INTRODUCTION

The moderator charged each of the speakers with a specific topic to address, asking them to provide the historical perspective, the influence of Lawson Wilkins, and the current state of knowledge that has arisen from the earlier studies that were undertaken under Lawson Wilkins. Each speaker presented historical vignettes relating to Lawson, descriptions of original case studies and recent advances in the diagnosis and management of their topic disorder. The speakers described Lawson as intellectually curious and honest, humble, energetic, hard working, loquacious, fond of singing (but could not carry tune), and a popular host. All stressed his powers of observation, his commitment to preparing graphic details of his patients, and his wise use of the laboratory.

PRESENTATIONS

Dr William W Cleveland: 2nd LWPES President: 1973-1974
  ▪ The early Years of Lawson Wilkins and the establishment of Pediatric Endocrinology as a discipline

Dr Claude J Migeon: 1st LWPES President 1972-1973
  ▪ Congenital Adrenal Hyperplasia

Dr Robert M Blizzard; 3rd LWPES President 1974-1975
  ▪ Growth and development assessment without GH assays

Dr Melvin M Grumbach: 4th LWPES President 1975-1976
  ▪ Gonadal differentiation and Turner syndrome

Dr Judson J Van Wyk: 5th LWPES President 1976-1977
  ▪ From Testicular Feminization to Androgen Insensitivity Syndrome
William Cleveland was one of two last fellows under Lawson Wilkins – the other being David Alexander. He reviews the birth of Lawson in 1894, his MD degree during WWI, service in France, and then entry into private practice. Lawson published his first paper in 1923. Lawson joined the staff at Johns Hopkins in 1935 when Dr Edwards Parks offered him the position as the first Director of the new Endocrinology Clinic in the Harriet Lane Home (HLH). He proceeded to develop the systematic study of complicated disorders, with detailed graphics, and to establish a training program that has provided several generations of clinician-scientists worldwide. Lawson died in 1963, aged 69, at the peak of his success.

Three editions of his seminal textbook of Endocrine Disorders were published, in 1950, 1957, and the third edition in 1965 was completed by Bob Blizzard and Claude Migeon after Lawson’s death.

Cleveland describes the major role that Lawson played in the training of future Pediatric Endocrinologists, providing the list of the original 40 fellows who trained at HLH from 1938-1960, to the over 500 fellows and associates in total when he retired. He describes Lawson’s favorite examination devise, a “phallometer” or 6” ruler used to measure the length of the penis.

Cleveland plays tribute to the legacy Lawson left behind: The Lawson Wilkins Pediatric Endocrine Society that was formed in his honor in, and the subsequent certification process that led to 640 members by 1994.
Dr Claude J Migeon: 1st LWPES President 1972-1973

- Congenital Adrenal Hyperplasia

Claude Migeon joined Lawson in 1955, relating his early years at Harriet Lane Home that was named after a niece of President James Buchanan, who donated the funds to establish the outpatient clinic for ‘invalid children’. He describes the early struggles to develop a treatment for Congenital Adrenal Hyperplasia or CAH, and the first studies using cortisone as a therapy to effectively suppress the adrenal hyper secretion. The first publication in 1950 described the benefits of cortisone therapy in a 15 year-old CAH patient who had been under investigation for 11 years, and who had had a previous right total and left partial adrenalectomy at age 6.

Lawson subsequently published a series of papers, pointing out that each patient had to have careful titration of the cortisone dose to avoid growth inhibition – this remains a therapeutic target to this day. The positive effects described in a series of CAH patients consisted of decreased pigmentation and decrease in blood pressure; in females: onset of breast development and menses in some; in males: testicular growth and progression of normal puberty due to advanced bone age.

Migeon describes the application of the developing field of molecular genetics to gene identification for CAH, and the progress in the study of CAH genetic variants.

Migeon refers to Lawson as a Francophile, using one of Lawson’s favorite quotations: “toujours la même damn dose.”
Blizzard describes his first supposed interview meeting with Lawson in a hotel room (a recurring theme with all of the presenters), with Lawson not speaking with him until he was leaving, saying “I hope to see you again some day”. Happily, Blizzard arrived at the HLH in 1955. He describes Lawson as being frustrated with his inability to accurately diagnose patients with hypopituitarism. In the mid to late 1950’s, GH deficiency was by diagnosed by inference in patients with sexual infantilism, decreased protein bound iodide, insulin sensitivity and inability to excrete water load. Lawson stressed the use of auxology (e.g., linear height and weight measurements, U/L body ratio, and dentition) and the careful charting of all growth parameters.

