GROVER POWERS LECTURE

Four Children and Yale: The Making of a Human Geneticist

The Grover Powers Lecture 2014

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Dr. Leon E. Rosenberg delivered the following presentation as the Grover Powers Lecturer on May 14, 2014, which served as the focal point of his return to his “adult home” as a Visiting Professor in the Department of Pediatrics. Grover F. Powers, MD, was one of the most influential figures in American Pediatrics and certainly the leader who created the modern Department of Pediatrics at Yale when he was recruited in 1921 from Johns Hopkins and then served as its second chairman from 1927 to 1951. Dr. Powers was an astute clinician and compassionate physician and fostered and shaped the careers of countless professors, chairs, and outstanding pediatricians throughout the country. This lectureship has continued yearly since it first honored Dr. Powers in 1956. The selection of Dr. Rosenberg for this honor recognizes his seminal role at Yale and throughout the world in the fostering and cultivating of the field of human genetics. Dr. Rosenberg served as the inaugural Chief of a joint Division of Medical Genetics in the Departments of Pediatrics and Internal Medicine; he became Chair when this attained Departmental status. Then he served as Dean of the Medical School from 1984 to 1991, before he became President of the Pharmaceutical Research Institute at Bristol-Myers Squibb and later Senior Molecular Biologist and Professor at Princeton University, until his recent retirement. Dr. Rosenberg has received numerous honors that include the Borden Award from the American Academy of Pediatrics, the McKusick Leadership Award from the American Society for Human Genetics, and election to the Institute of Medicine and the National Academy of Sciences.

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Editors’ note: The Introduction was written by Dr. George Lister, Chair of Pediatrics at Yale School of Medicine and Physician-in-Chief of Yale-New Haven Children’s Hospital.
INTRODUCTION

Dr. Leon E Rosenberg delivered the following presentation as the Grover Powers Lecturer on May 14, 2014, which served as the focal point of his return to his “adult home” as a Visiting Professor in the Department of Pediatrics. Grover F. Powers, MD, was one of the most influential figures in American Pediatrics and certainly the leader who created the modern Department of Pediatrics at Yale when he was recruited in 1921 from Johns Hopkins and then served as its second chairman from 1927 to 1951. His legacy, marked by many awards and a dedication in the Yale Journal of Biology and Medicine [1] was embodied in his facility to impart his skills as an astute clinician and compassionate physician and his renowned capacity to foster and shape the careers of countless professors, chairs, and outstanding pediatricians throughout the country. This lectureship has continued yearly since it first honored Dr. Powers in 1956.

The selection of Dr. Rosenberg for this honor recognizes his seminal role at Yale and throughout the world in the fostering and cultivating of the field of human genetics. Dr. Rosenberg began his long-standing relationship with Yale as a Senior Assistant Resident in Internal Medicine in 1962. He shuttled back to the National Institutes of Health (NIH), where he started his research career, and then returned in 1965 as a member of the Yale faculty, where his stellar career flourished. In 1968, he served as the inaugural Chief of a joint Division of Medical Genetics in the Departments of Pediatrics and Internal Medicine; he became Chair when this attained Departmental status. Then he served as Dean of the Medical School from 1984 to 1991, before he became President of the Pharmaceutical Research Institute at Bristol-Myers Squibb and later Senior Molecular Biologist and Professor at Princeton University, until his recent retirement. Early in his career at Yale, he, in conjunction with Joe Coleman and Bill Konigsberg, created the most compelling and exciting of courses on the molecular basis of disease, which surely inspired and shaped the career of generations of medical students. The pursuit of the unknown to solve vexing problems in patients was infectious and instructive and one of the highlights of the Yale curriculum. This passion is epitomized by the stories told in this article. The fellowship he developed in Genetics was equally as important as Yale developed a gravitational pull for talented young investigators worldwide to launch their careers.

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Thank you George, for that most kind and generous introduction and for the honor of delivering this year’s Grover Powers lecture. It’s good to be home again — not my boyhood home in which I was raised, but my adulthood home which raised me. Thomas Wolfe was wrong. You can go home again — as long as you’re willing to contend with the mixture of feelings that accompany each visit.

