Melvin M. Grumbach, MD, 1925–2016

Professor Melvin M. Grumbach, one of the founding members of the (Lawson Wilkins) Pediatric Endocrine Society and its fourth President, passed away on October 4, 2016, at the age of 90 (Fig. 1). Arguably the world's foremost Pediatric Endocrinologist and affectionately known as Mel, he was the Edward B. Shaw Professor of Pediatrics, Emeritus, and former Chairman of the Department of Pediatrics (1966–1986) at the University of California, San Francisco (UCSF). Mel was born on December 21, 1925, in New York City to a family that traced its roots to Alsace. The first in his family to attend college, he excelled academically and received his MD from Columbia University in 1948, at age 22. Arguably the most important event in Mel's life happened in 1950 during his pediatric residency. Mel came back from a vacation to his room at Columbia University's Babies' Hospital only to find a medical student sleeping in his bed; that student was Madeline F. Butt (MD, 1951), whom he married in 1951 and with whom he had 3 sons: Ethan Malcom (born 1953) (PhD, a psychoanalyst), Kevin Lawrence (born 1956) (MD, UCSF, 1985), and Anthony Havermeyer (born 1960) (JD, Harvard, 1993). Following an internship at Mount Sinai Hospital in New York (1948–1949), Mel studied pediatrics at Columbia (1949–1951), then served 2 years as a Captain in the Medical Corps of the US Air

Fig. 1. Melvin M. Grumbach, MD, 1925–2016.

Force (1951–1953). In the Air Force, Mel had the good fortune to be assigned to the Institute of Nuclear Studies at Oak Ridge Tennessee and then to the Biological Laboratories at Fort Detrick Maryland, exposing him to exciting new areas of radiobiology and biochemistry. He obtained fellowship support from the National Foundation for Infantile Paralysis (now known as the March of Dimes) and was accepted into Lawson Wilkins' legendary program in pediatric endocrinology at Johns Hopkins Uni-

versity in Baltimore (1953–1955). At Hopkins he learned clinical pediatric endocrinology from Wilkins and steroid chemistry from Alfred Bongiovanni and Claude Migeon, published 9 papers, and established a life-long friendship with Judson Van Wyk, who had also joined Wilkins in 1953. These early papers foreshadowed much of Mel's later career: 2 papers concerned sex chromatin, 5 concerned adrenal steroids and congenital adrenal hyperplasia, and 1 concerned the classification of "hermaphroditism" (now termed disorders of sexual development, DSD). Although much of the terminology used in 1955 to describe the various forms of DSD has been refined or discarded, this paper correctly defined much of the underlying biology. Four of Mel's papers at Hopkins have been cited over 100 times. A fully referenced version of this Memorial has been published elsewhere [1].

Mel returned home to New York in 1955 to establish Columbia's first pediatric endocrine unit, rising to the rank of Associate Professor by 1961. At Columbia he recruited his first nine fellows, who included Jacques Ducharme, Selna L. Kaplan, Akira Morishima, and Felix A. Conte. A major observation from this time, reported with Jud Van Wyk, was the first description of "hormonal overlap," in which very high concentrations of TSH resulting from hypothyroidism stimulated gonadotropin receptors and caused precocious puberty. These were highly productive times: Mel and his colleagues published 60 papers from his 11 years at Columbia, covering many areas, of which 2 stand out.

First, Mel continued his studies of sex chromatin. Murray Barr in Canada had identified the heterochromatin "Barr body," which was used to establish chromosomal sex via buccal smear cytology. Mary Lyon in Britain as well as Mel Grumbach and Akira Morishima at Columbia University independently showed that the Barr body was an inactivated X chromosome. Mel's work was contemporaneous with Lyon's, but his paper was contributed to the proceedings of a Symposium on Sex Chromatin; although the receipt date was October 25, 1960, it was not published for a year, so X chromosome inactivation is often termed "Lyonization" (besides, no one could pronounce "Grumbachianization"). Morishima, Grumbach, and J. Herbert Taylor in Columbia's Department of Botany then showed that the inactivated X chromosome replicated after the active one, then used tritiated thymidine labeling of DNA to show that one X chromosome replicates at the same time as the autosomes, while any inactivated X chromosome(s) replicated after the one in the euchromatin.

