

GROWTH

Genetics & Hormones

Vol. 19 No. 2

www.gghjournal.com

June 2003

LAWSON WILKINS - PIONEER IN PEDIATRIC ENDOCRINOLOGY AND GROWTH DISORDERS: REVISITED 2003

Robert M. Blizzard, MD

Editor-in-Chief

EDITORIAL INTRODUCTION

In March 1987 in *Growth, Genetics & Hormones*, Vol. 3, No. 1, the lead article with the same title as above was published (the original article is available at the *Archive* section of www.GGHjournal.com). Dr. Wilkins was the founder of pediatric endocrinology. His contributions to pediatrics and pediatric endocrinology were substantial. He was a consummate teacher, practitioner, and investigator, and his personal characteristics were of an exceptional human. He must be known by those who use his name frequently, including members of the Lawson Wilkins Pediatric Endocrine Society and those who utilize his articles in the pediatric literature as references for their own writing. It is for this reason that in this current issue of *Growth, Genetics & Hormones* the article published in *GGH* in 1987 is revisited. In respect to this updating, the two considerations incorporated include an updating of chronological time and the providing of references with highlights concerning Lawson Wilkins as a leader, teacher, pediatrician, and investigator.



Highlights In This Issue

BMI & Segmental Proportion in Children with Subtypes of Psychosocial Short Stature	page 21
IGF-1 Receptor Mutations	page 23
Inhibition of Glucose Production	page 25
A New Disorder of Zinc Metabolism	page 25
L-Thyroxine in Congenital Hypothyroidism	page 26
Survival Profile for Down Syndrome	page 28
Paternal Age Effect in Achondroplasia	page 28
IGF-1 in Assessing Response to Growth Hormone	page 29
Leptin in Urine & Relationship to Growth Peptides	page 30
Letter to the Editor: Epiphyseal Fusion	page 31
GI Complications of Russell-Silver Syndrome	page 31
Growth Hormone Deficiency in Salt-Losing Congenital Adrenal Hyperplasia	page 32
Clinical Guidelines for Growth Hormone use in Adults & Children - 2003	www.gghjournal.com

Forty years have passed since 1963, when Dr. Lawson Wilkins died at the age of 69. His demeanor, his accomplishments, and the esteem in which he was held by his peers and his extended family of pediatric endocrine fellows whom he trained are not known to the third and fourth generations of pediatric endocrinologists who are members of the Lawson Wilkins Pediatric Endocrine Society. Since volumes could be written about each aspect of Dr. Wilkins' life, an abbreviated biography is inadequate. Nevertheless, a brief history of Dr. Wilkins' life presents the opportunity to update the image of a man who should be known by pediatric endocrinologists, pediatricians, and geneticists.

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. Mrs. Wilkins' death, when Lawson was five years of age, significantly strengthened the already close bond between father and son.

After receiving a baccalaureate degree from Johns Hopkins University in 1914, Lawson Wilkins began medical school there. In 1917, along with many other medical students, he volunteered to go to Europe and served 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 Johns Hopkins Hospital where the influence of Drs. Blackfan, Park, Kramer, and the other giants of pediatric medicine of the period further whetted his keen intellectual appetite.

It was most likely his desire to follow in his father's footsteps as a practitioner that prompted him to enter pediatric practice in Baltimore in the early 1920s. Until the time he accepted a full-time academic position in 1946, Dr. Wilkins had practiced pediatrics for 25 years with intense intellectual curiosity and great compassion for his patients. This author has on several occasions in the past 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. Edwards Park, 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 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 tended 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. Possibly this was because Dr. Harriet Guild of the Harriet Lane staff had established a diabetes clinic and, characteristically, Dr. Wilkins would not intrude on the work of others unless invited. Interestingly, he never considered diabetes a disease of the endocrine system, although he believed hypoglycemia was.

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 bawdy songs long into the night. He loved to sail his boat on the Chesapeake Bay and tell jokes, which he masterfully embellished. He also adored - and was adored by - Lucile Mahool, his first wife, and Teence Anderson, to whom he was married after Lucile 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 Dr. Wilkins: "When I first met Wilkins, which was at a time I had heard about his studies that Dr. Park exalted, 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 us to come in. His whispers in a conference could cause consternation, for his 'That fellow is putting out pure hogwash' might have been 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 observations, this author 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.

Another mark of the quality of Dr. Wilkins' personality was the grace with which he relinquished his pediatric endocrine clinic and training program to Dr. Claude Migeon and this author in 1960. During the next three years, before he died in 1963, he was present much of the time, he remained intellectually curious, and he continued to contribute in all respects.

