ORAL HISTORY PROJECT

William L. Nyhan, MD, PhD

Interviewed by Laurence Finberg, MD

March 3, 2004
LaJolla, California

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Oral history has its roots in the sharing of stories which has occurred throughout the centuries. It is a primary source of historical data, gathering information from living individuals via recorded interviews. Outstanding pediatricians and other leaders in child health care are being interviewed as part of the Oral History Project at the Pediatric History Center of the American Academy of Pediatrics. Under the direction of the Historical Archives Advisory Committee, its purpose is to record and preserve the recollections of those who have made important contributions to the advancement of the health care of children through the collection of spoken memories and personal narrations.

This volume is the written record of one oral history interview. The reader is reminded that this is a verbatim transcript of spoken rather than written prose. It is intended to supplement other available sources of information about the individuals, organizations, institutions, and events that are discussed. The use of face-to-face interviews provides a unique opportunity to capture a firsthand, eyewitness account of events in an interactive session. Its importance lies less in the recitation of facts, names, and dates than in the interpretation of these by the speaker.

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Dr. Laurence Finberg was graduated from the University of Chicago and then received his MD degree from the University of Chicago in 1946. Following completion of his internship in Chicago he fulfilled his military obligation in the U. S. Public Health Service at the rapid treatment center at Hot Springs, Arkansas. Following completion of his service he became an assistant resident in pediatrics at Baltimore City Hospitals from 1949 to 1950 and chief resident at that institution from 1950 to 1951. After completing his residency he joined the faculty of Baltimore City Hospitals and became an instructor in pediatrics at John Hopkins University School of Medicine from 1951 to 1956 and an assistant professor of pediatrics from 1956 to 1963. Dr. Finberg became chairman of the Department of Pediatrics of Montefiore Hospital and Medical Center and professor of pediatrics at the Albert Einstein College of Medicine. In 1982 he became chairman of pediatrics at the State University of New York Downstate Medical Center in Brooklyn. Dr. Finberg also served as dean of the College of Medicine from 1988 to 1991. After 12 years as chairman of pediatrics he retired and moved to San Francisco where he continued working in pediatrics at UCSF and Stanford Universities. During his career Finberg received numerous honors and awards including the Distinguished Service Award of the National Board of Medical Examiners, the President’s Certificate for Outstanding Service of the American Academy of Pediatrics and the Nutrition Award of the American Academy of Pediatrics. Dr. Finberg co-authored Water and Electrolytes in Pediatrics and served as editor of Saunders Manual of Pediatric Practice.
Interview of William Leo Nyhan, MD, PhD

March 3, 2004

DR. FINBERG: This is Larry [Laurence] Finberg. I’m going to interview William Nyhan, whom I will call Bill. And we’re doing this in his house in La Jolla, California. I’m going to start out by asking him to tell us where he was born and what his early life was like.

DR. NYHAN: I was born in Boston.

DR. FINBERG: And did you spend your childhood there?

DR. NYHAN: Yes, I was there until I left to go to medical school.

DR. FINBERG: You went to public high school there?

DR. NYHAN: I went to Boston Latin School, and this year I had the distinct pleasure of going back to my 60th reunion of graduating from the Boston Latin School. And that had a major influence on my life. I was pleased, going back, to see that this still is a very special school and the students are all working very hard.

DR. FINBERG: How was it special?

DR. NYHAN: Well, it’s an elitist school. The criteria for getting in are very intellectual; it is one school that draws its students from all over Boston and the kids really have to work to get through the books.

DR. FINBERG: Did it point you toward medicine in some way?

DR. NYHAN: No, I did 6 years of Latin and 4 years of Greek. I had almost no science when I got to college.

DR. FINBERG: And where did you go to college?

DR. NYHAN: I went to Harvard [University].

DR. FINBERG: And tell us a little bit about that experience.
DR. NYHAN: That also was, I think, a memorable start to my life. That’s when I first began to do science. It was pretty much interrupted. I mean, I only went to college 2 whole calendar years because the war was launched.