I didn’t know Dr. Powers in the usual sense. I never shook his hand or heard his voice or watched him examine a sick child. But I was aware of his presence throughout my years at Yale. On many occasions, I viewed his portrait that hung outside the offices of the Department of Pediatrics. I visited Southbury Training School for the intellectually disabled that he helped found and sustain. I recall many previous Powers’ lecturers: respected scientists, like Dan Darrow; role models, like Barton Childs; dear friends, like Joe Warshaw. I have read some of the wise words Powers uttered here about gratitude to his colleagues and about the privilege and responsibility of being a Yale physician.

My connection to Grover Powers feels even more palpable today. He devoted him-
self to the health and welfare of children and to Yale. As is obvious from the title of my talk, “Four Children and Yale: The Making of a Human Geneticist,” I, too, want to talk of children and of Yale: of four children who were the inspiration for my research; of Yale, where my career reached its apex. I had intended to frame these subjects in the form of a standard mini-autobiography, that is, a detailed chronologic account: how I became a physician-scientist in Genetics; what scientific discoveries my many colleagues and I made; why I say that sick children and Yale were central actors in the arc of my professional drama.

But I jettisoned this plan for two reasons. First, because I’ve said and written my story that way before and can provide links to those of you interested in it. Second, because I realized that I hadn’t paid attention to the two cardinal questions any lecturer should ask in preparing his remarks: What has the audience come to hear, and what has the speaker come to say.

Those of you who are Generation Xers or Millennials are more likely here to find out if this living legend (so-called) can still say anything at all. To you, I offer some words by Henry Wadsworth Longfellow: “Age is opportunity no less than youth itself, though in another dress. And as the evening twilight fades away, the sky is filled with stars invisible by day.”

Those of you in the two or three pre-X generations are more likely here in the hope that I’ll finally reveal why in the world I chose to leave the light side — academia — for the dark side — industry. To you, I offer some words by Bob Dylan: “Ah, but I was much older then, I’m younger than that now.”

So much for the audience. What about the speaker? I know what I have come to say. In the spirit of Pediatric Grand Rounds, I want to say that with the privilege of doing research on children comes a special obligation to care for and about them. I want to say that research initiated at the bedside of sick people can be as seminal as that begun in the laboratory. I want to say that research-intensive schools of medicine, even those as fine as Yale, must now find yardsticks other than unlimited growth to assess their performance and sustain excellence. I want to say that my current wide-angle life-lens takes in things that my former telephoto lens could not.

Four sick children, ranging in age from 8 months to 11 years, marked my path as a physician-scientist. As I tried to ferret out their medical secrets, each of them, in turn, taught me different things about the uncommon value of studying uncommon disorders — and about the ethos of science. Here’s what I mean.

I met a 9-year-old boy named Steven in 1960. He had volunteered to be investigated at NIH’s clinical center: a 14-story-tall research hospital on the campus of the NIH in Bethesda, Maryland. I was a first-year fellow there on The Metabolism Service of the National Cancer Institute, desperately trying to find out if I belonged there, or for that matter, anywhere in research. My transition from medical residency at Columbia Presbyterian Hospital in NYC to research fellow had begun dismally. I had refused to undertake an hypothesis-lacking, data-mining project proposed by a hapless supervisor and had come to the conclusion that I didn’t have the “right stuff” to be a researcher, that I should retrace my steps to clinical medicine — something I had become good at. I told the head of the service, Nathaniel Berlin, that I wanted to transfer from NIH to some other part of the Public Health Service — perhaps an Indian Reservation. He agreed with my assessment of the project and the supervisor, but not with my decision to leave. He said I should look around before deciding that research wasn’t for me. After wandering around the NIH for a few months in an unsuccessful search for a project, I bumped into Steven (Figure 1). He looked like a survivor of a concentration camp or a famine: almost non-existent skeletal muscles in his arms, legs, and rib cage; difficulty breathing and walking because of profound muscle weakness. As shown on the left, Steven had been entirely healthy until about age 5, and then his muscles had begun to “melt away.” Remarkably, an older brother and sister had a clinical presentation identical to Steven’s and had died of respiratory
failure at the end of their first decade. The only chemical abnormality we found in Steven was a marked and generalized increase in amino acids in his urine. I combed the literature but found no description of cases like his. I could only watch as he died at age 11 of respiratory and right heart failure.

