1978	John D. Crawford	1993–1994	Gilbert P. August
1978–1979	Alvin B. Hayles	1994–1995	Thomas P. Foley, Jr.
1979–1980	John F. Crigler, Jr.	1995–1996	Margaret McGillivray
1980–1982	Alfred Bongiovanni	1996–1997	Ron G. Rosenfeld
1982–1983	Delbert A. Fisher	1997–1998	John S. Parks
1983–1984	Angelo M. DiGeorge	1998–1998	Peter A. Lee
1984–1985	Selna Kaplan	1999–2000	Stephen La Franchi
1985–1986	Maria New	2000–2001	Edward O. Reiter
1986–1987	Salvatore Raiti	2001–2002	Barbara M. Lippe
1987–1988	Allan L. Drash	2002–2003	Mark A. Sperling

Worldwide, six other pediatric endocrine societies and the Pediatric Endocrine Nursing Society have been established. Founding of The European Pediatric Endocrinology Club in 1962 [renamed The European Society for Pediatric Endocrinology (ESPE) in 1966] and the Japanese Society for Pediatric Endocrinology (1967) preceded LWPES. The British Pediatric Endocrine Group first convened in 1972 and in 1979 was renamed The British Society for Pediatric Endocrinology and Diabetes. The Australian Pediatric Endocrine Group was founded in 1982, the Sociedad Latino Americana de Endocrinologia Pediatrica in 1986, and the Asia Pacific Pediatric Endocrine Society in 1999. The Pediatric Endocrine Nursing Society was established in 1986. Joint meetings of the LWPES and ESPE have been held every 4 y since 1981. The sixth joint meeting, convened in Montreal in July 2001, included participation by the Australian Pediatric Endocrine Group, the Japanese Society for Pediatric Endocrinology, and the Sociedad Latino Americana de Endocrinologia Pediatrica. This meeting is evolving as an every fourth year International Pediatric Endocrine Congress.

DEVELOPMENT OF PEDIATRIC DIABETES AS A DISCIPLINE

Diabetes was not included among the disorders in Dr. Wilkins's first textbook, and children with diabetes were not included among his clinic patients. In the third edition of his textbook, he referred the reader to other sources of information on diabetes in children. Dr. Allan Drash, in personal communication, has written, "It is unclear why Dr. Wilkins chose not to include diabetes mellitus within the sphere of inquiry of the pediatric endocrinologist. It may have simply been the tradition of the day. Diabetologists were considered 'different.' Most were purely practitioners rather than academic teachers and investigators, and few were pediatricians. Another factor may have subtly influenced Dr. Wilkins thinking. Dr. Harriet Guild spent her entire academic career in the Department of Pediatrics at the Johns Hopkins Hospital specializing in care of children with a variety of serious chronic disease. Within that sphere, she tightly controlled a large and active pediatric diabetic clinic."

One of the earliest physicians to focus on childhood diabetes in the United States was Dr. Priscilla White, an assistant and co-worker of Dr. Elliot Joslin at the Joslin Clinic in Boston. In

1932, Dr. White published what probably was the first medical textbook to deal with childhood diabetes: *Diabetes in Childhood and Adolescence*. (44) Other first-generation pediatric diabetic centers in the United States before World War II included the University of Iowa (directed by R.C. Harden, followed by Robert L. Jackson and Charles Read), the University of Cincinnati Children's Hospital (directed by George Guest, followed by Harvey Knowles, an internist), and the St. Louis Children's Hospital (directed by Alex Hartman). The first summer camp for children and youths with diabetes was established in Michigan in 1925 by Dr. Leonard Wendt. This program has expanded and flourished and now serves some 15,000 children each summer.

In Canada in 1946, A. Lawrence Chute, after training in Boston with Joslin and White, established a pediatric diabetes/endocrine program at The Hospital for Sick Children and the Department of Physiology at the University of Toronto. Dr. Chute was selected as physician in chief at the hospital in 1957. Donald Hillman, after training in the Talbot program in Boston, returned to Montreal in 1958 to head a pediatric endocrine-diabetes program at Montreal Children's Hospital. Dr. Mimi Belmonti, after training at The Hospital for Sick Children and the Joslin Clinic, joined Hillman to head the pediatric diabetes program.

Physicians who focused on childhood diabetes during the early post–World War II years included Robert Schwartz, a pediatrician at Boston Children's Hospital, and T.S. Danowski, an internist at the Children's Hospital of Pittsburgh. In 1957, Dr. Danowski published his textbook *Diabetes Mellitus, with Emphasis on Children and Young Adults* (45). During the period 1965–1975, a number of pediatric investigators were involved in the evolution of diabetes as an academic discipline. These included Eleanor Colle at Montreal, Marvin Cornblath at Johns Hopkins and the University of Maryland, William Daeshner at Galveston, Donnell Etzweiler of Minneapolis, Robert Kaye at the Children's Hospital of Philadelphia, Robert Schwartz at Brown University, and Howard Traisman at the Children's Memorial Hospital in Chicago.