DR. FINBERG: And what year was that?

DR. NYHAN: 1943, and I was in the class of 1947. I was already in medical school by 1945.

DR. FINBERG: So you entered medical school without getting your Harvard degree?

DR. NYHAN: Yes, I’ve never gotten a bachelor’s degree. (Laughter).

DR. FINBERG: [Laughter]

DR. NYHAN: I know some people went back, but I was already doing a lot of things, and that’s a very long time. That’s it. We went to college 12 months out of the year in those days, so I completed my first half of the sophomore year and got drafted into the [US] Navy.

DR. FINBERG: So you went into the Navy before medical school?

DR. NYHAN: Yes. Actually, as it turned out, I got drafted into the Navy. And, in their wisdom, they saw that I was a pre-med student and they [Laughter] sent me right back to Cambridge, where I spent the next calendar year doing another year and a half, by which time they judged that we were all ready to go to medical school.

DR. FINBERG: So your Navy experience then was entirely at Harvard?

DR. NYHAN: Essentially. We spent one summer working as corpsmen at the Newport Naval Hospital. But yes, my entire experience. I didn’t get discharged until halfway through my freshman year of medical school; the issue there was the war was over.

DR. FINBERG: You were an enlisted man in the Navy? Or an officer?

DR. NYHAN: Well, I was both. [Laughter].

DR. FINBERG: [Laughter]
DR. NYHAN: I guess they thought we were, but …

DR. FINBERG: Was that midshipman?

DR. NYHAN: Yes. The V-12 program.

DR. FINBERG: Then where did you go to medical school?

DR. NYHAN: To Columbia [University College of Physicians and Surgeons].

DR. FINBERG: How did you happen to choose Columbia?

DR. NYHAN: I didn’t. The Navy sent me.

DR. FINBERG: [Laughter]

DR. NYHAN: That was, again, a wonderful experience for me, and I’m glad they did. It was the first time I’d been away from Boston in my life. And both medical school and New York were exciting experiences going in.

DR. FINBERG: And what, in particular, did you like about medical school?

DR. NYHAN: I’m not sure. [Laughter] I suppose it’s hard to remember all those things, but it was a time of what I would call real giants in medical education. While I was there, [Rudolph] Schoenheimer was in the Department of Biochemistry [and Molecular Biophysics] doing this early work on carbon 14 metabolic pathways, and the guy who taught us most of the freshman biochemistry, DeWitt Stetten, Jr., was, himself, going on to do interesting research and also had a leadership position at the National Institutes of Health. Probably the biggest influence on most of our lives then was Robert [F.] Loeb, the chair of the Department of Medicine and a legendary clinician, and a lot of us got very close to him. I more than many because, when we finished our sophomore course in laboratory methodology, a job opened up at [New York]-Presbyterian Hospital, and 4 of us were given the task and opportunity of running the lab at night for the whole Presbyterian Hospital. It’s hard to imagine, but in those days, one of us was on and another one had to be in the hospital. And we did everything that came along: all the clinical pathology, the emergency room, the injecting the mice with sputum to detect and type pneumococci, and ran the Van Slyke
apparatus to determine CO2. So it was kind of a trial by fire and a wonderful introduction to laboratory medicine.

DR. FINBERG: Was that Rusty [Rustin] McIntosh’s Department of Pediatrics then?

DR. NYHAN: Yes it was. Oddly enough, I don’t think that department had anywhere near as much influence on me as the Department of Medicine. I wasn’t sure if I was going into medicine or pediatrics when I got out of medical school. I can remember applying for 3 different kinds of internships: I applied for a rotating internship, internship to medicine, and an internship to pediatrics—it was only a small handful.

DR. FINBERG: Where did you get accepted?

DR. NYHAN: At Yale [University]

DR. FINBERG: At Yale?

DR. NYHAN: And that was a real landmark.