Steven sparked my hitherto-absent fascination with familial disorders, hence with genetics. He awoke my curiosity about amino acid transport. He led me to my first, and only, research mentor: Stanton Segal, in whose laboratory I experienced a eureka moment that moved my career vector toward research where it has been ever since. Finally, Steven represents an unsolved mystery, the medical equivalent of a “cold case.” If he had been born after completion of the Human Genome Project rather than 50 years before it, we very likely would have found out the nature of his disorder in 1 month — maybe less — by sequencing his genome and finding a mutation.

By the end of my 4-year-long association with Segal and NIH, I had come to several conclusions. I intended to be a physician-scientist who derived his research questions from seeing patients. I intended to join the then tiny band of MDs who called themselves medical geneticists. I intended to become a faculty member at a medical school devoted to all of its central missions — research, education, clinical service.

Having decided to leave NIH, I searched for a place to go. Three opportunities presented themselves. The chair of Medicine at Einstein College of Medicine in New York invited me for a job interview. He said he was not looking for a geneticist, but wondered whether I’d like to become a dermatologist. That quickly narrowed my opportunities to two: the University of Buffalo and Yale. Buffalo’s offer was attractive: a young department, a hefty increase in salary, two spacious laboratories, and generous start-up funds. Yale’s offer paled by comparison: a hefty decrease in salary, a single laboratory, and modest start-up funds. Yet I chose Yale, largely because of my admiration for Paul Beeson, the chair of Medicine at the time and one of the country’s acknowledged leaders of academic medicine. He recruited me by quietly suggesting that I had a much better chance of succeeding at this elite school than at one just getting off the ground.

Permit me a brief flashback. Three years earlier, I had taken a year away from NIH to complete my medical residency here so that I could become board-eligible. One particular vignette has remained with me.

It involved Frank Epstein, a full professor in the department of medicine and a leading nephrologist. He had wanted me to expand my interests in membrane transport to salt and water — and become a nephrol-
ogist. When I demurred, saying that I intended to specialize in medical genetics, he glowered and said, “Medical genetics; there is no such field.” Few would have disagreed with him at the time. I barely knew myself the names of the field’s pioneers (Barton Childs, Harry Harris, Kurt Hirschhorn, Victor McKusick, Arno Motulsky, James Neel). But I believed that the excitement being generated in molecular genetics would soon extend to the clinical world. If that belief had been erroneous, I wouldn’t be standing here today — would I?

Now, back to 1965. As luck would have it, just as I was preparing to leave NIH, Bee-son was preparing to leave Yale for Oxford University and the prestigious Nuffield professorship. I expressed to him my misgivings about coming to Yale as he was leaving it. He said, “I didn’t recruit you, Yale did.” Not truly reassured, I came anyway.

Let me try to paint in words a tableau of taking up my Yale faculty appointment. Picture me moving my family (we now had three children) into our own house, one proximate to good public schools in Hamden; being the first occupant in the barely finished LCI building, which had been designed by a well-known local architect who had forgotten to plumb the building with running distilled water; competing successfully for a research project grant and a career development award from NIH; recruiting a veritable odd couple of capable technicians and two MD postdoctoral fellows, Louis Elsas from Medicine and Richard Hillman from Pediatrics; and continuing to study renal and intestinal transport of amino acids and sugars.

But, within 1 year of arriving, another chance encounter changed my research direction and my departmental orientation. We had set up a method for separating and identifying amino acids in urine using paper electrophoresis and had begun offering it as a service to patients being screened for metabolic disorders. Almost as soon as we began such screening, we received a sample from the Child Study Center obtained from an 11-year-old boy with the diagnosis of autism. To our surprise, the urine contained a large amount of homocystine, an amino acid only recently shown to accumulate in an autosomal recessively inherited disorder named homocystinuria, which was characterized clinically by developmental delay, behavioral abnormalities, and (most prominently) dislocated optic lenses.

I arranged to see this boy named Dana (Figure 2). Sure enough, both of his lenses had been removed because they were so severely dislocated that they impeded his vision. Sadly, post-operative complications had left him blind. His parents said he had no friends and spent his days listening to music. He walked stiff-legged and had such a severe speech defect that his words were barely intelligible. I was so intrigued by him that I became his physician. He would come to the outpatient clinic with both his parents and begin each visit by hugging me, shouting his unique rendition of my name over and over, and demanding that we take a walk in the clinic’s corridor, hand in hand. Our mutually pleasurable relationship was also appreciated by his parents because I was able to assuage their profound guilt by convincing them that Dana’s condition was genetic and was not caused by their having drunk a bit too much wine on the night he was conceived. I followed Dana for several years before he was placed in a residential facility.

