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DNA and Other Strands: The Making of a Human Geneticist

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Abstract

This article—a mini-memoir—focuses on the first half of my half-century-long career as a human geneticist: its accidental beginnings; its early bad and then good fortunes at the National Institutes of Health; its serendipitous successes and career-making scientific productivity at Yale; and its incalculable fortuity in the form of the large number of talented and resourceful mentors, colleagues, postdoctoral fellows, graduate students, and technicians who worked with me. These years acted as a launchpad for positions of visibility and leadership that followed them. My personal odyssey, which began in Madison, Wisconsin, and meandered with no fixed plan to New York, Bethesda, New Haven, and Princeton, has offered me life views as a human and medical geneticist that are panoramic, splendid, and indelible. I doubt that many people have been as fortunate as I have been in the professional life I have lived—and continue to live.

INTRODUCTION

"Medical genetics. There is no such field," he exclaimed. These words were forcibly thrust in my direction in 1962 by a prominent professor in the Department of Internal Medicine at the Yale University School of Medicine. I had just told him that I intended to specialize in genetics rather than in nephrology—his field.

I wasn't surprised that he didn't recognize medical (or human) genetics as a discipline. Few people did at the time. I barely knew myself the names of some of the field's pioneers—Kurt Hirschhorn, Victor McKusick, Arno Motulsky, James Neel—and had not yet met any of them. My fateful decision might have been taken for a variety of reasons. I could have been influenced by an inherited disorder in my family, but I knew of none—then. I could have been fascinated by one or more courses in genetics that I had taken as an undergraduate or medical student at the University of Wisconsin, but I hadn't taken any. I could have been galvanized by Watson & Crick's electrifying paper in *Nature* in 1953 (76), published when I was a first-year medical student, but I confess that I was not even aware of their work for another six years. I could have been captured by seeing patients with phenylketonuria or cystic fibrosis as a medical student, or with sickle-cell anemia or thalassemia as an intern, but they did not hold my attention more than patients with a variety of other childhood or adult illnesses.

Then, you might ask, what did influence me to respond to a clarion call in 1962 that has continued to sound for 50 years? The answer in brief: a chance clinical encounter; a serendipitous selection of a research mentor; and a field (genetics) that was already thrilling its small cadre and beginning to impress the community of life scientists. To tell this story and the many stories that followed it, I must retrace my steps to 1959.

NIH: FROM DISAPPOINTMENT TO EUREKA

As 1959 dawned, I was preparing to finish my first year of medical residency at Columbia–Presbyterian Hospital in New York City. I came to the hospital believing that I would learn how to take care of sick people, and that such caring would be the principal direction of my professional life. Nothing had occurred during the 18 months of internship and residency that had disturbed my bent toward this well-trod path. Nothing, that is, except the decisions being made by my fellow house officers. Several of them announced that they were going to the National Institutes of Health (NIH) in Bethesda, Maryland, to become full-time associates (read: fellows) in basic or clinical research. Although I had spent two summers during medical school doing research, neither experience had been powerful or had moved my career vector. Nevertheless, I was intrigued enough by the vague idea of spending a couple of years in the laboratory, and had esteem enough for those of my compatriots heading in this direction, that I decided to traipse after them. In 1959 it was easy to get a job at NIH. MDs from the country's most prestigious hospitals were flocking there to try their hand at becoming physician-scientists. I landed a job as a clinical associate in the Metabolism Service of the National Cancer Institute (NCI).

Accordingly, in June 1959 my wife, our two children, and I trundled off to Bethesda. We moved into a small, tan, single-story rented house. It was box shaped and had two bedrooms, a fenced-in back yard, and a front stoop of four stairs. This made it the grandest place my wife, Elaine, and I had lived in during our five years of marriage. Once the family had been settled to a degree, I bounded off to NIH, only a few blocks from our house. By 1959, NIH already occupied a large campus. Though tiny compared to today's sprawling footprint, it already had seven institutes, named for diseases or organ systems that were being investigated. The National Cancer Institute, the first of these categorical organizations, had been established in 1937. Each institute was housed in its own

building. Sitting in the middle of all these squat 3- or 4-story structures was the imposing 14-story Clinical Center: a research hospital capable of housing several hundred patients who volunteered to participate in clinical investigative studies.

My clinical associate position meant that I would spend the majority of my time doing clinical research under the supervision of a senior scientist, and the remainder caring for patients on one or another kind of study protocol. I soon learned that our service was populated with several outstanding scientists. Sadly, my supervisor was not among them. Let me tell you why I describe him in such an unattractive way.

At our initial meeting designed to sketch out my research project, we sat down in a windowless room lined on three sides with shelves filled with lime green–shaded, clothbound notebooks. My supervisor, a handsome man in his forties with a shock of light brown hair, pointed to the shelves and said that he and his team had been admitting patients with a variety of cancers for a decade, and had proceeded to study their metabolic parameters in great detail. This meant that caloric intake and caloric expenditure had been measured; that dietary carbohydrate, fat, and protein had been quantified to the last gram; that concentrations of nearly 20 substances had been measured in blood, urine, and feces; and that all of this information had been carefully recorded in the bound notebooks. "You won't have to do any experiments," he told me. "Your job will be to figure out what all this data means." He then stood up and left.

I remained sitting for a good long while, feeling like I'd been a hit on the head by a two-by-four. As my mind raced, I silently asked, "What hypothesis is he trying to test? If this guy doesn't know why he's been measuring all these parameters for a decade—at great cost of time, effort, and money—why does he think I'd be able to find out? Why does he think I'd want to?"

That evening I told Elaine about the day's horrendous events. "Perhaps," I said, "I wasn't meant to be a scientist. Maybe I should devote myself to clinical medicine—something I understood and am good at." We agreed that I should tell the chief of the service that I found this assignment hopeless. The next morning I went to see the chief, Nathaniel Berlin. He was a diminutive, bespectacled, balding, quiet-voiced man in his early forties. After relating the events of the prior day in considerable detail, I said, "I won't do that project. I'd like you to find some other way for me to fulfill my obligations to the Public Health Service" (which all associates joined in lieu of being subject to the draft). His response came quickly. He agreed that the project proposed was a poor one, and that I shouldn't do it. He refused to accept my offer to leave NIH, and said I should take whatever time I needed to find a new supervisor and new research project—anywhere in NIH.

Berlin's response was among the most important events in my life. In retrospect, he became the third person—along with my father and Robert Loeb, the chief of medicine at Columbia–Presbyterian Hospital—who mentored me. After liberating me, Berlin followed through by arranging appointments, making himself accessible, becoming a personal friend, and seeing how things were going. I was to leave NIH before he did, but that only added to the strength of a relationship that lasted more than 40 years.

The trauma and stress of this 24-hour period had barely passed when something new entered my life, like an unwanted guest. I began to sleep fitfully and awaken in the middle of the night. I lost all interest in food, sex, and children. My vaunted quantum of energy and sense of self-worth evaporated, and life felt slow and empty. I had a strange feeling behind my eyes, as if I were in a fog. This slow-motion, glass-nearly-empty state hung on for a few weeks, but I forced myself to continue working.

At this time my duties included taking care of children with acute leukemia who were being treated with one or more chemotherapeutic drugs. This was a baneful, but necessary, time in the history of cancer chemotherapy. The side effects of the medicines were horrendous: baldness; bacterial and fungal infections; bleeding resulting from extremely low platelet counts. Worst of

all, none of the children I ministered to survived. It was to be nearly 20 more years before drug cocktails were developed that cured acute leukemia in children. But these cures would not have occurred without the trials and errors that I witnessed day by day.

However sobering and saddening this clinical experience was for me, it served to jolt me out of my funk. After about one month, the emotional fog lifted and the other symptoms disappeared as well. Though I didn't make the diagnosis then, I came later to realize that I had been typically, clinically depressed. I attributed this emotional disturbance to the circumstances surrounding the transition to NIH. I had left something I was good at—clinical medicine—for something that was completely new and strange—research. That may have been part of the answer, but it was not the entire answer. This was the first of many episodes of clinical depression that have haunted me throughout my life and that were manifestations of bipolar disorder, which was rampant in my family.

During the next few months, I searched for a new advisor and a new project. I went to see a distinguished PhD biochemist named Elbert Peterson, who, with a more senior colleague, Herbert Sober, had developed a means for separating proteins from one another using diethylaminoethyl cellulose. When I showed up at Peterson's office, I was still wearing the long white coat we wore when seeing patients, a stethoscope protruding from the coat's pocket. Peterson wore his black, neatly trimmed hair slicked down, and his eyes were dark and penetrating. He looked me over and then said something like this: "I'm willing to consider having you come to my lab, but"—pointing to the stethoscope—"I don't ever want to see that again." I interpreted this less-than-friendly comment as follows. Peterson viewed the stethoscope as the arch symbol of a physician, a group he disparaged as researchers. He wasn't in any way interested in clinical problems or those who studied them. He was focused on the basic science of protein separation and would accept me only if I shared that interest. I joined his lab and learned how to do protein separation expertly, but failed to get excited about this exclusively technologic investigation. Thus, I retreated and continued my quest for another laboratory in which I could try my hand at science.