The next generation of influential pediatric diabetologists included Lester Baker at the Children's Hospital of Philadelphia; Peter Chase in Denver; Robert Ehrlich at the Hospital for Sick Children in Toronto; Kenneth Gabbay at Boston Children's and the Baylor School of Medicine in Houston; Richard Guthrie, a protégé of Robert Jackson, at the University of Missouri; Anthony Pagliaria at St. Louis Children's Hospital; Elsa Paulson at the University of Virginia; Arlan Rosenbloom at the University of Florida; Luther Travis at the University of Texas at Galveston; and Allan Drash at the University of Pittsburgh. Dr. Drash was the first Johns Hopkins pediatric endocrine trainee specializing in diabetes care and research. He began his metabolism and endocrine training at Johns Hopkins in 1962 working initially with Dr. William Nyhan in the Department of Pediatrics and Dr. Thaddeus Prout in the Department of Medicine. With support of Robert Blizzard, then head of the Pediatric Endocrine Division, he established a half-day weekly diabetic clinic in competition with Dr. Guild's clinic. In 1966, Dr. Drash moved to the Children's Hospital of Pittsburgh to assume direction of the pediatric diabetic program developed by T.S. Danowski during the period 1947–1957.

In 1974, the International Study Group for Diabetes was founded in Europe by 22 pediatricians who were interested in the care of diabetes in children. A steering committee was elected and included H. Lestradet, president; Z. Laron, secretary; and H. Loeb, treasurer. Annual meetings were held, beginning in 1975. In 1993, the organization was renamed the International Society for Pediatric and Adolescent Diabetes. The society has promoted pediatric diabetes programs within the meetings of the International Diabetes Foundation and within the ESPE, but the International Society for Pediatric and Adolescent Diabetes and ESPE have retained individual autonomy.

During the 1970s, the pediatric diabetologists working within the American Diabetes Association promoted establishment of the Council on Diabetes and Youth in 1980. Membership now exceeds 600 individuals. Diabetes topics also were introduced in the annual meeting of the LWPES in the mid-1970s, and diabetes and diabetes research now compose a significant portion of the LWPES meeting programs. Medical and economic factors have led to increasing integration of pediatric diabetes and general endocrine care and training. In the United States, most pediatric diabetologists now come from a training background in general pediatric endocrinology, and diabetes care is a major activity within the subspecialty of pediatric endocrinology. Three pediatric diabetologists have served as presidents of the American Diabetes Association: Donnell Etzweiler (1976–1977), Allan Drash (1983–1984), and Francine Kaufman (2002–2003). Allan Drash also served as president of the International Study Group for Diabetes (1980–1986) and president of the LWPES (1987–1988).

PEDIATRIC ENDOCRINE TRAINING AND MANPOWER

The growth of pediatric endocrinology in North America has paralleled the growth of academic medicine during the past half-century. In 2002, there were 72 training programs in North America: 65 in the United States, and seven in Canada. Directors of these programs are listed in the Pediatric Endocrinology Program Directors State and Province Listing (www.abp.org/resident/appd/progdir/pest.htm). The endocrinology sub-board of the American Board of Pediatrics was established in 1978 to certify training and competence in endocrinology, including diabetes. By 2002, the board had certified 927 pediatric endocrinologists.

ADVANCES IN PEDIATRIC ENDOCRINOLOGY SINCE 1950

One view of the major advances in pediatric endocrinology since World War II is given in Table 6. Pediatric endocrinologists have made major contributions and led in many of these areas. All are the result of the advances in biologic and medical science created by growth of the academic medical enterprise; governmental, corporate, and foundation funding; the education of several generations of basic science and clinical investigators; and the contributions of the pharmaceutical industry during the past half-century.

Before World War II, the focus of endocrine research was the isolation and purification of hormones and the study of their

Table 6. *Major advances in pediatric endocrinology since World War II*

Availability of hormone and growth factor immunoassays
Development of high-resolution imaging equipment
Availability of tests for autoimmune endocrinopathies
Development of HbA_1c as a reliable indicator of metabolic control in diabetes
Production of human insulin
Development of insulin infusion pumps
Physiology of the growth hormone–somatomedin system
Growth hormone and IGF therapy for growth retardation
Thyroid system ontogenesis and physiology
Screening for congenital hypothyroidism
Understanding of mechanisms of sexual differentiation and puberty
Drug and hormone therapies for pubertal disorders
Development of management strategies for CAH
Screening for CAH
Intrauterine diagnosis and therapy for fetal thyroid dysfunction and CAH
Nosology and genetic testing for steroid, peptide, and hormone receptor diseases
Development of biochemical markers of bone metabolism
Development of pathophysiology, nosology, and therapies for the hypoglycemias
Testing for genetic predisposition for endocrine diseases
Evolution of diagnostic markers and therapies for endocrine neoplasias
Availability of cytogenetic and molecular genetic tests for dysmorphic syndromes

effects and description of the clinical syndromes resulting from hormone excess or deficiency. The development of immunoassay methods during the 1960s facilitated detailed studies of hormone systems physiology, including feedback control systems, hormone production rates and metabolism, chronological variability, and identification of new hormones and hormone classes present at low concentrations (25). The development of sophisticated imaging techniques coupled with the highly sensitive and specific hormone assay systems has facilitated early diagnosis of even subtle endocrine disorders (46).