SCIENTIFIC CONTRIBUTIONS

Lawson Wilkins greatly expanded our knowledge of endocrine physiology and pathophysiology. Some of us have been fortunate enough to have shared in his experiences in establishing pediatric endocrinology as a subspecialty. Drs. Albert Bongiovanni,* Claude Migeon, and Walter Eberlein shared his interest in adrenal steroid metabolism and the pathophysiology produced by deficiencies of various enzymes for cortisol synthesis, including defects in 21 hydroxylation and 11 hydroxylation that produce congenital virilizing adrenal hyperplasia. In 1950, Drs. John Crigler, Robert Klein, Lytt Gardner,* Claude Migeon, and Eugenia Rosemberg joined Dr. Wilkins in successfully treating the first patients with congenital virilizing adrenal hyperplasia with cortisone. As always, Dr. Wilkins applied the knowledge he gained from his physiologic studies to therapy.

(*Deceased)

Drs. Melvin Grumbach and Judson Van Wyk worked with Dr. Wilkins in his studies of sexual differentiation. In this area, Dr. Wilkins applied what had been learned from the animal experiments of Alfred Jost to postulate and prove that the anatomy in gonadal agenesis and pseudohermaphroditism in human beings could be explained by the presence or absence of androgens and Mullerian inhibiting factor.

It was with Dr. Wilkins that Lytt Gardner* developed his interest in genetics and cytogenetics. It was Dr. Wilkins and his students who were among the first to apply the cytological techniques of Dr. Murray Barr to identify the inactivated X chromosomes (Barr bodies) in the nuclei of patients with Klinefelter's syndrome and in female pseudohermaphrodites. These diagnostic aids facilitated the diagnosis and therapy of patients with abnormalities of sexual development.

With Dr. Wilkins, Dr. George Clayton demonstrated that enzyme defects in the synthesis of thyroid hormone metabolism produce pathologic changes in the thyroid that simulate thyroid carcinoma. Dr. Wilkins had previously demonstrated during his years in practice the effect of thyroid hormone on cholesterol and creatinine metabolism.

Dr. David Smith* and this author benefitted from Dr. Wilkins' astute record keeping; he was a master in maintaining growth charts and other documents. With him, we published the effect of thyroxin treatment on the mental development of cretins.

These were classic physiologic studies in which the effects of a hormone were investigated clinically. He had demonstrated during this same period that the epiphyses in patients with thyroid deficiency were misshapen as they calcified (epiphyseal dysgenesis) and delayed in appearance, and that epiphyseal dysgenesis was a frequent finding in the untreated cretin. With treatment, the epiphyses that had not appeared because of thyroid hormone deficiency were often dysgenetic when they did appear, but the epiphyses that were expected to appear following the chronologic age that treatment was begun were always intact in their development.

THE SECOND GENERATION AND BEYOND

Other pediatric endocrinologists from the United States who trained with Dr. Wilkins between 1946 and 1960 were Drs. Thomas Shepard, Gerald Holman, José Cara,* David Mosier, William Cleveland, Ralph David, Orville Green, Malcolm Martin, Samuel Silverman, and Robert Stempfel. Many students from abroad who are now professors also trained with Dr. Wilkins. These include Drs. Jean Bertrand, John Eckert, John Gerrard, Casaer

Bergada, Theodoros Papadatos,* and Andrea Prader* who followed in Lawson's image as a major founder of pediatric endocrinology in Europe, and Henning Anderson.* These endocrinologists and professors have trained the third generation of pediatric endocrinologists who in turn have trained the fourth generation.

Dr. Wilkins wanted to be called "Lawson" by "his boys" as he called those who trained under him, but esteem for him was so great that he remained "Dr. Wilkins" to most for many years.

It is not by chance, however, that there was only one female fellow, Dr. Eugenia Rosemberg, prior to 1960. It was simply Dr. Wilkins' policy not to accept women as fellows. He respected the intellect of female physicians, but he was reluctant to let them examine the male teenagers who came to him for consultation. With the acceptance of Drs. JoAnne Brasel, Virginia Weldon, and Irene Solomon as pediatric endocrine fellows at Johns Hopkins in the early 1960s (when he was professor emeritus but still active), he relented and realized that he had been unduly restrictive.

We in pediatric endocrinology, pediatrics, and genetics are indeed blessed to have had such a man to lead us. The history of Lawson Wilkins is well worth passing along to the third and fourth generations of pediatric endocrinologists, and it is to be hoped that they will pass it along to the fellows who train with them.