Within a short time two events changed the course of my professional life. The first had to do with a boy named Steven Busby. He had been admitted to the Metabolism Service at age eight with the far-fetched and soon-to-be-disproven notion that his disorder had something to do with cancer. His history and physical findings were extraordinary. He had been entirely healthy until age three, reaching all his developmental milestones normally. His photograph at age three confirmed that history: He was chubby and smiling—a picture of health. Then, according to his mother, he began to get thinner, and to lose the muscles in the chest, trunk, and all four limbs. The muscles seemed to melt away, as she put it. This had progressed to where he had trouble walking and was short of breath. Upon examination, he looked like a starved victim in a concentration camp. The muscles of his spindly arms and legs had atrophied and were notably weak. His ribs showed through his poorly muscled chest (**Figure 1**). Of the many laboratory tests undertaken to uncover the basis for his disorder, only two stood out. He evidenced abnormalities in his electrocardiogram, and he had a much larger concentration than normal of several classes of amino acids in his urine, i.e., a generalized aminoaciduria.

I reviewed the medical literature exhaustively, but failed to find even one report of a patient with a condition like Steven's. Upon discussing his puzzling situation with Steven's mother, she reminded me of something she had not told doctors earlier. Steven had had an older brother and an older sister whose clinical course had been identical to his. Each of them had died by age 10 of respiratory muscle failure. Three children out of six with the same disorder, I said to myself. This must be a genetic disease! So I proceeded to collect urine samples from his three healthy siblings, his parents, and several paternal and maternal relatives. Each of his parents excreted normal amounts of amino acids, but his three siblings showed modest increases. I concluded that Steven likely had a disorder inherited as an autosomal recessive trait. But what disorder? What kind of disorder?

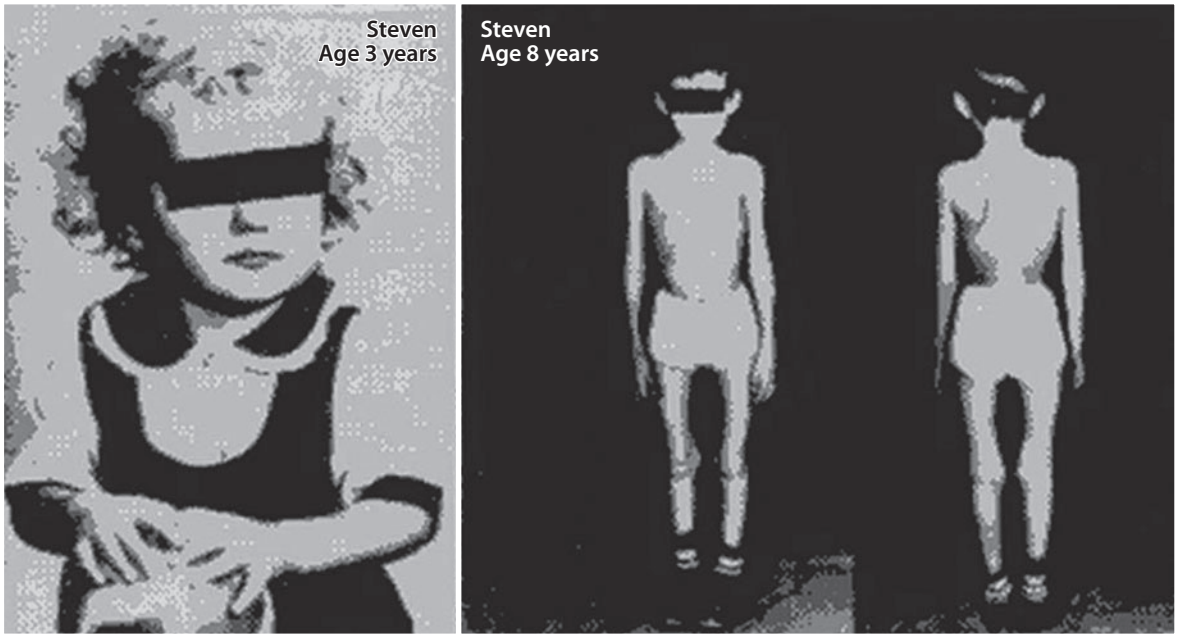

Figure 1

Steven at age three years (*left*) and eight years (*right*). While robust at age three, note how prominent his ribs had become at age eight due to the atrophy of his intercostal muscles, and how spindly his legs had become as his leg muscles atrophied.

Sadly, Steven got progressively weaker and died at age 11, following a clinical course almost identical to that of his affected siblings. Essentially, he died of suffocation and right-sided heart failure secondary to intercostal and diaphragmatic muscle weakness. Recognizing the uniqueness of his condition, my colleagues and I submitted two full-length papers to the widely read *American Journal of Medicine*. The first author on the first paper was Peter Rowley, who had taken care of Steven a year before I did. I was the first author on the accompanying paper. To our delight, both papers were accepted for publication (61, 62). Because these were my first scientific publications, the experience was exhilarating. I had led a piece of clinical investigation, organized the data, written the paper, and seen it in print.

Steven's story would not be complete without mentioning another lesson I learned about studying families. The pattern of amino acids in the urine of his teenage sister looked nothing like that of Steven or his two brothers. (Such patterns had been likened to fingerprints by earlier investigators, though judged to be not nearly as good markers of uniqueness or relatedness.) When I told Steven's mother about this puzzling finding, she began to cry and said that this daughter's father was not her husband. Ever after I have reminded my students how common this situation (called, erroneously, nonpaternity) is, how it may confound studying families, and how rarely it is detected.

You may ask whether the story ends here. The answer: a resounding no. I was unable to change the course of Steven's illness (which came to be called the Busby syndrome or the Rowley–Rosenberg syndrome). But he changed the course of my professional life. He showed me that asking research questions based on seeing patients was like medical detective work. Even more important, he ignited my interest in genetic disorders and kindled it. The next step was to test my hypothesis that Steven suffered from some kind of abnormality in the transport of amino acids in

the kidney as an explanation for their excessive appearance in the urine. I had to find a laboratory in which to test this idea.

I have no idea how I made the acquaintance of Stanton Segal, but it was the second career-changing event. He was several years older than I was, carried a bit too much weight on his strong frame, and had a warm smile and easy laugh. I told him about my work with Steven, including my ideas about what might lie behind his disorder, whereupon Segal said that we should test the idea. He proposed that we needed to simplify the experimental system and study in the test tube the transport of amino acids in muscle and kidney from rats. Having done that, we would be ready to study the next Steven. Thus, we embarked on such a study and, over a period of several months, defined the basic parameters of these transport systems. I learned quickly how to sacrifice rats, remove their kidneys and muscular diaphragm, and incubate the tissue with isotopically labeled amino acids in small Erlenmeyer flasks. I vividly recall standing at the radioisotope counter as the data from an early experiment were printed out on a rolling ribbon, like a newspaper coming off the presses. Though hardly groundbreaking in retrospect, the exuberance I felt at looking at this list of numbers was palpable. I was testing a reasonable idea in a controlled system. It wasn't a eureka moment in terms of scientific discovery, but it surely was one for me personally.

For the next year Segal and I performed experiments together almost every day. We were a great team because we were excited, knew each other's "moves," and agreed on the course of studies. Because no one had done such studies before, we had no trouble getting our work published in good journals (52, 56, 68). But my memories of this formative (for me) work run beyond the laboratory. After some months, we collected data on the transport of the dibasic amino acids lysine, arginine, and ornithine that demonstrated that these amino acids share a single specific transport carrier. We wanted to submit a paper to the prestigious *Journal of Biological Chemistry*. To test our interpretation and the importance of the work, Segal recommended that we have the manuscript reviewed by Robert Berliner, an acknowledged authority on renal physiology renowned for his scientific rigor and candor. I was pleased when Berliner agreed to review the paper, but was equally anxious about his response. Segal and I exhaled with relief when Berliner judged the paper positively and encouraged its submission to the journal, which accepted it (55). (Many years later, Berliner preceded me as dean of the School of Medicine at Yale. I reminded him of this early association—which I naturally remembered much more clearly than he did.)

I was so proud of this paper that I decided to send a reprint of it to my parents. They knew by this time that my career gaze was on the laboratory, not the clinic. They still hoped, of course, that I would finish my clinical training and find fulfillment as a "real doctor" practicing in my hometown of Madison, Wisconsin. When they received the reprint, they admitted to not being able to comprehend any of it, but they were sure that it must be good if it had my name on it. I wasn't surprised that they didn't get it, but it was important to me to show them what I was doing—even if it wasn't what they hoped I would be doing.