This time, our pathway of research went from screening laboratory to patient to investigative laboratory. We confirmed that his condition was caused by deficiency of cystathionine B-synthase (CBS), a vitamin B6-requiring enzyme in the sulfur amino acid pathway, thereby focusing my attention on reactions catalyzed by enzymes and coenzymes. Margretta Seashore, a postdoctoral
fellow then, identified two other patients with homocystinuria whose homocystine blood levels fell when they were given supplements of vitamin B6, thereby introducing us to the therapeutic potential of vitamins in metabolic disorders. I dismissed the diagnosis of autism at the time, but realize now that homocystinuria should be added to the growing list of single gene disorders that result in the characteristic triad of findings referred to as the autism spectrum. It is becoming clear that hundreds of genetic mutations and environmental insults may produce disturbances in synapse formation, brain plasticity, and neuronal connectivity whose final path is the frighteningly common syndrome called autism. Finally, interaction with Dana led to an appreciation on my part that Pediatrics was where clinical genetics was then centered and where I might make a greater impact than in Medicine.

So I asked Phil Bondy, the chair of Medicine, what he thought about my trying to get a joint appointment in Pediatrics. Bondy endorsed the idea and referred me to Dave Cook, the chair of Pediatrics. Cook was intrigued and pointed out that there was plenty of precedent for internists tilting toward children: Charles Janeway and David Nathan at Harvard; Kurt Hirschhorn at NYU; Dorothy Horstmann and George Miller at Yale. He understood my misgivings about not having had any formal house staff training in pediatrics, but didn’t see that as a great barrier. Other faculty in Pediatrics felt differently. One suggested that good fences made good neighbors. Another more directly advised me to stay where he thought I belonged. Nonetheless, Cook prevailed and offered me the appointment I sought. In retrospect, this may have been the single most important event in my career. Why? Because this move allowed me to make — in very short order — the two most important scientific discoveries of my scientific life. Both began at the bedside of gravely ill children. I’ll tell these stories sequentially, though, temporally speaking, they occurred in parallel.

One began almost as soon as I joined Pediatrics in 1968. I was asked to consult on a 20-month-old girl named Lorraine, who had been admitted to the pediatric ICU in deep coma. Her mother said she had been well for most of her life, but in the weeks before her admission had begun to stagger “like she was drunk,” even to falling over. Peter Huttenlocher, an astute pediatric neurologist, ordered a large battery of laboratory tests seeking to identify the cause of her coma. All test results were normal except one: her blood ammonia was sky high — in fact, the highest ever seen by the hospital’s laboratory. Huttenlocher asked me to see Lorraine, because he knew of my interest in metabolic disorders.

By the time I saw Lorraine, her blood ammonia had decreased markedly and she had begun to awaken, thanks to the efforts of house officers who had treated her with intestinal and peritoneal lavage and IV dextrose. She was bright and beautiful (Figure 3). In the absence of any other manifestations of liver failure, we asked ourselves what had caused her dramatic ammonia intoxication and would it happen again. We answered both questions as follows. As we slowly and carefully increased her dietary protein, her blood ammonia became elevated again, indicating that the cycle of reactions by which ammonia is converted to urea was impaired. Then, we assayed each
of the five enzymes in a biopsy specimen of her liver and found that one enzyme, ornithine transcarbamylase (OTC), was markedly deficient, whereas the four others were normal. This suggested a genetic defect of OTC, a hypothesis confirmed by a fellow in our group, Elizabeth Short, who performed ammonia tolerance tests in controls and in Lorraine’s parents. Her father’s test was normal; her mother’s distinctly abnormal. We were confused because we would have expected both parents to show abnormal results if they were carriers for an autosomal recessive trait.