DR. FINBERG: At Yale in pediatrics?

DR. NYHAN: Yes.

DR. FINBERG: Did you have to serve a hitch in the military then?

DR. NYHAN: No.

DR. FINBERG: Payback? You did not?

DR. NYHAN: No. I’ll get to that [laughter]. That’s an interesting story too. But back to New Haven—I mean those were the days of really very small faculties in the Department of Pediatrics. The inpatient service was divided into 2 wards and Grover [F.] Powers, who was the chief [pediatrician] and also a legendary clinician, made rounds every day on one of those wards except during the summer; then he took off to go to Nova Scotia, wherever it was he went. And for most of the year, Dan [Daniel Cady] Darrow did the other ward. They were wonderful clinicians, both of them. But Dan was special because, in those days, he was one of the very few pediatricians in the US [United States] who had a lot of clinical wisdom, did interesting research,
and influenced the lives of a lot of us—like Robert [E.] Cooke, who was a fellow with Dan when I was an intern.

DR. FINBERG: And you finished your residency there, then?

DR. NYHAN: Yes. That was a little convoluted too. I found myself vulnerable to another draft when the Korean War started. By that time, I really had decided I wanted to do research and wanted to do academic medicine. The then chief of medicine was a consultant for the [US] Army, and he recruited me and I think some other house officers in New Haven to do research in the US Army. And so I stopped worrying about the draft, and I signed up in the Army Medical Corps, and by the time I was going through basic training down in Fort Sam Houston in Texas, he dropped dead. And the next thing I knew, I was the battalion surgeon with an infantry outfit in Korea [Laughter]. So, the MASH [mobile army surgical hospital] hospital was far in the rear compared to where we were [Laughter].

DR. FINBERG: How did that come about instead of the research?

DR. NYHAN: Oh, I think this recruitment was just in the head of the man who disappeared.

DR. FINBERG: (Laughter).

DR. NYHAN: (Laughter). But the Army didn’t know anything about it.

DR. FINBERG: So you spent the next 2 years in Korea?

DR. NYHAN: No. They had a rotation system in those days. We were supposed to get back to the States [United States of America] after serving for a year. Sometimes that didn’t work, so I was over there for 15 months, and by the time I left I was the oldest man in the regiment.

DR. FINBERG: So you were taking care of freshly wounded soldiers?

DR. NYHAN: Yes, but also we were doing general medicine. I spent more time treating infectious disease than I did patching up wounds, but I did a certain amount of that too.

DR. FINBERG: Then you came back, and where did you go?
DR. NYHAN: I came back to New Haven and finished the residency. I had done 2 years before going off to the Army. So I came back and completed a third year, and then I went on to be chief resident.

DR. FINBERG: So you did 4 total years at New Haven?

DR. NYHAN: Yes.

DR. FINBERG: And then what?

DR. NYHAN: Well, at about that time, I decided to pursue fellowship training in biochemistry. I’m not sure I can remember what happened, but I got hooked up with a then young assistant professor at Yale by the name of Harris Busch. Harris was a typical researcher in a lot of ways. Most of the funding was for cancer, and Harris was working on the biochemistry of tumors. So I began my research career on amino acids and tumors. Interestingly, I was supported at that time by scholarships and the March of Dimes. These days, they probably wouldn’t be so liberal about supporting a young pediatrician who was working with cancer, but I tell you, they obviously did the right thing. But anyway, I’d just worked in that lab for one summer when Harris got a job that he couldn’t refuse at the University of Illinois [at Chicago] in Chicago. He became an associate professor in pharmacology, so I began to learn some pharmacology after moving to Chicago with him.

DR. FINBERG: He invited you to come along?

DR. NYHAN: Yes. And it was particularly smart of me to go because once I got there, I began taking some courses so that I’d learn some things that were bigger than just what I was doing in the laboratory. And before I knew it, I was a full-fledged graduate student, and I stayed on at that for years. All in all, I got the PhD.