Blizzard reviews the fact that the first edition of the Wilkins textbook in 1950 had only two paragraphs (142 words) about GH, and 875 words about pituitary dwarfism. These same two paragraphs reappeared in the second edition in 1957. The third edition in 1965, two years after Lawson’s death, first began to discuss pituitary extraction of GH, with an early study trying bovine GH in a patient, which was ineffective. The first patient treated with human GH at HLH was in 1960.

Blizzard describes many patients seen at HLH that were diagnosed with “primordial dwarfism” - a term ambiguous then as it is today. He then describes the first case of GH resistance seen at HLH; she had severe hypoglycemia, but survived, married and had a son with a GH receptor defect – clearly transgenerational proof of principle.

RMB Quotation:
"Lawson lived as a giant, died as a giant, and lives on as a giant".
Dr Melvin M Grumbach: 4th LWPES President 1975-1976
• Gonadal differentiation and Turner syndrome

Grumbach also recalls a hotel meeting with Lawson, in Zurich in 1953, and his eventual arrival at HLH. He describes the first paper on “ovarian dwarfism” published in 1942, and another titled “ovarian agenesis” in 1944, as Lawson initially did not use the term Turner syndrome to describe primary ovarian failure.

Grumbach reviews his establishment of the early detection of sex chromatin at HLH, based upon the work of Murray Barr: i.e., the Barr body, resulting in the publication of his first case of Turner syndrome in 1954. The patient had all of the classic features of the syndrome, including short stature, severe webbed neck, peripheral edema, dystrophic nails, coarctation and poor breast development on subsequent estrogen therapy. He mentions that early studies using GH administration to Turner syndrome patients showed some promise in growth acceleration.

Grumbach follows the advancement in diagnostics of gonadal differentiation that included chromosomal karyotype analysis that demonstrated the 45/X0 karyotype in Turner syndrome; the Lyon Hypothesis of X inactivation; aberrations in XY leading to gonadal dysgenesis; the discovery of SRY protein and the testes determining factor (TDF) on the Y chromosome; and the identification of the “Jost Hormone” – the anti-mullerian factor. He closes with reference to the identification of the androgen receptor – the topic of the presentation by Jud Van Wyk that would follow.
Dr Judson J Van Wyk: 5th LWPES President 1976-1977
  •  From Testicular Feminization to Androgen Insensitivity Syndrome

Jud Van Wyk studied medicine at Hopkins and was influenced by Lawson to eventually join in the “birth of a discipline” in 1953 as a postdoctoral fellow.

Van Wyk was struck by a photo, in the textbook by Talbot et al entitled “Functional Endocrinology”, of a 30 year-old sexually hairless woman with excellent breast development, but no menses and lumps in her groin that proved to be testes following their removal. In a proof of principle study, the patient was instructed to rub androgen creme on her genitals and then to take oral androgens, without any sexual hair development. However, while androgen receptor insensitivity was being discussed by clinicians, this was not accepted by the scientific community because it was too “imprecise” an observation.

Up to 1965, the concept of Testicular Feminization (TF) continued to be challenged. Frank French and Van Wyk, in Chapel Hill, then admitted two patients for metabolic balance studies: one with TF, and one with hypopituitarism taking estrogen. They administered graded does of testosterone to each and the positive anabolic response seen in the hypopituitary patient was not seen in the TF patient.

Finally, the androgen receptor (AR) was purified and the gene was cloned – the last steroid hormone receptor to be cloned. Studies back at Hopkins by Claude and Barbara Migeon identified the gene on the X chromosome near the centromere. What was now required was to demonstrate a defect in the androgen receptor in a patient with the now referred to Androgen Insensitivity Syndrome (AIS), and to explain the phenotypic variations. The three sisters with TF (AIS) in the famous picture in the Wilkins textbook were restudied using molecular biology technology: they all had a point mutation in the AR. Subsequently, it was possible to study the AR in other patients, such as those with prostate cancer.

Van Wyk concluded that the first meaningful description of patients with AIS has stimulated generations of studies in different areas of biology.