As the work progressed, it expanded. We demonstrated that our techniques could be used to study transport in gut mucosa (38, 44). We showed that amino acid transport was dependent on the cotransport of sodium ions (14) and sugars (69, 70, 72). We concluded that the kidney tubule reabsorbed amino acids using different carrier systems specific for the different classes of amino acids (e.g., aliphatic, dibasic, dicarboxylic, cystine). I poured myself into the work in Segal's lab. There were so many avenues to follow that it was just a matter of prioritizing them and carrying out the necessary experiments. I was spending almost as many hours in the laboratory as I had as a house officer in New York. My usual schedule was to rise early, do some morning exercises, jog for about 20 minutes, shower, eat breakfast, and head to the lab—getting there by 8 AM. I did an experiment almost every day, sometimes two, and would return home for dinner and playtime with my children, Bob and Diana. After giving everyone a hug and kiss, I would return to the lab

to calculate the results of the day's experiments. Elaine was stoic about the huge amount of time I was spending at work. She didn't demand more of my time, and she didn't get it—rather devoting herself to our children, and to a third one, David, born in 1961. Not infrequently I would call Segal at home to discuss the day's findings and plan tomorrow's experiments. His wife was not overjoyed to hear my voice on the phone so frequently, but she always got Segal on the line. He was as enthusiastic and frenetic about the work as I was. I was his first postdoctoral fellow, and he was enjoying the experience.

As this research progress accelerated, I received a call from a young pediatrician named Charles Scriver. He was a through-and-through Canadian, then an assistant professor at McGill University in Montreal. He brought to my attention a paper he had recently published in *Nature* that addressed exactly the same subject I had been pursuing (65). We had used virtually identical methods and had obtained very similar results (66, 80). We realized instantly that this set of circumstances meant that we would become either arch competitors, racing to outdo one another, or trusted colleagues whose common interests enhanced both of our efforts. We chose the latter course, thereby establishing a friendship that has lasted to the present. We have written a book together (64), won awards together, exulted in genetics together, and shared private and public lives together. We have rejoiced at each other's visibility and respect. We have never tired of remembering how our friendship was born and raised.

I then did something that you might find incongruous. Within six months of deciding to extend my appointment at NIH for a third year, I hedged my professional bets, deciding to return to clinical medicine and complete my qualifications in internal medicine. I wanted to be board certified in medicine in case my research hit a stone wall or I tired of it. I told Segal and Berlin of my intention. Both were remarkably supportive. Berlin made a generous offer: Go and finish your residency training, then come back to NIH, where I'll make you a senior investigator in the Metabolism Service. This offer carried with it a full stipend during my residency year and travel expenses to and from the place I would spend that year. It also offered me the opportunity to continue my research in my own laboratory during my absence—with the able assistance of a superb technician, Sylvia Downing. Further, Segal assured me that our collaboration would continue.

Armed with this green light, I set out to find a residency. I wanted to stay on the East Coast so that I could make trips back to Bethesda to oversee the work that would be conducted in my absence. There were two programs that looked attractive: one at Massachusetts General Hospital, the other at Yale–New Haven Hospital. My visit to the former was memorable. I had a one-on-one visit with the chief of medicine, the much-admired Walter Bauer. I was struck by Bauer's bald head, prominent eyebrows, deep-set eyes, and furrowed cheeks. He said, "I would like to have you on my house staff, but I have only one position available, and there are three good people who want it." Then with a broad smile, he continued, "So I guess I'll just have to shit or get off the pot." Years later I was to learn that Bauer suffered from bipolar disorder (then called manic depression) and that his words became salty or flamboyant when he was "up."

My visit to New Haven was quite different. The chief of medicine at Yale–New Haven Hospital was Paul Beeson. He was as celebrated a national figure as Loeb and Bauer. However, when I entered his office, the differences between him and these other giants of internal medicine were palpable: no portrait of himself on the wall; no loud, florid speech; no commanding presence; no condescension. Rather, he sat behind his desk in his small office and inquired about my reason for desiring another year of clinical training. I remember noting that he was handsome, wore his gray hair parted on the left side, had a quiet voice, and carried himself in a dignified manner. He said he would like to find out more about me from Loeb. I guess he must have been satisfied by what he heard, because within a few days he offered me a position, and I accepted. (Today, such selection

would require weeks or months, and would also require the actions of a committee composed of faculty members.)

NIH AND YALE: TWO ROUND-TRIPS, ONE FINAL DESTINATION

In July 1962 I again donned the white suit of a medical resident. After taking some weeks to remove the rust from my clinical tools, I supervised interns and assistant residents caring for many of the most common adult disorders: coronary artery disease, cancers of all types, emphysema, cirrhosis of the liver, and many more. My years in research, however, had changed my approach to patients. In addition to asking what the diagnosis was and how to treat the patient, I asked why the condition had occurred in the first place, and what genes had to do with it. Although it is a truism today that most common disorders are multifactorial, the notion that mutations were somehow involved in the pathogenesis of common disorders was almost never discussed. When clinical genetics was mentioned at all, it was limited to cursory discussion of Mendelian disorders or chromosomal defects.

I had two interesting encounters relevant to the former class of disorder. One involved adult polycystic kidney disease; the other, familial polyposis of the colon. Each condition is inherited as an autosomal dominant trait. Accordingly, I counseled members of both families, only to be scolded in both cases by senior attending physicians who said that a physician's responsibility was to the individual patient he was caring for and to no one else. Genetic counseling, I was told, was "playing God." Uncowed, I remonstrated but changed no minds. These experiences had one major effect on me: They told me that thinking about the genetic basis of disease would come and that I wanted to be among the cadre who would bring it.

Something else happened during this year. Even as my clinical acumen reached the highest point it would achieve, I felt progressively pulled toward science. I was drawn to becoming a physician-scientist who derived his scientific questions at the bedsides of sick patients. Those questions, I said to myself, would be asked using the language of genes and mutations. These preoccupations had the result of keeping me informed about what was happening in my laboratory at NIH, about what Segal was doing, about what I would do upon my return. So, in June 1963 we moved back to Bethesda. In the ensuing weeks, we enrolled the children in public schools, achieved such momentous milestones as teaching Bob to ride a bicycle, and took up our usual roles: Elaine running the home, I running off to NIH.

I was excited (and relieved) to find that the research had gone well in my absence. The characterization of amino acid transport systems in the kidney, gut, and muscle had moved forward. Importantly, Segal and I had decided to redirect some of our efforts toward a human disease resulting from an amino acid transport defect—cystinuria. Cystinuria was one of four conditions inherited as autosomal recessive traits that had been investigated by Archibald Garrod at the turn of the twentieth century. He called these disorders "inborn errors of metabolism" in his prescient, brilliant work that first directed application of Mendel's recently rediscovered laws to human disorders (15, 16). Dent and his associates (6, 7) had subsequently shown that—in addition to the excretion of excessive amounts of cystine, whose insolubility resulted in the serious clinical consequences of the disorder, kidney stones composed of cystine—other naturally occurring amino acids with two NH_2 groups also had abnormally large renal clearances. Dent proposed that cystinuria was a genetic disorder of amino acid transport, not an enzymatic defect in cystine metabolism. Subsequently, Milne and his colleagues (42) presented evidence that intestinal transport of this group of amino acids was also defective.

A team composed of Sam Their, Maurice Fox, Segal, and myself set out to examine these hypotheses (developed from studies on patients in vivo) using kidney and intestinal biopsies in

vitro. We confirmed that cystinuric patients had a specific defect in dibasic amino acid transport in the gut and kidney, and that cystine had a transport mechanism unshared with the other dibasic amino acids—the first in vitro demonstration of a specific human transport defect. This work was duly published and presented at major meetings, thereby propelling my career as a clinical investigator studying genetic disorders (13, 45, 53, 73).

At this point I wanted to advance my meager knowledge of medical genetics, but there were no training programs in the discipline. So I did the next best thing: I paid a visit to Victor McKusick at his program in the Department of Medicine at Johns Hopkins and asked whether I could attend his weekly genetics outpatient clinic. He agreed graciously and enthusiastically, thereby enabling me to watch him and his associates in action. They saw adults and children, individuals and families. Every evaluation included a detailed family history aimed at elucidating, where possible, the pattern of inheritance. McKusick was a walking encyclopedia of inherited disorders, most of them rare. He was a genius at cataloging conditions, and soon established the universally respected compendium named *Mendelian Inheritance in Man*. He focused his own efforts on various forms of dwarfism and on Marfan syndrome. He recognized that certain ethnic groups, such as Ashkenazi Jews and the Old Order Amish, had their own set of "private" disorders because they were so inbred. Every week my horizons would be broadened by these visits.