DR. FINBERG: That brings us to about what year?


DR. FINBERG: So you were there in Chicago for quite a while?

DR. NYHAN: Three years.
DR. FINBERG: Three years. And then you got an offer where?

DR. NYHAN: At Johns Hopkins [University], where we first met.

DR. FINBERG: And Bob Cooke [Robert E. Cooke] was chairman by then?

DR. NYHAN: Yes.

DR. FINBERG: And, of course, he knew you from when you both were at Yale. And so he invited you to come?

DR. NYHAN: That’s true.

DR. FINBERG: You were what, an assistant professor of pediatrics at that point?

DR. NYHAN: Yes. And that was, again, an offer I thought I couldn’t refuse. I thought the Hopkins at that time was a very exciting place. It was my first academic job, and I thought it was a wonderful way to get an academic life. All of us did kind of a mix of clinical work and research, but I think in all the time I was there, nobody ever told me what to do. I had to fight to get a month as an attending on the inpatient service. I’ve heard people struggled to get teaching opportunities too. Of course, nobody gave us money do anything either. We had to be entrepreneurs. That kind of learning experience is the kind of training you need to survive in academic life.

DR. FINBERG: Did you get funding for some research while you were there?

DR. NYHAN: Oh sure.

DR. FINBERG: Where did it come from?

DR. NYHAN: It came from a variety of sources. I had an NIH [National Institutes of Health] grant, I think, all the time I was with [Johns] Hopkins [University]—that would be an RO1 grant. But I can remember, too, while we were there, the NIH developed the General Clinical Research Centers program. I remember being pretty up to my ears in the applications of a Hopkins GCRC [General Clinical Research Center], and that was interesting, too, as a sort of sign of the times. Whereas, here and everyplace else I’ve been, we’ve banded together and developed a GCRC that involved the whole institution. At Hopkins that probably would have been unheard
of, so we had a separate pediatric GCRC, and the Department of Medicine essentially had the other GCRCs.

DR. FINBERG: And so you studied at Hopkins till, if I remember correctly, 1963?

DR. NYHAN: Yes. In 1963, I got again what I thought was an offer I couldn’t refuse. I had at that time been at Hopkins only 5 years. And as I suggested, I loved Baltimore and I loved what I was doing. Well, I got the opportunity to be a departmental chairman; in retrospect, probably younger than optimal. I think the other thing I did, which was kind of a condition of employment at the University of Miami, was getting a professorship in the Department of Biochemistry [& Molecular Biology], which gave me the option that I’ve had here, too, of having graduate students in biochemistry. Over the years, I haven’t had a lot of those, but it’s been a very warm relationship to have that opportunity.

DR. FINBERG: Before you got the offer in Miami, you must have, by that time, been a published researcher. What field were your publications in?

DR. NYHAN: Well, they were a mix too. The Hopkins years marked a real change in direction. When I left Illinois, I was still doing cancer research. And we were busy looking for significant pathways that might be different from tumors than non-tumor tissues, in the hope that once such a pathway could be identified, it would lead to therapy. Well, I was studying amino acids, and—there are stories there too [Laughter]—while I was doing all this, a patient was admitted to the Harriet Lane [Home for Invalid Children], who turned out to be the first reported patient with propionic acidemia. I guess he was first admitted on Bob Cooke’s service, but it turned out that Bob was, at that time, busy being departmental chairman and trying to start the NICHD [National Institute of Child Health and Human Development] and doing all of the kinds of things that he did publicly. Barton Childs was working on this patient, and he recruited me to work up the amino acids in this boy because it had become evident that the patient had a lot of glycine in the blood. And we initially reported him as a patient with idiopathic hyperglycinemia, essentially an inborn error of amino acid metabolism. These patients—I saw one the other afternoon—still have sky high concentrations of glycine in the blood, but the basic defect is the propionic pathway, which is the catabolic pathway for a bunch of branched-chain amino acids. Well, the kind of research Barton and I did on that patient laid the groundwork for that discovery. It also immediately laid the groundwork
for what is still the dietary treatment of the disease. We simply were able to fractionate what it was that made these kids sick: recurrent episodes of ketosis and acidosis. Just breaking down the diet is the sort of thing clinical research centers were made for; we first were able to demonstrate it was protein that was doing it, and then we worked on individual amino acids and found that these children were sensitive to isoleucine, leucine, methionine, and valine—a terrible mix for trying to develop treatment. But, at any rate, that ultimately pointed the way to the fundamental defect, which is propionyl-CoA carboxylase.