Then we got a lucky break. I was interviewing Lorraine’s mother before a group of medical students in a course entitled “Biochemical Mechanisms of Disease” that I taught with Joe Coleman and Bill Konigsberg. I took a brief family history from her — as I had done several times before. Did anyone else in the family have a problem like Lorraine’s, I asked. As before, the answer was “no.” Then, as an afterthought, Lorraine’s mother said, “I don’t think I’ve ever mentioned that I had two sons and three uncles on my mother’s side who died before they were 1 week old.” For a moment, I was speechless — an uncommon occurrence for me, as many of you know. The proverbial light bulb of understanding had just been turned on brightly. OTC deficiency had to be an X-linked trait: it profoundly affected males, modestly or moderately affected females. This hypothesis was soon confirmed by another unfortunate New Haven couple who had four sons in a row die in the NICU, the last being shown to be hyperammonemic and to have zero OTC activity in hepatic tissue obtained at post-mortem. The story I’ve just told took a bit more than 1 year to unfold, but this was just the beginning.

Diagnostic and therapeutic advances followed. Margetta Seashore and another postdoctoral fellow, John McReynolds, showed that females with partial OTC deficiency could be treated successfully with a low-protein diet. Males with complete OTC deficiency were destined to die without, as shown years later, liver transplantation performed as early as 1 month of age. We learned that OTC deficiency could be diagnosed prenatally by genotyping fetal cells obtained from amniotic fluid. Lastly, we were responsible for adding hyperammonemia to the differential diagnosis of coma in neonates.

The work in the laboratory was as consequential as that in the clinic. I realized that we couldn’t address all the questions we were posing without broader scientific expertise. So I recruited not one but three superb PhD biochemists: Franta Kalousek, Wayne Fenton, and Jan Kraus. Together, we constituted a strong team that stayed together for nearly 2 decades. Our lab succeeded in purifying human OTC to homogeneity; in making a monospecific antibody to it; in demonstrating that OTC was synthesized as a precursor bearing a cleavable leader peptide (i.e., a zipcode) that directed it to mitochondria; and in cloning OTC’s gene and sequencing it. It was exhilarating to climb the scientific mountain from clinical phenotype to genotype. Art Horwich, then a fellow, determined the amino acid sequence of the leader peptide and demonstrated that it was necessary and sufficient to enable import by mitochondria. I needn’t tell this audience of Art’s subsequent extraordinary, prize-winning work on chaperone proteins. What were the broad lessons learned here? I can distill them to four: revelations from a family history; gender-dependent treatment; fundamental insights from clinical investigation; and versatility of a multidisciplinary team.

On many occasions, I’ve pointed out that I would have been fortunate indeed to have made one contribution of the kind that began with Lorraine. Yet, my good fortune was doubled within 1 year in the person of an 8-month-old boy named Robby (Figure 4). Again the story began at the bedside of this comatose child, whose neurologic status had deteriorated over a period of weeks. His coma resulted not from hyperammonia, but from profound ketoacidosis. Robby’s blood pH was 6.9 on admission. He survived only because an astute Pediatrics resident had treated him quickly with very large amounts of bicarbonate. Again the question: What had
caused his life-threatening ketoacidosis? After ruling out diabetes and some kind of exogenous poison, we were stumped.

By chance, I had just read a paper by Norwegian pediatricians describing a child who died in coma resulting from a previously unreported condition characterized by accumulation of a dicarboxylic acid named methylmalonic acid (MMA). MMA is an intermediate in the metabolism of several amino acids and fatty acids, and it is rapidly transformed to succinate in mitochondria by a mutase enzyme. “Let’s test Robby’s urine for MMA,” I exclaimed to my postdoctoral fellows. They had better things to do, I was told. They thought I was preparing to go off on a rather silly fishing expedition or zebra-hunt. Undeterred, I decided to follow my hunch myself and, with the expert assistance of a technician named Anne Lilljequist, set up the assay for MMA. When assayed this way, MMA produced an emerald green color, the intensity proportional to MMA’s concentration. We obtained samples of Robby’s urine and were startled to see a stunning green color, deeper that any of the standards. So we knew what acid was accumulating.

Then I played another (informed) hunch: Knowing that the mutase enzyme required a vitamin B₁₂ co-factor, I proposed that we administer vitamin B₁₂ and see if it had any effect on Robby’s MMA excretion. At physiologic doses, nothing happened; at 50 times the physiologic dose, nothing happened. But when we administered 1,000 times the physiologic dose, his MMA excretion fell by about 80 percent, stayed down as long as we continued the daily supplements, and rebounded when we stopped them. We had discovered the first patient with an inherited disorder of a B₁₂-requiring enzyme who responded to supplementation of the vitamin.