Soon thereafter I met Kurt Hirschhorn, Arno Motulsky, and James Neel at the annual meeting of clinical investigators in Atlantic City. Each had made original contributions published in top journals: Hirschhorn in chromosome abnormalities, Motulsky in founding the field of pharmacogenetics, and Neel in family studies in sickle-cell anemia. They joined McKusick in proselytizing me to join their tiny band. I didn't need much coaxing. Although little was known about the mechanisms of human inherited disorders, the field of molecular genetics was exploding in what Nobel laureate François Jacob termed "the great adventure of the century." It was obvious to me that this information would soon penetrate the secrets of human inheritance and disease. I was hooked. Thereafter, I never wavered in my resolve to join those scientists—PhDs and MDs—marking out the territory of human genetics.

The outside world rarely intruded on this exuberant period of personal discovery, but occasionally it did so—once devastatingly. Early in the afternoon of Friday, November 22, 1963, I was sitting in my laboratory chatting with Sylvia. Then someone burst into the room and said that President Kennedy had been shot in Dallas. We huddled around someone's radio and soon learned that he had been assassinated. Like most Americans, we were speechless and disbelieving. Everything else was blotted out. For the next three days, I joined our country and the world in mourning his death and reflecting on his life. I went to downtown Washington with a friend to witness the funeral cortege. I recall how silent the streets were, how few words were spoken, how many tears were shed, and how peoples' sobs were muffled. After three terrible days, the country sadly stirred, and I did too.

A year later, it was decision time—again. Berlin and Segal wanted me to stay at NIH for the long term, and made that opportunity attractive: a tenured position, a salary of $19,000, good laboratory space, and the promise of attracting rising young MDs interested in finding out, as I had, whether they had the right stuff for a career in medical research. Despite these inducements, my restless self was whispering otherwise. I wanted to separate myself from Segal to convince everyone, including myself, that I could make my own way without his support. Further, the year at Yale had made me aware of the excitement of having medical students and house officers to teach—something simply not possible at NIH, where research was the only opportunity offered. I needed to test the academic market.

Two serious opportunities presented themselves. The chair of medicine at the University of Buffalo, Evan Calkins, made a fine offer: two large laboratories, a distinct raise in pay, and a

promise of being in on the ground floor of this new medical school. I was attracted, but decided to examine an offer from Yale as well. Paul Beeson had understood before most chairs of medicine did that medical genetics represented part of the future. He decided to inaugurate a small section of medical genetics, as had recently been done at Johns Hopkins, Michigan, and the University of Washington, and recruit two young faculty to staff it. One was Herb Lubs, who had made original contributions in the study of human chromosomes and had accepted Beeson's offer. The other person Beeson wanted was me. His offer: an assistant professorship, a 50% pay cut, and one small laboratory. When I told him of Calkins's much superior offer, he said, "Lee, academic medicine is tough, and being a pioneer [referring to Buffalo] makes it tougher. You have about a 90% chance of succeeding here. If those odds are not good enough for you, then I suggest you stay at NIH." Having made it into the top tier of research-intensive medical schools, I was determined to stay there. I accepted Beeson's offer.

About two months before my family and I were to retrace our steps from Bethesda to New Haven, I learned that Beeson had decided to leave Yale and accept the prestigious Nuffield professorship at Oxford. With considerable anxiety I called him and said that he was one of the most important reasons I had accepted Yale's offer. After some soothing words, which I'm sure he had been saying to many people at Yale, he said, "I didn't recruit you; Yale did." That did little to erase my misgivings, but I stayed my course.

YALE: PINNACLE OF PERSONAL SCIENTIFIC ACCOMPLISHMENT

Let me try to paint, in an impressionistic style, the tableau of taking up my first faculty position at the Yale School of Medicine. (From this point on, my previously idiosyncratic career journey followed a path very similar to the one young faculty travel today.) I moved my family into a comfortable, purchased house in a community (Hamden) with good public schools; occupied a new laboratory in a recently constructed research building (which the architect had designed without running distilled water); hired two technicians (Isadora Albrecht, an outspoken refugee from Germany, and Joe Durant, a soft-spoken African American). Less propitiously, I experienced a second bout of clinical depression whose symptoms and duration were much like the first, and which made clear to me that I had a mood disorder requiring watching and attention. Finally, I competed successfully for a career development award and a research project grant from NIH.

Soon, the laboratory became functional. My first (Yale) postdoctoral fellow joined us: Louis J. Elsas (always called Skip). He, Isadora, Joe, and I began to study transmembrane transport of sugars as well as transport of amino acids (8, 9). A second MD postdoctoral fellow, Richard Hillman, soon joined the lab and extended the work on renal amino acid transport by using isolated renal tubules (18, 19). Skip and Richard were the last of my brood to study transport. While they worked with animals, I continued to study cystinuria. From family studies emphasizing experiments with heterozygous carriers, we showed that cystinuria is genetically heterogeneous (46, 47, 54, 57, 74). This allowed me to become acquainted with another leading human geneticist from the United Kingdom, Harry Harris, who was a committed Garrodian—as I was becoming—and who had produced evidence for heterogeneity earlier. Thereafter, the laboratory changed directions, as you will now see.

Fortuitously, something happened during my first year on the faculty that established my credentials in the medical school. We had set up a method for separating amino acids in urine using paper electrophoresis and began offering it as a service to faculty seeking a means of screening patients' samples for metabolic disorders. Almost as soon as we began testing, we analyzed urine from an 11-year-old boy who had been diagnosed with autism by faculty in the Yale Child Study Center. To our surprise, the urine contained large amounts of homocystine, an amino acid only

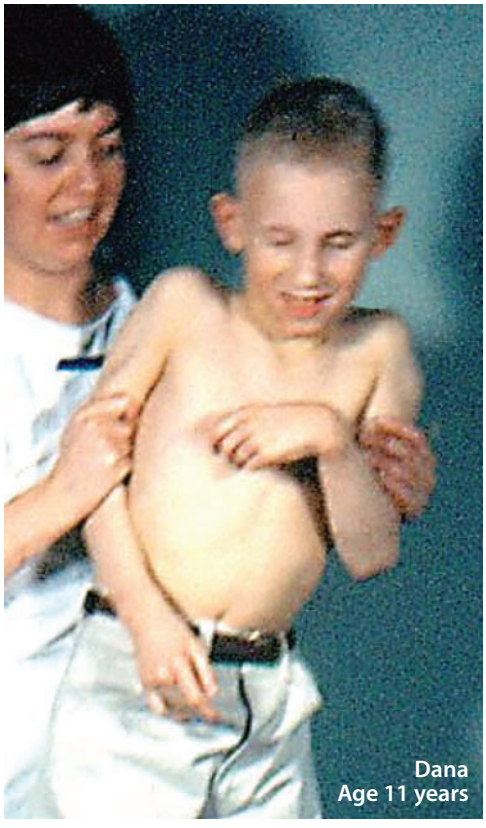

Figure 2

Dana at age 11 years, being supported by a nurse in the Yale–New Haven Hospital genetics clinic. Note his tightly closed eyes and pallid skin and the way his arms were held.

recently reported to accumulate in an autosomal recessive disorder named homocystinuria, characterized clinically by developmental delay, behavioral abnormalities, and dislocated optic lenses. I arranged to see the "autistic" patient, whose name was Dana. Sure enough, both of his lenses had been removed because they had been so dislocated that they impeded vision, leaving him blind. In addition, Dana had such a severe and unique speech defect (called verbal apraxia) that his words were barely intelligible (**Figure 2**).

I took over Dana's care. As we got to know each other better, Dana would begin each visit by hugging me and saying my name over and over in a run-on, staccato way (*doctarodenboog*, *doctarodenboog*) that I can still hear clearly but cannot imitate in writing. Then he would insist that we hold hands and take a walk down the clinic's corridor. This routine gave him great pleasure and established trust between me and his parents, whose guilt concerning Dana's condition was consuming. I described to them the genetic nature of Dana's disorder and emphasized that his condition had nothing to do with their behavior (drinking a bit too much on the night he was conceived, I was told). In the absence of any treatment for homocystinuria, the emotional support I gave Dana and his parents was the sum total of my contribution to them, but this was not trivial. I followed Dana for about 15 years, after which his behavioral difficulties made it necessary for his parents to place him in residential home. To end this story, I will mention that the faculty in the Child Study Center learned from Dana, as did I, that certain kinds of autistic behavior can result

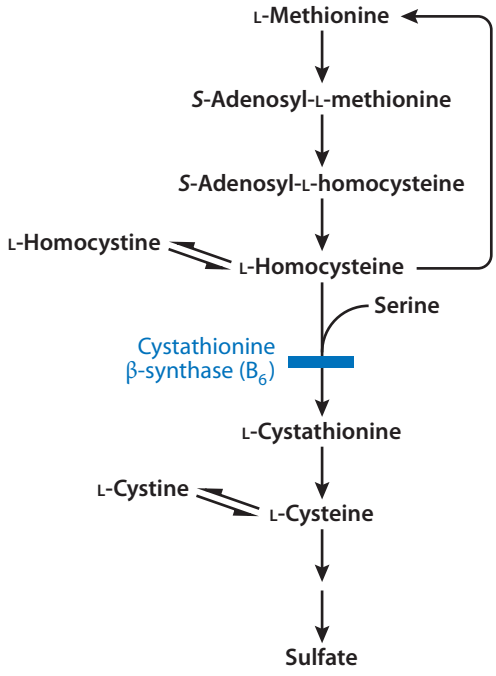

Figure 3

Localization of the metabolic block in homocystinuria resulting from mutations in cystathionine β-synthase, a pyridoxal phosphate (denoted B_6)–dependent enzyme catalyzing the conversion of homocysteine to cystathionine. The pathway from methionine to sulfate is rich in other genetic defects affecting catabolism and remethylation.

from many different conditions—something that is becoming increasingly clear as I write these words nearly a half century after coming into contact with this odd, loving, and lovable boy.