DR. FINBERG: Were you successful in treating it?

DR. NYHAN: Oh yes. That was a mixed bag too. I mean, by the time we came up with this approach to treatment, we still didn’t know the molecular defect. This particular boy was microcephalic and severely retarded, and he went on, actually, to die in a clinical research center in another institution, where his father had come to work. But meanwhile, a little girl was born into the same family, and we were able to diagnose—again by the amino acids in the blood and the high glycine content—that she, too, had this disease. And we were able to start the treatment at, I think, 5 days of life. Well, she was born in 1963, the year I moved [Laughter], so she’s now, I guess, 40 years old. And I don’t hear from her regularly, but I think she has obviously been our longest treatment success.

DR. FINBERG: How do you devise a treatment schedule for somebody who is having a problem with essential amino acids?

DR. NYHAN: What we do is, essentially, to walk a tightrope between protein malnutrition because if you get too little essential acids, sooner or later you’ll die of that. But before that, you’ll become catabolic and make these toxic organic acids accumulate. We must provide just enough of those so that one can grow, without having too much of it. And we still do this in the CRC [Clinical Research Center] with an infant. We literally take the protein content down to the point where growth stops and then increase it; a little beyond that. We do nitrogen balances; and on the other side, we measure the toxic metabolites that turn up in the urine.

DR. FINBERG: In infants you can concoct a formula, but as the patient grows into childhood and adulthood, how do they handle protein intake?
DR. NYHAN:  It’s the same approach. In many of these kids we’re still using formulas on them when they’re adults.

[Tape 1, Side 2 of Interview]

DR. NYHAN:  One of the patients we saw yesterday afternoon was a patient with maple syrup urine disease. We’re currently managing a number of those patients, some of whom have gone on to liver transplantation. And they’re almost impossible to manage without a special formula that is composed of fat, carbohydrate, and a mixture of amino acids that’s lacking the ones that cannot be metabolized.

DR. FINBERG: Who at Hopkins influenced you or with whom did you particularly enjoy working besides Bob Cooke and Bart Childs?

DR. NYHAN:  Oh, it was such a wonderful atmosphere. I probably can’t do justice to all of the people that were there. It’s so important, I think, what I thought of as the development of the young faculty members. My lab was right next to Harold [E.] and Helen [C.] Harrison’s lab, and I saw a lot of them. We were dirt poor, and we lived on Eutaw Place. I often, especially in the wintertime when it was the only way I could get some exercise, would walk back and forth to Hopkins to work. The Harrisons often felt sorry for me on a snowy or rainy day and drove me home. I got to know them and their kids quite well. They were both wonderful human beings and great scientists. And Lawson Wilkins’ office was right next door. Lawson was a lot more a friend than colleague and teacher, but he was always around.

DR. FINBERG: And he was training a number of people who became well-known endocrinologists. All right, we’ll get you now to Miami.

DR. NYHAN:  Okay.

DR. FINBERG: Who did you succeed as chairman there?

DR. NYHAN:  Bob [Robert B.] Lawson. But he had gone from there to Northwestern [University] by the time they started recruiting me. So the place was functioning at that time without a chair.

