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American Pediatric Society's 2011 John Howland Award Acceptance Lecture: Lessons From Models of Disease

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I thank you deeply for the honor of this award, the highest of the American Pediatric Society. To receive the John Howland Award is both an exhilarating and a humbling experience. This honoree recognizes that he has worked and collaborated with hundreds of extraordinary pediatricians in an effort to improve child health. From my first pediatric teachers to the latest group of interns and residents in our program—all have influenced me over the past 47 y of my career in pediatrics. This journey with bright, curious, often brilliant and highly accomplished pediatricians has brought joy to my life.

Careful mentoring is a prerequisite for an academic career. I have been incredibly fortunate to be exposed to nine former Howland Awardees (Table 1). These teachers were able to focus on large problems and stimulated their trainees' curiosity. They asked big questions. Other Howland recipients encountered along the way also have had great influence on this journey in pediatrics. We share a passion for the enhancement of childhood and child health status for our patients and, indeed, all children. However, today I have not chosen to focus on legislative activities that improve the status of children; on systems biology that better explain infection, inflammation, congenital anomalies; and on the molecular biology of health and disease. Also, I will not discuss the process of pediatric education. Instead, this talk will concern the use of animal models of disease by several previous Howland Awardees to illuminate the pathogenesis and therapy of important conditions in children.

For a number of years, I have had an interest in Dr. John Howland, one of the first and most successful academic pediatricians. John Howland was a direct descendant of a Mayflower passenger who not only survived the first cold winter of 1620–1621 but also shared the same name. John Howland, the descendant, built a Department of Pediatrics in the Harriet Lane Home of the Johns Hopkins Hospital. He emphasized the clinician scientist, research questions relevant to patients, and the actively engaged mind. His disciples left and spread out to build many other Departments of Pediatrics across the United States (1).

Many of these teachers and many Howland awardees stressed the critical importance of the science of nutrition to accomplish optimal growth and development of the child. Several of these scholars, including several of my teachers, were experts on the pathogenesis and treatment of rickets and on the factors that influence bone health. Rickets is a disorder of the growing child with a still remarkable prevalence a century after its "cure" (2). We rediscover rickets every generation (3). Vitamin D has been said to be the "hot" vitamin of the 21st century (4). However, before understanding the role of vitamin D (a fat-soluble secosteroid that can both treat and prevent rickets), the importance of nutrition, sunshine, and mineral balance had to be demonstrated in well-designed dietary studies in animals. In essence, this concept of an animal model of a disease (rickets) was exploited by a number of Howland recipients, including my teachers (Table 2).

Now let us examine these Howland Awardees and their roles in the elucidation of rickets. The first obvious academic leader was John Howland himself (1). Elmer V. McCollum, the discoverer of vitamin D, left the University of Wisconsin in 1917 to take up a position in chemistry at the Johns Hopkins University and its School of Public Health (5). McCollum was the first to use the albino rat in growth studies. He, John Howland, and Edwards A. Park—the first Howland awardee—developed a highly effective Baltimore-based collaboration. They used the white rat to develop an animal model of rickets. They demonstrated the importance of minerals and a substance found in cod liver oil that was not vitamin A (6,7). They could create and then cure and/or prevent rickets in accordance with dietary interventions (8). Howland and Park then translated their findings to children with rickets and announced a "cure" (9). Grover Powers was a collaborator in several of these studies (10). These studies and others led to the supplementation of dairy products with 400 IU of vitamin D per liter and a marked decline in the prevalence of rickets (11–13).

The Harrisons—Harold and Helen—were gifted scholars who studied the physiologic and biochemical roles of vitamin D in mineral balance. Harold Harrison was the attending physician and my clinical mentor when I was at the National Institutes of Health, and both he and Helen became friends. I was fortunate to have stimulating lunches with one or the other in the doctors' dining room at John Hopkins and the Baltimore City Hospital. Teaching several generations of trainees, Dr. Harold Harrison was a superb diagnostician whose ward rounds were like a Sherlock Holmes performance.