In due course members of the laboratory made significant contributions to our understanding of homocystinuria. Margretta Seashore studied two boys with the pyridoxine-responsive form of the disease (67) (**Figure 3**). Jan Kraus led the work purifying the responsible enzyme, cystathionine β-synthase (CBS) (30); studying its interaction with pyridoxal phosphate (32, 33); and cloning its gene (29, 31).

By the time I had been at Yale for two years, it was becoming clear that I was contributing little to medical student or house staff education from my vantage in the Department of Medicine. Most of the advances of clinical relevance in the field of medical genetics were coming from studying children with a variety of disorders such as Down syndrome, phenylketonuria, and cystic fibrosis. Accordingly, I told Philip Bondy, the chair of the Department of Medicine, that I would like to seek a joint appointment in the Department of Pediatrics. He was supportive and suggested I speak with Charles Davenport Cook, the chair of that department. Rather than rebuffing me because I had not had any formal training in pediatrics, Cook was enthusiastic about my desire to move my interests toward children. Certain other members of Cook's department were less enthusiastic. One, who felt threatened by the idea that his leadership in the area of metabolic disease might have to be shared, told me that "good fences make good neighbors," to which I replied, "I think good fences only make good fences." Several other senior pediatricians also wished I would stay where they thought I belonged. But whatever opposition existed among the pediatrics faculty, Cook overcame. I was offered a secondary appointment in the department, with its attendant responsibilities.

I slowly became a more than adequate attending physician on the pediatric services, though clearly not in the same league as the card-carrying pediatricians in the department.

In 1968 this collaboration between the Departments of Medicine and Pediatrics was extended. Bondy and Cook established an interdepartmental section of medical genetics and asked me to lead it. This gave me more visibility in the school and more laboratory space for the work of my team, which now included Maurice J. Mahoney and Seashore, as fellows, and Y. Edward Hsia, a talented junior faculty member from the Department of Pediatrics. You may rightly infer that this tilt toward sick children must have had important consequences; otherwise, it wouldn't be described in such detail. Without exaggeration, this redirection allowed me to make the two most important discoveries of my scientific life. Although I will describe these discoveries in sequence, they actually occurred in parallel.

One of those voyages began in 1968 when I was asked to see a 20-month-old child named Lorraine, who had been admitted to the pediatric intensive care unit in deep coma. Her mother said that she had been well for most of her life, but had been walking unsteadily in the weeks before she slipped into coma, "as if she was drunk." An astute pediatric neurologist named Peter Huttenlocher had ordered a battery of laboratory tests. All gave normal results save one: Lorraine's blood ammonia level was more than 10 times normal, and was the highest blood ammonia ever reported by the hospital laboratory up to that time. Ammonia is an end product of protein breakdown and is toxic to the brain when in excess. This accounted for Lorraine's coma, we thought, but begged the question of why the ammonia was so elevated. It had been shown previously that patients with severe liver disease became ammonia intoxicated because ammonia is detoxified in liver cells by being converted to the harmless molecule urea, which is then excreted in the urine. Yet Lorraine had no other clinical or laboratory evidence of liver disease.

As we pondered this metabolic puzzle, a gratifying event occurred. Lorraine was treated in the way patients with liver failure were, with intestinal lavage and intravenous glucose. She woke up (**Figure 4**). Thus began a lengthy series of studies to unravel her medical mystery. A small piece of Lorraine's liver was obtained and assayed for the five enzymes required to convert ammonia into urea (**Figure 5**). One of them, ornithine transcarbamylase (OTC), was deficient but not absent (2). Earlier in the decade, investigators from the United Kingdom had reported similar findings in a few girls but not in boys. Why this selectivity for OTC deficiency? Why this gender difference? Was the abnormality inherited or acquired? In short order, my colleagues and I—notably Elizabeth Short, a postdoctoral fellow with clinical training in medicine—answered each of these questions. We reasoned that if Lorraine's ammonia intoxication had resulted from some kind of environmental toxin, it likely wouldn't occur again. So we slowly increased the amount of protein in her diet and reproduced the hyperammonemia and the intoxicated-like behavior her mother had described. These manifestations subsided rapidly when dietary protein was withdrawn. We concluded that Lorraine had an inherited abnormality, not an acquired one. Then we obtained a detailed family history from Lorraine's mother. When asked repeatedly whether anyone in the family had a problem like Lorraine's, she said no. Undaunted, I invited her to talk to a group of first-year medical students to whom I was presenting Lorraine's case history. When asked yet again about other affected family members, Lorraine's mother said, "I don't know if it matters, but I had two sons and two uncles on my mother's side who died before they were a week old." I was speechless for a moment (an unusual state for me) and then the proverbial light bulb of understanding went on. This brief exchange, carried out right in front of students, had answered unequivocally the questions about the biology of OTC and its deficiency. OTC deficiency had to be an X-linked trait (**Figure 6**). That would explain why boys were more severely affected than girls. If the single X chromosome in boys carries a deleterious OTC mutation, they wouldn't be able to detoxify ammonia at all and would die soon after birth. Girls, on the other hand, would likely be partially affected because

Figure 4

Lorraine soon after recovering from coma at age 20 months. Significantly, she has survived and thrived for 40 years on a low-protein diet.

they would be heterozygotes for OTC deficiency, not hemizygotes (71). Our hypothesis about the OTC locus was cemented by observing another unfortunate family (3). This couple had four sons in a row who died of ammonia intoxication in the newborn period, each of whose liver tissue was devoid of OTC activity. Subsequently, a fifth son did well neonatally and thereafter.

The foregoing information took about one year to collect and interpret. But it was just the beginning. This piece of clinical investigation, begun at the bedside of a sick child, had multiple spin-offs, clinical and scientific. On the clinical side, it led to the following: All newborns, and some older children, who lapse into coma are now tested for ammonia intoxication, and many are treated successfully; males with complete OTC deficiency cannot survive without liver transplantation (40, 75), which has cured a number of infants when employed during the first month of life; and females with partial OTC deficiency can be treated successfully with a regimen consisting of a low-protein diet and a chemical (phenylbutyrate) capable of tying up ammonia, thereby preventing

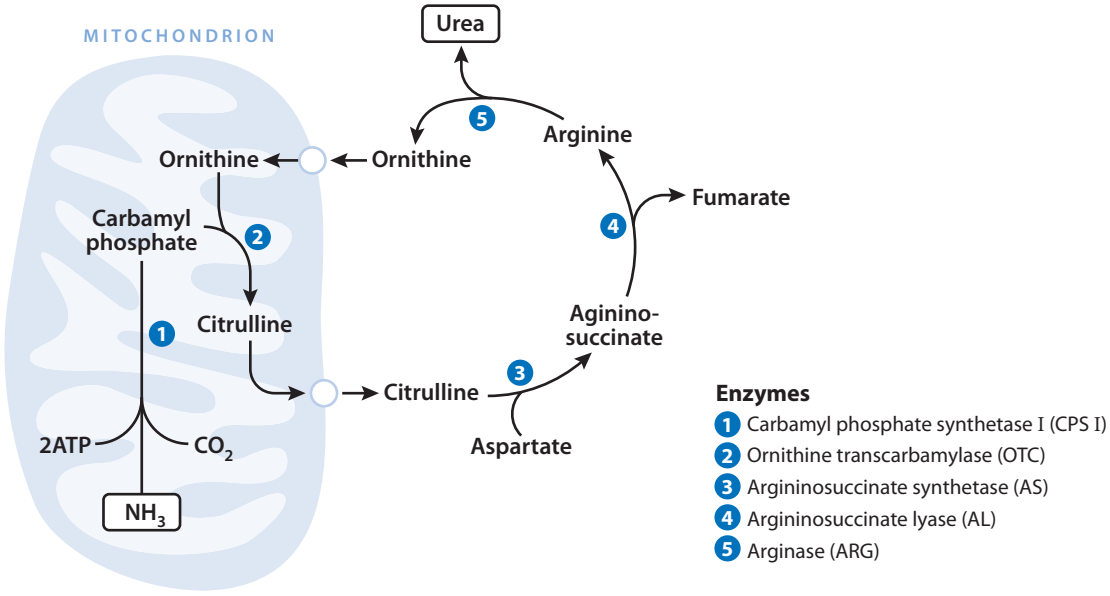

Figure 5

The Krebs-Henseleit cycle by which ammonia (NH_3) is converted to urea in the liver. The cycle begins in mitochondria under the control of carbamyl phosphate synthetase I and ornithine transcarbamylase (OTC). The cycle's final three reactions occur in the cytoplasm. Inherited defects in each of these enzymes have been described and characterized.

its accumulation. Another postdoctoral fellow, John McReynolds, played a significant part in establishing these practices.