DR. FINBERG: And how did you adapt to all that administrative responsibility?
DR. NYHAN: Well, again, I’m not sure. I think in all the years I was an administrator, I probably was most often a fairly reluctant administrator. I really enjoyed the teaching relationship with the students and, particularly, the house staff. I think when that relationship is good, you get people who years later say, “I was a resident with Bill Nyhan or Bob Cooke or Larry Finberg.” And over the years, I think I was able to pull off that role quite well. The other thing that I did in Miami and here was, I think, probably fairly selfish as a department chairman because I always maintained my own lab and tended to get NIH grants—I continued to be very involved in the clinical research center. And somehow the administration did get done. But maybe to some extent because I happen to be good at finding good people to delegate things to.

DR. FINBERG: Whom did you recruit there?

DR. NYHAN: Jim [James D.] Connor, who is here; Faith Kung, who is here; and Sam [Samuel T.] Giammona, who came here and then went to San Francisco before he retired. I’m sure there are others, but it’s sort of vague memory. And, of course, I said something before about graduate students. The only graduate student I had in Miami—we were only there 6 years—was Larry [Lawrence] Sweetman, whom I ultimately recruited here. He’s gone on to do interesting things. He is currently in Baylor University in Dallas expanding newborn screenings.

The other thing that happened while we were at Miami, and Sam Giammona was big on this, is in the early years of the [John F.] Kennedy administration, the development of centers for dealing with mental retardation. And one of the monuments I left in Miami was the Mailman [Center for Child Development] building; we essentially created, then, that federally run program with a small grant from The Kennedy Foundation [The Joseph P. Kennedy, Jr. Foundation] and a major grant from the Mailman Foundation [A. L. Mailman Family Foundation, Inc.].

DR. FINBERG: Let me step back a moment in your personal history. When did you get married?

DR. NYHAN: I got married while I was in medical school, back in 1948.

DR. FINBERG: And your wife is?

DR. NYHAN: My wife is Christine [Nyhan].
DR. FINBERG: How did you meet?

DR. NYHAN: We were introduced by a friend. She was then living in Portland, Maine. And we really were introduced just before she took off for France for a summer with The Experiment in International Living. And I guess we got to know each other well enough that she called me once she came back, and the rest is history.

DR. FINBERG: Okay. And when did you start to have children?

DR. NYHAN: During the residency. All of our kids were born then.

DR. FINBERG: How many children do you have?

DR. NYHAN: We have 2. We had 3, but one died.

DR. FINBERG: All right. Now we’ll turn to you finishing your tenure at [University of] Miami. What led you to want to leave Miami when you got the offer in San Diego?

DR. NYHAN: Oh, it was literally an offer I couldn’t refuse. The situation in Miami was an interesting and formative one for me, but I didn’t have any illusions that it was a great university. We had a wonderful president, a man named Henry King Stanford, and he is one of the reasons I was able to raise the money to lead that Mailman donation. I can remember when I was recruited to Miami, he was one of those people who was talking about a sudden influx of federal money to American universities and it was like “instant excellence.” Well, a lot of excellent things happened in the medical school, but there wasn’t any underpinning. If you wanted to go and find an organic chemist, for instance, at the University of Miami, you would find somebody who was teaching a class of hundreds of students and didn’t have a laboratory, and there wasn’t any research going on. In contrast, my first experience with UC San Diego [University of California, San Diego] was when I was on an NIH program project committee, and I was chairing a site that was in the department of biology. And the number of people on the site included Nate [Nathan Oram] Kaplan and a biochemist who was then at Brandeis [University], Morris Freidkin, who was a biochemist at Brandeis at that time and Gordon [H.] Sato, a cell biologist. Anyway, we reviewed all this wonderful research with these exciting young people, and within about 2 years, all of us were working at UCSD [University of California, San Diego].
I think, what we’ve been able to accomplish here would have been impossible had I stayed in Florida.

DR. FINBERG: So this was in 1968 or 1969 you left Miami?

DR. NYHAN: Nineteen sixty nine.