Radioisotope technology after World War II led to hormone tracer studies characterizing cell membrane and nuclear hormone receptors followed by identification of the complex second (intracellular) messenger systems mediating hormone actions. Molecular genetic technologies have allowed cloning of the genes for virtually every known hormone and most hormone receptor systems (47). The ability to identify mutations in these genes has expanded the disease nosology of every endocrine system, and this information and technology is rapidly moving into the clinic for diagnosis and management of pediatric endocrine disorders. One of the surprises has been discovery of both gain of function and loss of function germline mutations of many of the hormone receptors, accounting for constitutive activation phenotypes as well as deficiency and resistance syndromes (47, 48). Examples include the activating and inactivating mutations of the TSH receptor, producing congenital hyper- or hypothyroidism, and the PTH receptor, producing congenital hyper- or hypoparathyroidism.

The application of modern immunologic techniques has demonstrated an autoimmune pathogenesis for a variety of endocrine diseases (49–54). Type 1 diabetes is the most common, and autoantibody tests are now available for early diagnosis of pancreatic islet β-cell autoimmunity before development of the overt diabetic phenotype. Autoimmune thyroid disease, including Hashimoto thyroiditis and Graves' disease, are other common examples for which diagnostic autoimmune antibody testing is now available. The autoimmune polyglandular syndromes types 1 and 2, with respective autosomal recessive and polygenic causes, present as complete and incomplete phenotypes involving endocrine and nonendocrine tissues and organs; autoantigens have been identified for essentially all of the involved organs and tissues.

Advances in cytogenetics and availability of molecular genetic technologies have provided new insights regarding causative mechanisms for birth defects and provide diagnostic tests for many previously idiopathic dysmorphic syndromes (55, 56). Examples include the translocation syndromes; microdeletion syndromes; and the Turner, Prader Willi, McCune-Albright, and DiGeorge syndromes. Molecular testing now is available to identify disease predisposition, including endocrine-related disorders. Examples include BRCA 1 and 2 mutations predisposing to breast and ovarian cancer and RET gene mutations predisposing to the syndrome of multiple endocrine neoplasia type 2 (57, 58). Testing for the latter in high-risk families now allows early thyroidectomy in affected children to prevent development of medullary thyroid cancer.

Other areas of important advances in pediatric endocrine science include the disorders of sexual differentiation, the mechanisms of puberty, steroid hormone metabolism, hypertension, and the genetics and physiology of growth and development (59–67). These advances have been associated with development of a growing list of therapeutic agents to manage the disorders of growth and pubertal development, which comprise as much as 40% of patients in some pediatric endocrine clinics (68). Research in animal models and in human gestation have advanced our understanding of endocrine systems ontogenesis and perinatal and neonatal endocrine dysfunction (69–73). Newborn screening and early treatment for congenital hypothyroidism now prevents growth retardation and mental deficiency in most cases (74). Therapies for management of fetal hyperthyroidism and hypothyroidism and fetal adrenal hyperplasia have been developed, as well as experimental approaches to therapy of fetal growth retardation (75, 76). The growth of neonatology has led to new insights regarding developmental endocrinology and the diagnosis and management of the endocrine system immaturities in term and preterm infants (73, 77–81). Considering the pace of development of science and medicine and growth of the pediatric endocrine infrastructure of clinical investigators and practitioners during the past 50 y, we can anticipate even more rapid, continuing progress in endocrine science and the treatment of children with endocrine and metabolic disease.

Endocrine science is increasingly focused on the cascade of endocrine, paracrine, and autocrine pathways of hormones, growth factors, and second messenger systems involving a cascade of receptor systems amenable to pharmacologic perturbation. The ability to identify and characterize these receptor systems and design agonist or antagonist drugs already has had a widespread impact, and new molecular and proteomic technologies will accelerate progress and availability of more effective therapeutic agents. Directed antibodies and gene ther-

apies also may offer important therapeutic advances. The growing focus on genetic predisposition to disease and associated prospects for disease prevention strategies will have an impact on endocrinology as well as other medical disciplines. This is particularly relevant in pediatrics, in which cellular, organ transplant, and gene therapies offer special promise for major advances during the next 50 y.

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