RETROSPECTIVE

Melvin M. Grumbach 1925–2016

Shlomo Melmed[a,1]

Generations of clinicians have been faced with often striking developmental and acquired hormonal syndromes associated with reproductive, growth, and metabolic phenotypes. These syndromes have included ambiguous genitalia, anomalies of sexual development, intersex forms, accelerated or delayed puberty, gigantism, and short stature. Although clinical phenotypes of these disorders have been well-established, elucidating their pathogenesis remained elusive until the mid-1950s. Drawing on his incisive application of novel diagnostic techniques to study neuroendocrine pituitary control, Mel Grumbach elucidated critical mechanisms underlying both normal physiology and pathogenesis of clinical syndromes, ranging from ontogeny of reproductive and growth axis control circuits, to effects of gonadotropin-releasing hormone (GnRH) pulse generation and timing of puberty onset, to control of adrenal androgen production and virilizing syndromes, to male estrogen receptor mutation sequelae.

Mel, an icon of investigative endocrinology, passed away on October 4, 2016, at the age of 90. Born, raised, educated, and trained as a physician, pediatrician, and endocrinologist in New York, Mel spent the latter 50 years of his stellar career at the University of California, San Francisco (UCSF), where he founded much of the knowledge base for our understanding of endocrine control of human reproductive development and growth. At the onset of his remarkable career of endocrine discovery in the mid-20th century, structural identification of peptide hormones and regulation of pituitary function were yet obscure. Hypothalamic hormonal control of normal and diseased human pituitary function was not yet characterized, assays for measuring hormones in the clinic were not sophisticated and were technically laborious, and mechanisms underlying hormone action mediated by receptor signaling were unknown (1). By the end of Mel's career, he had both intimately witnessed the explosion of hormone discovery and also actively participated in the unprecedented knowledge spurt unraveling genetic and acquired mechanisms for a myriad of endocrinopathies, primarily but not limited to children. Mel created an enduring legacy and comprehensive standard body of scholarship for reproductive development, meticulously describing mechanisms underlying normal human growth and sexual development.

Melvin M. Grumbach. Image courtesy of Susan Merrell (University of California, San Francisco).

Graduating in 1948 from Columbia University, Mel embarked on a remarkable career trajectory in investigative pediatrics, intrigued by the then embryonic specialty of endocrinology. After fellowship training with the legendary Lawson Wilkins at The Johns Hopkins University in Baltimore, Mel was appointed founding director of Pediatric Endocrinology at Babies Hospital in 1955. In 1965, Mel moved to UCSF to chair the Department of Pediatrics, his home for 50 years. He propelled the department to the highest rankings and in 2010 was

[a]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048

Author contributions: S.M. wrote the paper.

The author declares no conflict of interest.

[1]Email: melmed@csmc.edu.

www.pnas.org/cgi/doi/10.1073/pnas.1705693114

the recipient of the UCSF medal recognizing his remarkable career.

Mel could only have dreamed of the extent of our biomedical knowledge base when he embarked on his remarkable 60-year career of endocrine discovery, which culminated in arguably one of the most prolific cluster of scholarly papers defining normal and diseased neuroendocrine development and function in childhood. Mel's publication record spanned the history of modern endocrine discovery and was propelled by wise application and development of several generations of biologic tools for hormone purification and assay.

Mel was the first to define the relationship of sex chromosomes with disorders of sexual development. In 1957, he postulated—based on his early clinical and chromosomal studies—that in the absence of male gonadal development, the fetus develops female accessory sex structures, regardless of chromosomal sex (2). In studying DNA replication in children with endocrinopathies and an "extra" X-chromosome, Mel demonstrated that expression of late-replicating X-chromosomes is in fact repressed, accounting for heterochromatinization and formation of what would be termed the Barr body. Mel hypothesized independently of Lyon that X-chromosome replication and function may in fact be inactivated (3), and yet were required for ovarian development. These studies, coupled with meticulous phenotypic observations, led to the comprehensive understanding of pathogenesis of ovarian dysgenesis syndromes.