These clinical applications developed within a few years. The scientific directions took decades. One of my colleagues, Frantisek Kalousek, purified OTC from liver tissue and determined its subunit structure (a trimer of identical subunits) and amino acid sequence (28). This led ultimately to the isolation of the gene by Art Horwich, ably supported by several members of the laboratory (21, 25). It is noteworthy that this took two years, several person-years, and the laborious technology of functional cloning starting with isolation of the OTC mRNA.

Florence Ricciuti and Tom Gelehrter teamed up to demonstrate directly that the X inactivation proposed by the Lyon hypothesis, which states that one of the two X chromosomes in cells from all females is inactive, occurs in human liver (43). Finally, OTC became a model for the study of transport of nuclear-encoded proteins into liver mitochondria (where OTC resides). This work was begun by John Conboy (4, 5), who discovered that such proteins are synthesized in the cytoplasm as precursors containing a leader peptide; as demonstrated by Horwich et al. (20, 22–24), this peptide behaves like a ZIP code, and then directs the proteins to mitochondria. Subsequently, the work has been carried forward in a two-decade-long series of elegant experiments by Horwich and his colleagues, whose work has earned them numerous national and international prizes for discovering that mitochondria possess molecular chaperonins that allow native proteins to fold into their active conformation (1).

In retrospect, I would have been fortunate indeed to make one discovery of the kind I've just described. But I did have the great good fortune to make two within a year of each other. The second, like the first, began at the bedside of comatose child, this time a boy named Robby. He was eight months old (**Figure 7**). His neurologic status had deteriorated over a period of weeks. His coma was caused not by ammonia but by a major disturbance in his blood pH. Ordinarily the

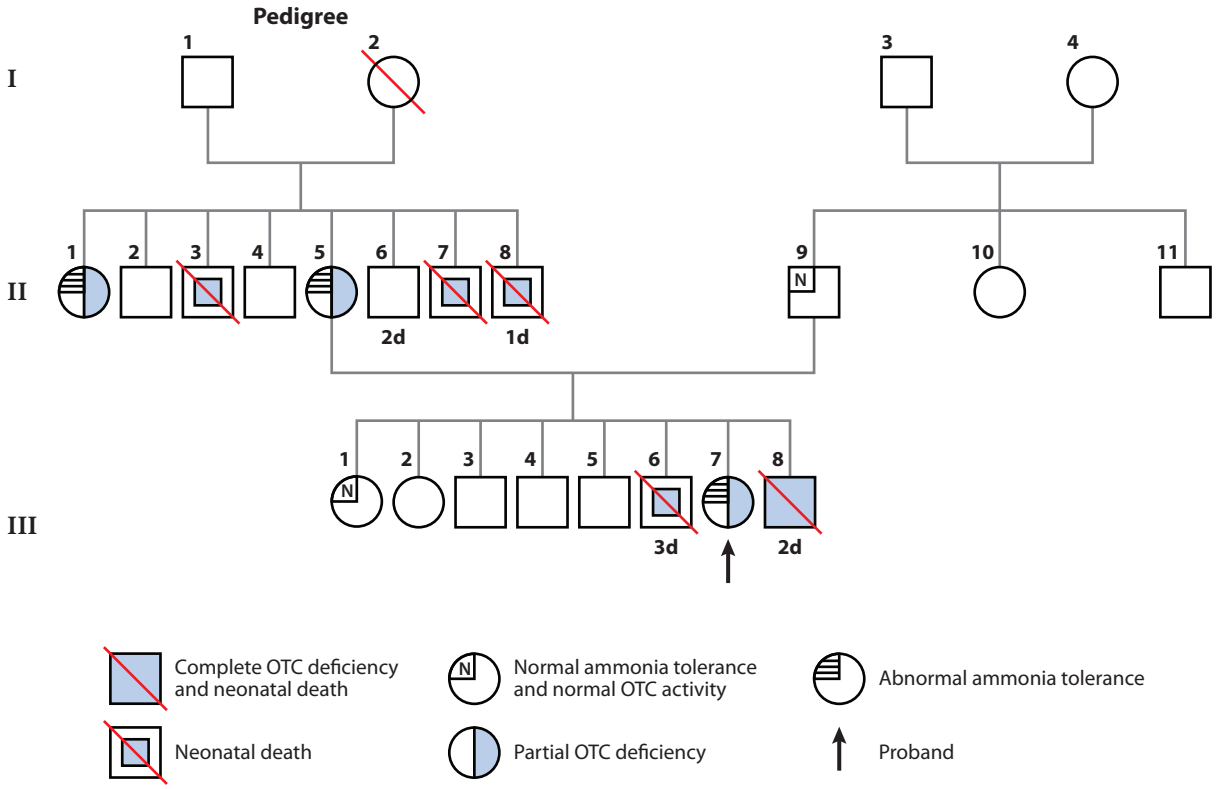

Figure 6

Lorraine's pedigree. She is identified by the arrow. The deceased males in her mother's sibship and among her own siblings solved the puzzle concerning the mode of inheritance of ornithine transcarbamylase (OTC) deficiency.

blood pH is carefully controlled at 7.4; Robby's was 6.9—a value generally incompatible with life. By the time I saw him, an alert and astute pediatric house staff had treated his profound acidosis successfully, and Robby was beginning to awaken. Again, the questions: What was the cause? What acid was accumulating? We were stumped initially. None of the usual causes for acidosis were found. Fortunately, I had just read a paper by investigators from Norway describing a child who died in coma from a previously unreported condition characterized by accumulation of a compound called methylmalonic acid (MMA). This acid forms during the breakdown of several amino acids and fatty acids and is normally rapidly catabolized by the enzyme methylmalonyl-CoA mutase (**Figure 8**). I said to my team, "Let's test Robby's urine for MMA." Most members of the laboratory thought this was foolish—a fishing expedition very unlikely to catch anything. So I decided to follow my hunch myself. With the expert assistance of a recently recruited technician, Anne Charlotte Lilljeqvist, we set up the chemical assay for MMA and standardized it. MMA produces an emerald green color when assayed this way, and the intensity of the color is proportional to the MMA concentration. We obtained a sample of Robby's urine and were stunned when we observed a green color much darker than any of the standards. We obtained other samples of Robby's urine and tested them. Each time the result confirmed that his urine contained huge amounts of MMA. In fact, we estimated that he was excreting more MMA in a 24-hour period than did all the people in the medical center combined (58).

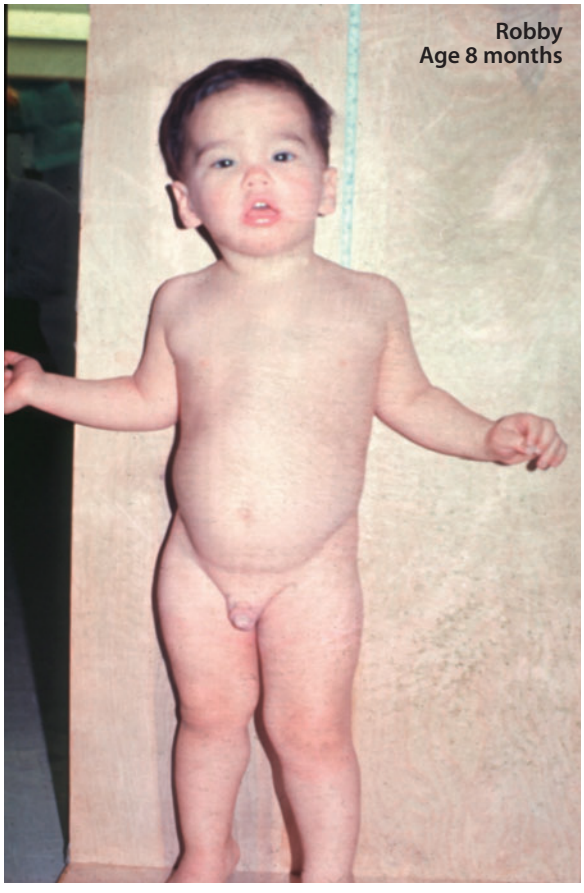

Figure 7

Robby at age eight months, almost immediately after being revived from coma. He was the first child shown to respond to massive supplements of vitamin B_{12} with a dramatic fall in methylmalonate excretion.