Second, Mel and Selna Kaplan initiated their long-term studies of growth and growth hormone (GH). Selna, a native New Yorker and pediatric endocrine fellow who had obtained a PhD in anatomy while pursuing her MD at Washington University (St. Louis), pursued immunologic approaches to studying protein hormones and spent time at the Bronx Veterans Administration Hospital learning the new techniques of radioimmunoassay from Solomon Berson and Rosalyn Yalow. In 1962, Josimovich and MacLaren reported the existence of a placental "substance" immunologically related to GH that had prolactin-like activity but lacked GH-like activity in various bioassays. Mel, Selna, and John Sciarra, a research fellow in Obstetrics and Gynecology, confirmed that the early-gestation human placental syncytiotrophoblast cells produce a protein that is immunologically related to GH, but also showed that this protein had both prolactin-like and GH activities. At that time they termed this protein "chorionic growth hormone-prolactin" and others have called it "placental lactogen," but this protein is now known as "human chorionic somatomammotropin" (hCS). Multiple later studies showed that hCS is structurally very similar to growth hormone and is encoded by a duplicated GH gene that is only distantly related to the prolactin gene.

In 1966, Mel was appointed Chairman of the Department of Pediatrics at UCSF where he grew a regional clinical program into one of the world's preeminent departments of pediatrics. Mel brought his whole program from Columbia to San Francisco, including Selna Kaplan, Akira Morishima, two lab technicians, his secretary, and a huge pile of stuff on his desk (but Mel always knew where everything was). Morishima brought the karyotyping and cytology, but soon returned to New York, turning this work over to Felix Conte who had re-joined the group in 1970. Selna brought the radioimmunoassay lab and the ultra-sensitive hormonal assays that permitted the investigation of sexual differentiation, growth, and puberty in children. Selna ran the lab and trained fellows in immunoassay technique, permitting work to proceed while Mel ran the Department. Mel once said: "She was the police-woman in our lab, always demanding perfect accuracy and keeping track of every last detail; she was one tough lady." Mel, Selna, and Felix developed a robust population of patients with all manner of nondiabetic endocrine disorders and investigated the relevant hormonal axes in detail. Their early years in San Francisco were remarkably productive. By finding 46,XY karyotypes in some of the lymphocytes of pregnant women, Mel and Felix were the first to show that fetal cells and DNA entered the maternal circulation, permitting diagnosis of fetal sex by the 14th

week of gestation; this study from nearly 50 years ago is still widely cited today. Mel's ability to ask incisive questions, backed up by Selna's sensitive hormonal assays permitted them to delineate the pathophysiology and diagnostic criteria for GH deficiency, the ontogeny of fetal hormones, and the changes in the concentrations of gonadotropins and sex steroids during infancy, childhood, and adolescence. They were the first to use synthetic hypothalamic peptides (releasing factors) to study pituitary disorders in children, showing that most patients with idiopathic hypopituitarism had hypothalamic disease with otherwise normal pituitaries, and permitted a new mode of hormonal diagnosis of hypothalamic/pituitary disorders. Studies of patients with gonadal dysgenesis revealed both a basal and GnRH-stimulated biphasic pattern of gonadotropin secretion along the developmental timespan. They defined the syndromes in which congenital hypopituitarism is accompanied by hypoglycemia and microphallus, in which cranial irradiation causes hypopituitarism, of hypopituitarism caused by child abuse, and the syndrome of familial male-limited gonadotropin-independent sexual precocity ("familial testotoxicosis") (first reported by Schedewie and colleagues), which was later shown to be due to activating mutations of the LH receptor. They described the endocrine sequelae of craniopharyngioma and of pediatric Cushing disease, separated adrenarche from puberty, and proffered the rational use of GH for short stature.