DR. FINBERG: You came then directly to University of California, San Diego Medical School.

DR. NYHAN: Yes.

DR. FINBERG: As I recall that period, wasn’t there some town-gown competition in San Diego between a children’s hospital and the medical school?

DR. NYHAN: Oh, I think there has been in a continuing fashion. It’s essentially completely resolved now. My clinic is at [Rady] Children’s Hospital; virtually all of my sick patient admissions are at the Children’s Hospital and have been for a while, maybe 10 years. That relationship has been formalized as such the last few years.

DR. FINBERG: Tell me some of the highlights of your career here. It’s now more than 30 years. And you were chairman almost all that time?

DR. NYHAN: No. I’m not sure I have my dates on when I stopped being chairman. But it’s significant that there have been 2 chairmen and now an interim chair, who’s into his third year, since I stopped. I’ve been out of that for a sufficient time, so I’ve pretty much settled into a non-administrative role in the department.

DR. FINBERG: Well, when you first came here, you were the chairman. And this was a relatively new department at the time?

DR. NYHAN: Oh, yes. When I first came here, there wasn’t any department. The inpatient service was at what’s now called the UCSD [University of California, San Diego] Medical Center, at that time San Diego County Hospital. There were no pediatric patients on the ward. I got here in June; our first interns and residents came in July. So that first year was kind of formative. Initially, there were only 2 or 3 of us who were on the faculty.
DR. FINBERG: And those are people you brought with you from Miami?

DR. NYHAN: Yes.

DR. FINBERG: And then?

DR. NYHAN: That was a great time. The first class at UCSD began the year that I had accepted the job, but I didn’t move for the whole year, traveling back and forth across the country. I had done some teaching with that class, pretty much in their biochemistry course, so we really got to know them very well. And those were the days when the national boards would tell you who did well and who didn’t, and UCSD was first in the whole country. It was a fun time to teach. Again, I think we were very lucky. UCSD School of Medicine really did start out as an intellectual dream, pretty much by Dave [David] Bonner in biochemistry. He came here from Yale and had met Roger Revelle, a geologist, and he essentially single-handedly designed this school. I think they were a little unrealistic. They had originally thought of it as a school with no undergraduates, and that couldn’t happen in California. But still, they ended up recruiting a first-class faculty, and that brought with it a caliber of students that we had to teach.

DR. FINBERG: Was it difficult to recruit a house staff to the new service?

DR. NYHAN: Yes, it was. But it was much easier than I would have imagined. When I was in Miami, we worried every year that we weren’t going to fill the internships, and sometimes we didn’t. And all the years I was involved in recruiting house staff here, our only concern was that we get the best people that were applying to us. There wasn’t any question of filling them.

DR. FINBERG: Location probably was an additional incentive.

DR. NYHAN: Yes, absolutely. [Laughter]. But, you know, the Miami location was pretty good too. But it hasn’t caught the imagination of people the way California does. The California graduates don’t want to leave California. And people graduating elsewhere want to come here.

DR. FINBERG: By the time you got out here, you were already a well-known figure in pediatrics with a pretty strong bibliography. When did you get into the practice of writing books?
DR. NYHAN: I guess while I was here.

DR. FINBERG: What was your first book, and how did you happen to start it?