Before endeavoring to find the source of this metabolic problem, I chose to follow another hunch. It had been reported previously that the enzyme needed to convert MMA to its catabolic breakdown product, succinate, requires vitamin B_{12} as a cofactor. So, thought I, let's see what happens if we give Robby increasing amounts of B_{12} by injection. At low doses nothing happened, but when we gave him 1,000 times as much of the vitamin as is needed daily by healthy people, the amount of MMA in Robby's urine plummeted by 80% and stayed down as long as we continued the vitamin supplements (26, 59). This was the first time that a patient with an inherited disorder involving B_{12} had been shown to respond to cofactor supplementation. Indeed, it was the first time that any vitamin-responsive inherited disease had its mechanism defined.

For a second time my team climbed the mountain from clinical observation to patient investigation, biochemical characterization, and molecular understanding. Hsia and Mahoney demonstrated that the pathway of MMA formation and breakdown is expressed in leukocytes and cultured skin fibroblasts (27, 36, 60). Once we had collected cell lines from many affected children in the United States and abroad, we were able to identify two kinds of disorders: one that was resistant to the addition of B_{12} to the culture medium, and one that responded. The former class was shown to reflect mutations in the gene coding for the mutase enzyme (referred to as the apoenzyme),

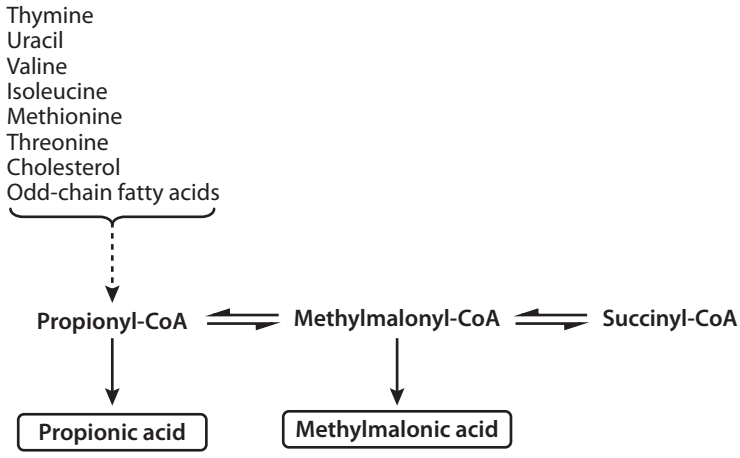

Figure 8

A scheme showing the many precursors of propionyl-CoA and, in turn, the reactions by which the latter is converted to methylmalonyl-CoA and finally to succinyl-CoA. Methylmalonic aciduria results from defects in the conversion of methylmalonyl-CoA to succinyl-CoA, either because the mutase apoenzyme is deficient or because its cofactor, adenosylcobalamin (adenosyl B_{12}), is not made in sufficient quantity. Similarly, propionic acidemia is caused by impaired activity of propionyl-CoA carboxylase, a biotin-requiring enzyme.

and the latter to defects in the genetic pathway by which cobalamin (vitamin B_{12}) is converted to its coenzyme forms (34, 35, 37). Roy Gravel, Ira Mellman, Huntington Willard, and Maurice Mahoney performed the many genetic studies—some employing genetic complementation—that identified several different nonallelic defects in B_{12} metabolism (17, 41, 77–79).

This work, carried out in a few years, again was followed by decades-long studies at many levels. Wayne Fenton led a team that isolated the human mutase apoenzyme and determined its subunit structure and its binding of cobalamin (10, 11). Youngdahl-Turner et al. (82, 83) demonstrated that, when bound to transcobalamin II in serum, vitamin B_{12} is taken up by cells via adsorptive endocytosis. Our work, along with that of others, has now identified at least nine different genetic defects in B_{12} metabolism, some involving the synthesis of both B_{12} coenzymes (adenosylcobalamin and methylcobalamin), others only one of them (39) (**Figure 9**). This has facilitated prenatal and postnatal diagnosis of these conditions.

Another discrete inherited metabolic disorder, propionic acidemia—resulting from deficiency of the enzyme propionyl-CoA carboxylase (PPC), which acts immediately proximal to the mutase enzyme just discussed—was found and dissected chemically and genetically (39). In work led by Barry Wolf, a vitamin-responsive form of the condition—called biotin-responsive propionic acidemia—was discovered that results from defects in the enzyme biotinidase, which is required for binding biotin to this carboxylase and other biotin-dependent apoenzymes (48). Our studies of vitamin-responsive forms of homocystinuria, methylmalonic acidemia, and propionic acidemia were important contributions to establishing that more than 20 different inherited disorders have such vitamin-responsive forms (51, 81). Today, all children found to have methylmalonic acidemia are given a therapeutic trial of B_{12} supplements because it has been shown clearly that children who respond to B_{12} do considerably better clinically when assessed by survival and developmental progress (12, 39).

This interval from the late 1960s to the late 1980s—my "Yale period"—was the most fertile period of my scientific life. The abbreviations CBS, OTC, MMA, B_{12}, and PPC are stamped

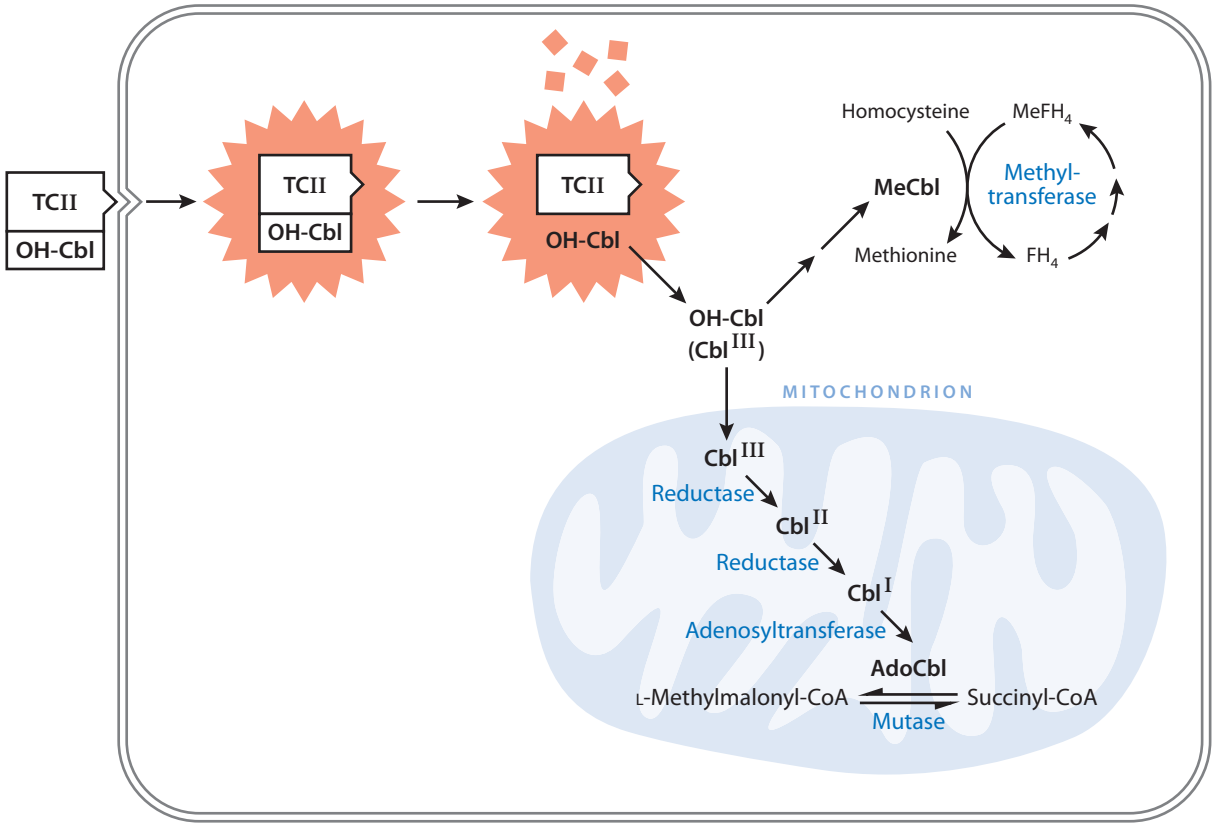

Figure 9

The cellular pathway by which vitamin B_{12} (OH-Cbl) bound to its serum binding protein transcobalamin II (TCII) is internalized and ultimately converted to the B_{12} (cobalamin) coenzymes, adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl). Inherited defects at each of the reactions depicted here have been identified and characterized. Vitamin B_{12}–responsive methylmalonic aciduria results from discrete defects in the mitochondrial reductases or adenosyltransferase enzyme.

on the dossier of my scientific career in bold letters, and on my heart as well. Serendipitously, I asked the right questions and found ways to answer them. Further, the questions I answered led logically to more questions that we (and others) sought to answer. In all of this I was incredibly fortunate to have a long list of faculty colleagues from Yale and elsewhere, postdoctoral fellows, graduate students, medical students, and technicians whose talents and insights were instrumental to our success. I regret not mentioning each of them in this review. I consider the 28 individuals named herein to be seen as representatives of the total number of people—157 in all—who were my coauthors during the years of my active research career (1965 to 1991). I hope each of them knows of my esteem for them and their efforts.