The Harrisons' experiments were well designed to answer the questions posed. They used growing rats and chicks to

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Table 1. *Howland awardees who mentored Russell Chesney*

Helen Taussig
Harold Harrison
Helen Harrison
Barton Childs
Robert E. Cook
Gilbert Forbes
Robert J. Haggerty
Mary Ellen Avery
Charles R. Scriver

Table 2. *Other Howland awardees investigating rickets*

Grover F. Powers	Sunshine and ultraviolet light in rickets
Martha M. Eliot	Incidence of rickets in children in New Haven, CT
Irwin McQuarrie	Photoactivity of substances curative of rickets
Julius Richmond	Clearance of phosphate in infants and children
Alan M. Butler	Hypophosphatemic rickets and renal tubular acidosis

show that vitamin D would, over time, play a role in the gastrointestinal absorption of both calcium and phosphate (14–17). This substance in conjunction with PTH could also affect the renal handling of both divalent minerals (15,16). These findings were applied to the treatment of hereditary forms of rickets, including of X-linked hypophosphatemic rickets. Harold Harrison described and devised a therapy for both autosomal recessive and autosomal dominant hypophosphatemic rickets (18,19). We are now aware that autosomal dominant hypophosphatemic rickets is due to a mutation in fibroblast growth factor-23 (FGF-23) (20).

Gilbert Forbes, at the University of Rochester, was an essential career advisor. He was a brilliant scholar who strove to understand bone. His Howland Award was for his distinguished research career and his phenomenal insights into the structure and formation of bone. The scope of his knowledge of mathematics and mathematical modeling was breathtaking. Forbes performed some of the key studies of the role of sodium, along with other minerals and ions, on the growth of bone in rats (21,22). He exploited the radiation biology facilities at Rochester to perform clearly designed isotopic studies of bone (21). Forbes was also interested in the problem of muscle weakness in rachitic children (23). He and his colleagues were among the first to describe the rickets and osteomalacia associated with chronic anticonvulsants (24,25).

Charles R. Scriver at McGill, last year's winner of the Howland Award, always thought "outside the box." I have described his wonderful imagination and ability to perceive downstream consequences and events that would result in large-scale change (26). He recognized that an accident of nature, detected in the PHEX HyP mouse at the Jackson Laboratory in Bar Harbor Maine, could be a murine model for X-linked hypophosphatemic rickets (27). Studies using this strain illuminated the pathophysiology, hereditary pattern, therapy, and prognosis of this most common form of inherited rickets in man. His clinical contributions were to create a logical and refined therapeutic strategy for hypophosphatemic rickets in infants and children (28). He was a pioneer in the use of 1,25-$(OH)_2$vitamin D in several forms of hereditary rickets (29,30). He used his public policy skills to have vitamin D supplements added to the milk supply in Quebec (26).

Table 3. *Comparison of fat, vitamin D, and taurine levels in polar bear milk and in formula given to hand-reared puppies*

	Polar Bear Milk	Formula
Lipid	35%	6%
Vitamin D	600–700 IU/L	400 IU/L
Taurine	3171 μmol/L	120 μmol/L

Here, I describe a new animal model of rickets; namely, the polar bear cub hand-reared in captivity (31,32). I fear that it is presumptuous to describe this form of rickets, especially in light of the first rate minds of the Howland Awardees who studied animal models and human children with various forms of this disorder. However, one can "stand on the shoulders" of these luminary figures (33). Captive polar bear cubs must be reared by hand if the sows die or show cannibalistic tendencies (34). Because of the remarkable growth rate of a polar bear cub, which weighs 600 g at birth and 100 kg by 1 y of age (Table 3), this species could serve as a model for the calcium, phosphate, and vitamin D nutrition of the very LBW preterm human infant (31). Indeed, previous models did not examine this age and weight group.

The first cub hand-reared was named Pike, meaning "little girl," who was fed a cow milk-based formula. Gail Hedberg of the San Francisco Zoo is an expert on hand-rearing large mammals (35). She used a formula that she knew was designed for canine pups. From her experience in rearing exotic felines (tigers and lions), she was aware of the dietary requirement for taurine in amounts greater than those required for dogs and cows. The rachitic and nonrachitic polar bear cubs were receiving formulae with two different taurine contents. Plasma taurine values in several cubs were low (34).

We surmised that the normal diet of free-ranging polar bears would provide a high dietary intake of taurine and that the canine formula might not provide sufficient taurine to accomplish conjugation of bile acids. All bile salts in polar bears are conjugated (esterified) with taurine and can never be glycine-conjugated (36). We collected milk from lactating dams in the wild to assess composition. The milk from 16 dams contained higher levels of fat, more vitamin D, and, in particular, more taurine than is found in formula (Table 3). This is likely due largely to the diet of polar bears, which consists of artic marine seals, whales, and fish. The hepatic and adipose tissue of these animals contain remarkably high levels of these dietary constituents, as well as vitamin A.