(*Deceased)

REFERENCES AND THEIR HIGHLIGHTS

1. Wilkins L. Presidential Address to American Pediatric Society. *Am J Dis Child* 1962;104:449-456.

Dr. Wilkins wished to chastise pharmaceutical firms for their focus on the commerce of manufacturing and marketing drugs and to warn physicians to avoid the pitfalls of over prescribing medications and/or prescribing the newest medicine in the pipeline when its efficacy and the potential long-term toxicity are obscure. This masterful presentation was both educating and chastising. The following capsulizes Wilkins' closure: (1) Remember the Oath of Hippocrates, (2) Give no drug if it is not needed. Placebos rarely have a place in pediatrics, (3) Remember that practically every effective drug has potentials for toxic side-effects, (4) Neither discuss nor prescribe drugs by brand name, (5) Never use a drug or mixture without full knowledge of its chemical nature and pharmacological action, (6) Do not attempt to learn your new therapeutics from the trade brochures or even the PDR, (7) Do not hasten to use the 400+ new drugs coming on the market each year -

particularly if they are variants of drugs with which you already have had experience, (8) Wait, wait, wait - and then wait. Let the other fellow poison his patients.

2. Bongiovanni AM. Presentation of the John Howland Medal and Award of the American Pediatric Society to Dr. Lawson Wilkins. *J Pediatr* 1963;63:803-807.

Dr. Bongiovanni pays tribute to Lawson Wilkins for all of his accomplishments with the help of Wilkins only sibling and records: "He had a child like curiosity and spirit of inquiry that kept him young. He was never struck with the prejudices of a prior era. His advantages were scholarly acquaintance with earlier discoveries, an intimate knowledge of clinical aspects, and a firm hold on the basic sciences. His multiple interests are reflected in the diversity of titles to his innumerable publications, which include studies on serum potassium, ulcers of the tongue, rickets, immunization against dysentery, meningitis, pyuria, epilepsy and many diverse aspects of endocrinology." The presentation in this reference was a remarkably successful rendering of insight about the personality and personal characteristics of Lawson Wilkins.

3. Wilkins L. Acceptance of the Howland Award. *J Pediatr* 1963;63:809-811.

Dr. Wilkins paid extensive gratitude to his mentors and colleagues, including fellows, which reflected his true sincerity for his colleagues' contributions and collaborations, and to educate his listeners. As he stated, "I wish to take the privileged opportunity to emphasize the importance of the clinician and clinical investigator in contributing to basic and fundamental knowledge." His views about clinical investigation in abbreviated wording was as follows: It is the clinician who must seek out and bring to attention the human experiments of nature . . . no one can reproduce in the laboratory most of the inborn enzymatic defects

. . . I always permitted my assistants to delve into any type of problem which interested them . . . The scientist must have an insatiable curiosity to seek knowledge along any lines

. . . The clinical investigator must have curiosity and, if he has such curiosity, nearly every patient he sees will call forth many questions of real importance which have never been answered. The clinical investigator will be impelled to attempt to answer these questions by studies upon the patient.

4. Wilkins L. The Evolution of Endocrine Diagnosis and Treatment: The Addison Lecture. *Guys Hospital Gazette* 1954;March 19th, pages 1-9.

Dr. Wilkins gave a masterful presentation of the history of clinical endocrinology beginning with Graves' classical description of thyrotoxicosis in 1834 and a current (1954) discussion of the interrelationships of the endocrine glands and their hormones including diagnostic methodology available, differentiation of CAH in males from other types of sexual precocity, diagnosis of sexual infantilism, etc. The result was a very erudite lecture revealing how successful Dr. Wilkins was in sorting out the diagnoses and treatment of various pediatric endocrinopathies. The content of this lecture was incorporated into the 2nd Edition of his textbook, *The Diagnosis and Treatment of Endocrine Disorders in Adolescence and Childhood* (1957).

5. Blizzard RM. Pediatric Profiles: Lawson Wilkins (1894-1963). *J Pediatr* 1998;133:577-580.

Dr. Blizzard was invited to write such a profile as the *Journal of Pediatrics* was composing a series on the profiles of those who had pioneered in the specialty of pediatrics. His initial goal was to introduce an unusual story to the readers of his first encounter with Lawson Wilkins. This unusual encounter characterized Wilkins' personality - honesty, directness, a no nonsense approach, leadership, preciseness, and the expectation that one hearing a private conversation would keep the confidence of the discussants. The paper also describes in subsections The Wilkins personality, Wilkins as a physician, Wilkins as an investigator, and Wilkins as a teacher. The article ends with brief descriptions of his last years and conclusions.