A DASH THROUGH FOUR DECADES

The years focused on up to now constitute but half of my career as a human geneticist. Space constraints make it impossible to do justice to the ensuing years, but I must at least mention the many opportunities offered to me as a direct result of the work I've recorded here. First, the national and international recognition of my work established my scientific reputation—and

more. It led to my appointment as the founding chair of Yale's Department of Human Genetics. This position, held for 12 years, enabled me to demonstrate leadership qualities required for further academic advancement. Our department was the first human genetics department in the United States that housed both basic scientists and clinical investigators. Thus, it served as a model for departments at other institutions. As chair, I had the extraordinary opportunity to frame the department's vision and strategy; to bring together as its charter members faculty from several other university departments; to have a major voice in recruiting new faculty; to raise money for facilities and programs; and, by amalgamating all these activities, to plant the flag of human genetics deeply and firmly into the landscape of Yale University and its School of Medicine. This period was made even more gratifying for me because, with the help of talented postdoctoral fellows, graduate students, and technicians, my own research continued to thrive.

Second, as a direct result of our department's success, my institutional visibility rose. This led logically to my being offered the deanship of the School of Medicine in 1984. I accepted and served in this role for seven exciting years. I did what deans do: raised money for the endowment and for construction and renovation of facilities, recruited nearly a dozen new chairs, and set what I believed to be a moral and ethical tone that would keep the school from being humbled on my watch. With the invaluable help of colleagues who had been my compatriots in science for many years, I tried to preserve a part of my professional life for research. Although I succeeded in holding onto my NIH grants throughout my years as dean, science slowly moved from the front of my mind to a less accessible place. I experienced considerable sadness as I watched this inevitable progression.

Third, these internal opportunities at Yale were matched by many external ones. I will mention three that relate directly to my involvement with genetics. In 1980, I was elected president of the American Society of Human Genetics. Accordingly, I gave the presidential address at the society's annual meeting (49). Here are my favorite words from that speech (in a kind of charge toward its end):

> Biomedical scientists . . . and other self-appointed pundits have discovered a new song in recent years. It is called the "biomedical wail," and it goes something like this: Why is federal funding for biomedical research leveling off? Why doesn't the public thank us for our marvelous work? Why aren't today's medical students stampeding to follow in our academic footsteps? Why must we work so hard and get paid so little? This "hit" song is played so often that you would think we were mimicking the Rolling Stones' blockbuster whose sad refrain is: "I can't get no satisfaction." I have a few thoughts about this song for the young and not-so-young alike.
>
> To my eager, ebullient, energetic young colleagues I say, don't believe a word of it. The complaints you hear are. . .the self-conscious responses of people who feel guilty about having a good time. . . . If you get tired of having your shoulder cried upon, ask the weeper about such academic perquisites as travel, freedom, and challenge. . . . [R]emember that the field of human genetics promises to be as exciting (or more so) in the 1980s and 1990s as it has been in the 1960s and 1970s, and it would be a shame for any of you to miss the fun.
>
> To my weary, wary, and worried not-so-young comrades I say, be fair. When your experiments don't work, or your grant deadline is approaching, or your patients appear ungrateful, don't unburden yourself to [your young colleagues]. Lock yourself in the closet, jog, complain to your spouse, have a beer, but don't frighten the kids. They might just take you seriously. If you must tell it like it is, please be sure to give equal time to the privileges and pleasures of academic life, to the dazzling sense of well-being that follows a scientific discovery, and to the excitement that each of us knows lies beyond our current horizons. (p. 336)

No one reading these words can doubt their aptness to today's scientific climate.

One year later, in ways still mysterious to me, I was invited to testify before a subcommittee of the US Senate that was considering a bill aimed at prohibiting all abortions by stating that science had proven that life begins at conception and must, therefore, be absolutely protected from that point on. The bill's author, Senator John East, had hand-picked six scientists and clinicians—including Jérôme Lejeune, the discoverer of trisomy 21—to argue in support of its passage. I was the sole dissenter and said so in what surely were the most important public words of my life (50):

> [W]e all know that this bill is about abortion and nothing but abortion. If this matter is so compelling that our society cannot continue to accept a pluralistic view that makes women and couples responsible for their own reproductive decisions, then I say pass a constitutional amendment that bans abortion and overturns. . .Roe v. Wade. But don't ask science and medicine to help justify that course because they cannot. Ask your conscience, your minister, your priest, your rabbi, or even your God, because it is in their domain that this matter resides.

The bill ultimately was tabled and didn't reappear (but the societal wound that abortion represents shows no evidence of healing).

A very different kind of opportunity presented itself in 1986. I was appointed to a congressionally mandated committee of the National Academy of Sciences impaneled to offer advice on whether the United States should embark on what came to be known as the Human Genome Project. Although I had served on many committees by this time, this one was special. The stakes were high. The Human Genome Project was controversial, with opposition coming from a number of internationally renowned scientists. The committee was composed of four Nobel laureates and a dozen earthlings like me. The deliberations were heated, even bombastic, in tone and substance. The unanimous positive recommendation set in motion a project that reshaped science and is reshaping society.

To round out this front-loaded, back-hurried story, I want to mention three seemingly incongruous parts of my later career in genetics. In 1991, the restless and ambitious genes that had propelled me sequentially from NIH to Yale, and from scientist to chair to dean, prompted me to leave academia for industry. I accepted the position of Chief Scientific Officer at the Bristol-Myers Squibb Pharmaceutical Company (BMS). I've been asked scores of times why I made this existential decision, one that had enormous repercussions on my professional career. Five reasons: to see whether I could make a difference in an entirely new world; to use my knowledge of genetics to contribute to the discovery and development of important new medicines; to understand the culture of an important industry that had puzzled me throughout my years in academia; to catalyze mutually beneficial interactions between academia and industry; and to gain a hitherto unavailable degree of financial independence for myself and my family. It would, of course, be absurd to attempt to describe my seven years at BMS in a few words. Suffice it to say that even though I accomplished, in part, each of the goals just listed, I found the culture of business not nearly as comfortable as that in academia, and barely managed to make it to mandatory retirement at age 65.

At this ripe young age, I moved again—this time from industry back to academia, to join the faculty at Princeton University. Princeton, too, was an unlikely place for me to land. Why? Because it has no medical school, and because I was one of only two faculty members who had ever cared for sick people, and because I had never before taught undergraduates (which was why I was appointed there). Regardless, I have spent 16 generally satisfying years at Princeton: learning how to teach courses solo rather than in teams; organizing the only human genetics course at the university, entitled Genes, Health, and Society, which has been taken by more than 500 students; advising 36 molecular biology majors and those in the Woodrow Wilson School of Public and

International Affairs on their junior independent work and required senior theses; and being an advocate for careers in science (read: genetics) and medicine.

The last incongruity concerns authoring a recently published book. Thirty-seven years ago I was approached by an acquisitions editor from Plenum Press named Diane Drobnis, who wanted me to write a human genetics textbook. I declined the proposition but became interested in the proposer, whom I wisely wed. Throughout her years in the publishing industry, and for many years thereafter, Diane kept at me about the book. In 2010, the time was right, and we wrote the book together. It is entitled *Human Genes and Genomes: Science, Health, Society*. Obviously, some good things take longer than others.

AFTERWORD

I must conclude this narrative now, but not because I have run out of thoughts, feelings, or memories. Let me liken my career to an odyssey. This journey began in Madison, Wisconsin, where I was bequeathed the genome passed to me from my parents, and shaped by the early years that sculpted my character and direction. It continued on to New York City (for medical residency) before picking up the meandering path that led from Bethesda to New Haven to Princeton. As is the case for everyone's life path, my journey is about much more than the places I've lived. It is, first and foremost, about people: family, mentors, teachers, colleagues, students, patients, competitors, and adversaries. They are etched in my mind for their own sake, as well as for the thoughts and feelings they have engendered.

And what a panoply of thoughts and feelings my odyssey has generated! These include the strengths (high intelligence and the determination to make a difference) and weaknesses (bipolar disorder and attendant recurrent depressions) of my genetic endowment; the chance occurrences and serendipities that ignited my scientific career; the exultation of making significant scientific discoveries that had relevance to sick people; the thrill of becoming a pioneer in a nascent field and moving with it as it exploded over half a century; the bittersweet emotions called forth by the inevitability of making way for the next generation of human geneticists and the ones after that.

Those of you who know me can attest that I am not like Dr. Pangloss, extolling this best of all possible worlds. I have been a dissenter as well as an assenter, a critic as well as an apologist. But I am unabashed in saying that I have been remarkably fortunate to call myself a human geneticist—the badge I will wear proudly and happily as my odyssey continues.

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