Our hypothesis is that significant quantities of taurine are needed to conjugate bile acids, especially ursodeoxycholic acid. Tauroursodeoxycholic acid will then permit absorption of vitamins A and D, thus preventing rickets. The taurine level in polar bear milk is at least 30-fold higher than in formula. By contrast, vitamin D concentration is only 1.5-fold higher. There exist many other differences among polar bear milk, human milk, and cow milk, especially in terms of protein content, carbohydrate type, and amount and percent fat (32).

Not only is taurine necessary for the absorption of fat-soluble vitamins, but fat-soluble vitamins may influence the

sodium chloride-dependent taurine transporter (TauT) abundance and activity. A decade ago, our laboratory cloned the full-length rat and human taurine transporter gene (*TauT*) (37) and explored the sites in the promoter region where transcription factors, oncogene products, cell cycle-related proteins, and hormones could bind. We found that these factors, including p53, cJun, *WT1*, estradiol, SP1 binding sites, and lengthy CG repeats, either promote or repress the transcription of *TauT* (38).

Does the *TauT* gene have a vitamin D response element (VDRE)? The vitamin D hormone functions after binding to a vitamin D receptor (VDR) and is closely related to the retinoic acid and thyroid hormone superfamily (39). The RXR is a type of nuclear receptor that is activated by both all-*trans* retinoic acid and 9-*cis* retinoic acid (40). There are three RXRs: RXR-α, RXR-β, and RXR-γ, encoded by the *RXRA*, *RXRB*, *RXRG* genes, respectively. RXR heterodimerizes with subfamily 1 nuclear receptors, including RAR, thyroid receptor (TR), and VDR (41). Upon activation by vitamin D, the VDR forms a heterodimer with the RXR and binds to hormone response elements on DNA, resulting in expression or transrepression of specific gene products (41). In humans, the vitamin D receptor is encoded by the *VDR* gene.

When cultured renal cells were coincubated with 1,25-$(OH)_2$ D_3 alone, no change in gene reporter activity occurred. Preincubation of LLC-PK1 cells (of renal proximal tubule origin) with either all-*trans* retinoic acid or 9-*cis* retinoic acid increased *TauT* promoter activity significantly. Coincubation with 1,25-$(OH)_2$ D in addition to retinoic acids increased promoter activity even more. Incubation with either of the retinoic acid isomers and 1,25-$(OH)_2$ D_3 increased uptake of taurine by LLC-PK1 cells in culture. Moreover, a Western blot using antibody to the taurine transporter showed increased protein abundance in the LLC-PK1 cell membranes. Is it possible the substantial concentrations of vitamins A and D in polar bear milk may promote taurine transport across epithelial surfaces?

The ultimate proof of concept will depend on how well the milk composition of free-ranging polar bears can be adapted to a relevant captive rearing milk formula. As the habitat of the polar bear shrinks, more cubs will be raised in captivity (42). Some of these bears will be reared with formulae. If rickets can be prevented, this will represent another animal model with a lesson for pediatricians and students of nutrition. To the old adage——cow milk is for cows and human milk is for humans—we can add, polar bear milk is for polar bears.

In closing, I want to acknowledge the gratitude I feel by thanking those who recommended me for this award. I appreciate the support of those universities who provided the opportunity for teaching, clinical care, and scholarship: The University of Wisconsin, Madison; The University of California, Davis; and particularly, The University of Tennessee Health Science Center, Memphis. Over the past 23 y, I have been fortunate to interact with two children's hospitals: St. Jude Children's Research Hospital and the flagship of our department, Le Bonheur Children's Hospital. I appreciate my interactions with house staff, fellows, and faculty members. I name three important colleagues: Xiaobin Han, MD, PhD, my laboratory compatriot; Andrea Budreau Patters as my able scientific and editorial magician; and Karen Willard, who told me what to do next and where to go.

My family, including my children, Karen, Chris, and Gillian, and my grandchildren, Will and Eleanor, have been the consuming joy of my life. Finally, I met Joan Cook as an intern in 1967, and we have been a wedded couple for 43 y. We have supported, sustained, and advised each other for more than four decades, and much of any success I have had has depended upon her support.

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