6. Bongiovanni AM, et al. To Honor Lawson Wilkins, MD in His 65th Year. *J Pediatr* 1960;57:317-325.

Dr. Bongiovanni provides a personal accounting given by Dr. Edwards A. Park (pages 317-322) of his professional relationships with Lawson Wilkins and accountings of personal relationships with Lawson Wilkins by some of his colleagues of the early historic days, including Douglas Hubble of Scotland. The accountings of Hubble and Park are particularly insightful and should be read by those wishing to more completely understand Dr. Wilkins as a clinical investigator and as a unique personality.

7. Money J. Foreword to the 3rd Edition of *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*. By Lawson Wilkins with the editorial assistance of Robert M. Blizzard and Claude J. Migeon; 1965;pages vii-xi.

Dr. Money wrote this foreword after Lawson Wilkins' death with the primary objective of recording Dr. Wilkins' professional and personal characteristics by one who had worked closely with him for more than a decade.

Dr. Money delivered a very thorough and appropriately lengthy personal and professional history of Dr. Wilkins. Dr. Money's closing paragraph is particularly pertinent as it is conceptually flattering and truthfully accurate: "Lawson Wilkins achieved fame, but as a by-product of accomplishment. His life's goal had been to achieve, not to become famous."

8. Fisher DA. A Short History of Pediatric Endocrinology in North America. *J Pediatr* 2003 (In preparation).

The purpose of this article is to record for posterity a historical perspective of the founding and development of pediatric endocrinology as a subspecialty, of the Lawson Wilkins Pediatric Endocrine Society, of pediatric

endocrine training programs, of pediatric diabetes as a discipline, and of advances in understanding, diagnosing, and treating pediatric endocrinopathies since 1950. A very excellent and complete presentation of the topic has been written by Dr. Fisher. As part of this, Lawson Wilkins' major roles as pediatrician, founder of the subspecialty, clinical investigator, and academician are evident.

9. Migeon CJ. *The Origins and Establishment of the LWPEES*. <http://www.lpwes.org/history.html>. The concept and history created by Lawson Wilkins invitation in 1963 of a scientific gathering to the formal creation in 1972 of a Society is interestingly detailed.

Abstracts from the Literature

Body Mass Index and Segmental Proportion in Children with Different Subtypes of Psychosocial Short Stature

Psychosocial short stature (PSS) has been classified by the authors into 3 categories: (1) Type IIA are hyperphagic children, in whom there is reversible growth hormone (GH) insufficiency with rapid catch-up growth with a change in their living environment but with minimal response to exogenous GH; (2) Type IIB is a heterogeneous sub group of non-hyperphagic children who have normal GH secretory dynamics and minimal or absent increase in growth rate with change in their environment and variable response to GH; and (3) Type III are children with anorexic eating habits, with an onset as early as infancy, with failure to thrive, depression, normal GH secretory dynamics, and significant growth response to exogenous growth hormone. Gohlke et al

report anthropometric evaluations of 46 children with PSS, before and after change in their environment (Table 1).

Significant improvement in height velocity SDS after intervention was observed in all groups. ANOVA failed to show any significant differences in growth velocity between groups. There was no significant change with treatment in body proportion in type IIA (hyperphagic) or in type IIB (heterogenous) children. In type III (anorexic) children, the body proportions decreased significantly after intervention indicating relatively shorter upper segments after treatment. In those who received GH treatment (n = 21), there was no significant change in body proportion after GH therapy. Body Mass Index

Table 1

Clinical Data of 46 Children with PSS

Classification	Type IIA (n = 20)	Type IIB (n = 16)	Type III (n = 10)
Mean age at presentation (years)	8.6	7.6	10.2
Age range (years)	4.9-15	3.8-14.9	5.4-14.9
Sex	9F. 11M	4F. 12M	6F. 4M
IUGR	2F. 2M	0F. 5M	2F. 2M
Mean bone age delay at presentation (years) (SD)	1.69 (1.0)	1.69 (1.3)	2.0 (1.5)
Prepubertal at presentation	18	15	9
Type of intervention			
Social services only	17	5	3
Social services and GH therapy	3	11	7

Adapted from: Gohlke BC, et al. *Eur J Pediatr* (220) 161: 250-254.