In 1958, Selna Kaplan, a pioneer female MD/PhD, joined Mel and subsequently moved with him to UCSF, and this formidable and ingenious scientific partnership endured for over 50 years. The two determined the structure of human growth hormone (GH)-related placental hormones, and applied radioimmunoassay—discovered by Solomon Berson and Rosalind Yalow—to measure circulating pituitary hormones to understand normal and disordered fetal and neonatal development, the temporal cyclicity of hormone rhythms, and to imaginatively explain complex gonadal endocrinopathies with elevated pituitary hormone levels by predicting peripheral receptor mutations as causes of hormone resistance.

For the first time, Mel administered GH, purified by Maurice Raben, to premature infants (4), highlighting then unknown metabolic GH actions. These early studies paved the way for his and colleagues' subsequent large-scale trials, and ultimate approval of appropriately dosed GH as a safe treatment for short stature. In 1969, Mel and Selna published a landmark paper (5) that determined that puberty onset is associated with temporally decreased pituitary sensitivity to sex steroid suppression of follicle stimulating hormone (FSH) and luteinizing hormone (LH) secretion. Their conclusions were compatible with the subsequent discovery of hypothalamic GnRH pulse generation, GnRH receptor mutations, as well as complex peptide regulation of pubertal onset and associated hereditary acquired disorders of sexual development.

Working with Abraham Rudolph, the researchers published a remarkable series of 27 papers from 1979 to 1993, reporting on hypothalamic–pituitary target organ hormone ontogeny in the ovine fetus. Using a unique catheterized model, coupled with the then novel availability of hypothalamic-releasing and inhibiting factors discovered by Roger Guillemin and Andrew Schally, enabled Mel to characterize hypothalamic–pituitary target gland feedback regulation for reproduction, growth, and thyroid axes. He defined exquisite in vivo mechanisms for hypothalamic hormone signaling to specific pituitary cell types, thereby enabling the appropriate regulation of differential hormone synthesis and secretion. These studies defined maternal–fetal and neonatal-negative and -positive control circuits for hypothalamic GH-releasing hormone, somatostatin and pituitary GH, prolactin, LH, FSH, and peripheral sex steroids. This platform series of papers serves as the paradigm for defining fetal neuroendocrine physiology and regulation of pituitary hormone production. Their observations of human temporal pituitary and peripheral hormone expression remain our classic foundational knowledge base for fetal, infant, and childhood endocrinology generally, and specifically for precise timing and regulation of puberty onset (6).

Mel was honored with the most prestigious recognitions bestowed by both his pediatric and endocrinology peers, recognizing his exceptional scholarship and impactful research achievements. The Endocrine Society honored Mel with its highest laureate awards: the Robert H. Williams Distinguished Leadership and the Fred Conrad Koch Awards. Mel was elected to the Institute of Medicine, the American Academy of Arts and Sciences, and, in 1995, the National Academy of Sciences.

I met Mel in 1978 when he was presiding over the annual Clinical Research meetings set in bucolic Carmel, California. At these fertile formative incubators for launching a generation of clinical science careers, Mel was an iconic, charismatic, and spirited leader renowned for asking formidable and persistent questions to untried presenting fellows. His knowledge base was truly encyclopedic, and certainly not restricted to his mastery of pediatric endocrinology. Although he instilled appropriate anxiety and did not suffer fools, Mel's probing and sensitive insights, punctuated with a sparring unlit pipe, usually elucidated a creative path forward for the stressed fellow being questioned publicly. As a committed mentor, Mel was instrumental in training and nurturing the careers of generations of the most distinguished global pediatric and endocrinology leaders.

For many decades Mel was a master of didactic pediatric endocrinology, as exemplified by his most prolific creative writings. The 1968 publication of his first chapter in Williams' *Textbook of Endocrinology* on normal and disrupted childhood hormonal regulation has been updated as a classic masterpiece for no fewer than nine editions over 48 years (6)! As editor, I recall his dining room table strewn with hundreds of reference reprints, and him arguing valiantly to be allowed to exceed 1,000 "absolutely vital" references. His last chapter, published in 2016 with his longtime colleague, Dennis Styne, is a meticulously crafted *tour de force* of the fundamental and clinical spectrum

of complex pubertal physiology and associated phenotypic disorders (7). This monumental work continues to endure as the standard worldwide reproductive development reference.