Again we climbed the mountain of discovery from clinical observation to biochemical characterization to molecular genetic understanding. I am forever grateful to the group that trekked with me: Anne Lilljeqvist, Roy Gravel, Ted Hsia, Wayne Fenton, Maurice Mahoney, Ira Mellman, Hunt Willard, and Pamela Youngdahl-Turner. Once we determined that the MMA pathway was expressed in cultured cells and blood leukocytes, we could study patients from elsewhere and soon learned that there were two kinds of patients: those whose cellular abnormalities were resistant to addition of B₁₂ to the culture medium and those whose cells responded.

The unresponsive cells and patients turned out to have defects in the mutase apoenzyme and did poorly; the responsive ones had abnormalities in the pathway by which vitamin B₁₂ was converted to its coenzyme, and many of them, including Robby, did well. Ultimately, we and others found a large series of mutations, each effecting a different step in the B₁₂ pathway, each with its own, corresponding clinical phenotype.

The special lessons from studying Robby are these: playing hunches pays off (in science and elsewhere); vitamin supplements may be life-saving (in special circumstances); cultured human cells expand scientific reach; and studying one patient can lead to myriad insights.

I’m sure you’ve noticed that no two of these stories are even close to being the same. But there is sameness here, namely
that they reflect the work of a single, fortunate person — me. I have always worn proudly the badge emblazoned with the words, physician-scientist. I have always seen myself as a member of a small slice of the medical research workforce. How small? We count for only 1 to 2 percent of all MDs and are outnumbered 3 or 4 to 1 by PhDs in the pool of NIH-funded investigators. Over the years, I’ve been asked hundreds of times why this country’s research enterprise needs physician-scientists at all. My answer: Physician-scientists are imprinted by their clinical experiences and by the scientific questions they ask that are born from taking care of sick people. I don’t believe that anyone who had not seen the sick children I’ve presented to you could have kept their eye on the real prize: finding out something scientifically that can be translated into understanding, comforting and occasionally curing a human being who is unique genetically and clinically. This is the special niche of physician-scientists.

The scientific work just summarized unquestionably constitutes the most gratifying part of my professional life. It captivated me as nothing else has. It made me agree with the Nobelist Max Perutz who said, “Discovering something is a wonderful thing; it’s like falling in love and getting to a mountain top at the same time.” It produced in me a dazzling sense of well-being and exuberance that has thrilled and sustained me. And there was more. As my scientific reputation was secured, my opportunities multiplied here and elsewhere. Here, the sequence of events led to ascending the faculty ladder from being an investigator to becoming the head of a section, then a department chair, and finally the Dean of the School of Medicine. Elsewhere, I was invited to speak, to participate in all manner of NIH-related policy discussions, and even to espouse before a Senate subcommittee my support for abortion rights.

For all of this, I owe a huge debt to this institution. Yale was an ideal place for me. In the late former president of Yale Bart Giamatti’s words, it was “a free and open space.” It freed me to express myself in as many ways as I was able. It was open enough for me to move among its people and its departments simply by wanting to. These are the institutional qualities that made me proud to be here for a longer interval than I’ve been anywhere else.

And then, despite what I’ve just said, I shocked this school and myself by leaving. I uprooted myself and took a job in the pharmaceutical industry as Chief Scientific Officer (CSO) at the Bristol-Myers Squibb Company (BMS). I agonized for months before making this existential decision. It was a tough call — about 50.5 percent for leaving, 49.5 percent for staying here. I’ve since concluded that when the pros and cons are so nearly equal, one ought to stay put, but I didn’t. However complicated my reasons were for leaving and however ambivalent I have been about this decision ever since, the abrupt way I departed was disrespectful to my friends and colleagues here and to this school. For that I am deeply sorry, and I apologize.

Let me close with this. If some of what I’ve said sounds like a valedictory or, worse still, a song that swans sing before dying, I say you’ve got it wrong. I’ll come back whenever I’m invited and for however long I am able. And each time I return, I’ll express my gratitude to this school for giving me the chance to prove myself, to become as good as I could be, to satisfy my restless ambition — in truth, my lifelong need — to make a difference. Thank you, Pediatrics. Thank you, Yale School of Medicine. Thank you, Yale University.

REFERENCES

1. Darrow DC. Grover Francis Powers and pediatrics and Yale. Yale J Biol Med. 1952;24(4):243-51.