Starting in 1976, Mel and Selna began a series of studies termed "Hormone Ontogeny in the Ovine Fetus," which eventually numbered 27 papers (the last in 1993), each with a sequential Roman numeral. This work was initiated by Peter Gluckman (then a fellow from New Zealand, now Sir Peter Gluckman, FRS) in collaboration with UCSF pediatric cardiologist Abraham Rudolph, who had developed the chronically catheterized fetal sheep system to study fetal cardiovascular physiology. From the mid 1980s to the early 1990s, productivity continued, but not with the same impact as before. However, starting in the late 1970s, Felix Conte had followed a female patient with newborn and progressive genital virilization, hypogonadotropic hypogonadism, and dramatically delayed bone age despite grossly elevated serum androgens but low estrogens; Felix and Mel concluded that she had a new disease, aromatase deficiency, which they described in detail. In collaboration with Evan Simpson in Dallas they found the responsible mutations in the aromatase gene, and soon thereafter with Akira Morishima, his former fellow from Columbia, Mel described the male phenotype of progressive growth and macrogenitosomia

with elevated androgens and delayed bone age, establishing that estrogens, but not androgens, mediate epiphyseal fusion. These studies of aromatase deficiency revolutionized the understanding of the roles of estrogens in bone health. In all, Mel published 389 research papers, reviews, and book chapters. According to the Thompson Web of Science, through January 2017 his work had been cited about 19,000 times and his h-index was 82.

Mel stepped down as Chairman of Pediatrics in 1986 and retired as "Distinguished Professor, Emeritus" in 1994, but remained active academically until December 2014. Mel made a lasting impact on Pediatric Endocrinology. From 1956 to 1990, he supervised the training of 82 fellows from 15 countries on 5 continents. Of these, 42 became Professors, 40 became division chiefs, 14 became department chairs, and 2 became deans. No single individual trained as many leaders or had a broader impact on Pediatric Endocrinology. Mel was a ubiquitous force in academic leadership. He protected the time of young faculty, encouraged them to write papers and grants, fought for lab space, and insisted that clinical presentations be backed up with the relevant science. He was elected President of the Association of Medical School Department Chairs (1973), the Lawson Wilkins Pediatric Endocrine Society (1975), the Western Society for Pediatric Research (1978), the Endocrine Society (1981), and the American Pediatric Society (1989). Mel's research, teaching, and leadership were widely recognized: he received the Endocrine Society's Fred Conrad Koch Lifetime Achievement Award (1992; shared with Selna Kaplan), its highest award; the Lifetime Achievement Award from the American Academy of Pediatrics (1996); the John Howland Award from the American Pediatric Society (1997), and was the first recipient of the Judson J. Van Wyk Prize for Career Achievement from the Lawson Wilkins Pediatric Endocrine Society (2006). He was elected to the Institute of Medicine (1983), the American Academy of Arts and Sciences (1995), and the National Academy of Sciences (1995); he received honorary doctorates from the University of Geneva (1991), the University of Paris 5 (René Descartes) (2000), the University of Athens (2008), and was awarded the UCSF Medal (2010). Outside the hospital, Mel was a devoted father and grandfather who treasured quiet (and not so quiet) time with his family at their second home in Sea Ranch, on the Sonoma Coast, north of San Francisco. Mel was a devoted fan of the San Francisco 49ers and held season tickets from 1966 to 2013 (on the 47-yard line!). He would routinely take faculty, friends, and fellows to games, a major treat for young trainees on a budget, and argued football

vigorously with Felix, a life-long Steelers fan. They would bet 1 dollar on games, and when he lost, Felix would tape a one-dollar bill to Mel's office door (Mel never spent it).

Mel always believed that his legacy was not in the papers he wrote or awards he received, but in the people he taught. He created a vibrant, dynamic Pediatric Endocrine Program and Department of Pediatrics at UCSF. The staying power of this program speaks volumes for Mel. Beyond UCSF, his training of deans, chairs, and chiefs is unequalled; his influence unmatched; his impact all-pervasive. One cannot write the history of Endocrinology without writing of Mel. He was predeceased by his wife Madeline in 2007 and is survived by his brother Lee,

his sons Ethan, Kevin, and Anthony and his 5 grandchildren, Jacob, Matthew, Aimee, Zoe, and Fletcher.

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Reference

- 1 Miller WL: In memoriam: Melvin M. Grumbach, MD, 1925–2016: pediatric endocrinologist, scientist, educator, leader. *Pediatr Endocrinol Rev* 2016;14:96–102.