Mel did not restrict himself to scientific debate. In his 1990 presidential address to the American Pediatric Society, Mel issued a strident clarion call to "let the walls come tumbling down," urging synergy between clinicians and scientists to enable productive translation of discovery to directly impact patient care. With his passionate vision, Mel foresaw that when the next generation looks back on our era of advanced medical practice coupled with scholarly discovery as a common enterprise, "let them say we laid the groundwork for a new Golden Age of child health and well-being," leading to an "unprecedented assault" on disease in general, and for sick children in particular (8, 9). The expert on disorders of sexual development, Mel opined on the contemporary discourse related to gender identity. One of the most anguishing and often urgent clinical decisions facing an endocrinologist is determination of gender assignment in a child born with ambiguous genitalia. Mel stressed that anatomic or physiologic phenotype should not be the sole such determinant and gender identity decisions should include patients, families, and counselors in ultimate assignment or reassignment of gender choices (10). In 1980, with his long-time colleague Walter Miller, Mel published a prescient but frightening study on child-abuse leading to posttraumatic pituitary failure (11), a forerunner of the awareness of insidious growth and reproductive dysfunction arising from childhood head trauma, which drove subsequent child-abuse prevention and care management. These observations continue to inform the current debate on effects of contact sports on long-term pituitary function in children and adults.

As an energetic and accomplished investigator, teacher, clinician, department chairperson, professional society leader, and global torchbearer for children's health and well-being, it was Mel's "style, grace and class" that were instrumental in his peers awarding him the American Pediatric Society John Howland Award in 1997, as lauded by his long-time colleague Larry Shapiro (9). In his Presidential address to the Endocrine Society, Mel, in extolling Herbert Evans—who had discovered GH—cited Arthur Koestler: "The principal mark of genius is not perfection but originality—the opening of new frontiers." Mel Grumbach, by all accounts, was such an original genius, opening new frontiers of translational endocrinology for generations of physicians, scientists, and most importantly, young patients.

Acknowledgments

I thank Larry Shapiro for critical reading of the manuscript.

1 Melmed S (2016) Pituitary medicine from discovery to patient-focused outcomes. *J Clin Endocrinol Metab* 101:769–777.
2 Grumbach MM (1957) Chromosomal sex and the prepuberal diagnosis of gonadal dysgenesis. *Pediatrics* 20:740–746.
3 Grumbach MM, Morishima A, Taylor JH (1963) Human sex chromosome abnormalities in relation to DNA replication and heterochromatinization. *Proc Natl Acad Sci USA* 49:581–589.
4 Grumbach MM, Ducharme JR (1960) The effects of androgens on fetal sexual development: Androgen-induced female pseudohermaphrodism. *Fertil Steril* 11:157–180.
5 Kulin HE, Grumbach MM, Kaplan SL (1969) Changing sensitivity of the pubertal gonadal hypothalamic feedback mechanism in man. *Science* 166:1012–1013.
6 Van Wyk JJ, Grumbach MM (1968) Disorders of sex differentiation. *Textbook of Endocrinology*, ed Williams RH (WB Saunders Co., Philadelphia), 4th Ed, pp 537–613.
7 Styne D, Grumbach M (2016) Physiology and disorders of puberty. *Williams Textbook of Endocrinology*, eds Melmed S, Polonsky S, Larsen PR, Kronenberg HM (Elsevier, Philadelphia), 13th Ed, pp 1074–1218.
8 Grumbach MM (1990) American Pediatric Society Presidential Address at the 100th annual meeting: Let the walls come tumbling down. *Pediatr Res* 28:562–566.
9 Shapiro LJ, Grumbach MM (1997) American Pediatric Society John Howland Award 1997: Presentation and acceptance. *Pediatr Res* 42:902–908.
10 Wilson JD, et al. (2012) Advice on the management of ambiguous genitalia to a young endocrinologist from experienced clinicians. *Semin Reprod Med* 30:339–350.
11 Miller WL, Kaplan SL, Grumbach MM (1980) Child abuse as a cause of post-traumatic hypopituitarism. *N Engl J Med* 302:724–728.