DR. NYHAN: Well, these things are often somewhat accidental. I really first got into the book that was a project that Bob Cooke developed for McGraw-Hill [Inc.]. It was another one of those imaginative projects that he thought of—developing a textbook that expressed pediatrics not only as a clinical discipline, but as a subdiscipline of biology—and conceived a 2-volume textbook that a number of us working all over the country participated in. But as it turned out, it was a big commercial flop, and it had only one printing before it died. At any rate, Bob was good at starting things like that. But when it came to proofreading the whole book and getting it between covers, somebody else had to do it, and I ended up doing it. As a result, I got to know the editors at McGraw-Hill. When they moved, Bill [William] Keller headed that division. When he moved from New York to the Year Book [Medical Publishers, Inc.] in Chicago, we sort of continued to keep in touch. One day they were talking to me about doing a book of my own. It’s funny the way things go. I had a fellow at the time who was interested in becoming a clinical geneticist. We had fellows over the years, all the time, who came to us, and they would spend a little time seeing patients. But most of the time, they worked in the lab and got projects accomplished. Well, this one lady was completely unsuited to the laboratory. Nadia [O.] Sakuti was a Syrian who is now part in Saudi Arabia, at King Faisal Specialist Hospital [and Research Centre]. But at any rate, in those days she was trying to learn clinical genetics. I felt I had to dream up a project for her. And this was a time when Dave [David W.] Smith really had just created the discipline of dysmorphology. But he hadn’t yet written his book on dysmorphology, so there was a void there. And so we sent Nadia out to collect pictures and do some writing of text, but mostly I had to help her with that. The first book was literally a compendium of our experience. So it contained a certain amount of biochemistry and also a smattering of what we had seen.

DR. FINBERG: What was the title of that book?

DR. NYHAN: *Genetic & Malformation Syndromes in Clinical Medicine.* We did a sequel of that a few years later. But then, more recently, a British publisher asked me to put together a book that was less dilettantism and more a reflection of our own special experience in inherited diseases of metabolism; the most recent book is called *Atlas of Metabolic Diseases.*
That’s done very well, and I’m now, I guess, about three quarters through putting together a second edition of that book.

DR. FINBERG: Have there been other books besides?

DR. NYHAN: Yes, just last year, Georg [F.] Hoffmann and I developed the idea of putting together a handbook of inherited metabolic diseases [Inherited Metabolic Diseases: A Clinical Approach]. The sort of thing that a clinician and house officer might find useful—designed to go from clinical manifestations to the way one would work up a patient and seek a diagnosis. And ultimately, Georg, whom we got to know first as a fellow here and now is chair at the University of Heidelberg, recruited a couple of his faculty members to join in that effort. And I also recruited Steve [Stephen G.] Kahler, now a visiting professor of pediatrics at Hopkins. So that was a multi-authored book. Whereas my other books, although I had some co-authors, I’ve really written the book essentially.

DR. FINBERG: Have we touched on all the titles of your books?

DR. NYHAN: I think so.

DR. FINBERG: So you’ve been a successful writer of medical specialty texts, I would say.

DR. NYHAN: I think successful in the fact that at least the recent books are things that people read and find clinically useful. Not that they would be commercially successful, but successful enough that people want to get new editions.

DR. FINBERG: The clinic that you started even while you were chair is called what?

DR. NYHAN: Metabolic Clinic. The division is called Biochemical Genetics [UCSD Biochemical Genetics]. So to some extent our clinical offerings are more in the laboratory than they are in the clinic, but we take care of a full range of disorders of metabolism.

DR. FINBERG: And that includes diabetes, for example?

DR. NYHAN: No, it doesn’t. The endocrinologists have historically taken care of the diabetics.
DR. FINBERG: That wasn’t true at Hopkins when you were there, although it ultimately became so.

Tell me a bit more about what you look upon as your most important contributions over your career?

DR. NYHAN: Well, I think the things that will live on most are the research and discoveries that we took part in. I feel fortunate that we came into biochemical genetics at a time when the definition of the molecular nature of disease, at least of the enzyme level, was just beginning. And we were fortunate in finding the molecular nature of something like a half dozen diseases.

DR. FINBERG: What are they?

DR. NYHAN: Let me tell you one story because I think this is one of the best achievements. I had indicated earlier that Barton and I had been involved in studying what turned out to be the first patient with propionic acidemia. The year that I moved here, I was still trying to study propionic acidemia. But that’s such a terrible disease.

[Tape 2, Side 1 of Interview]

DR. FINBERG: We were talking about various things. You were in the midst of a story which took you back you to your work with Bart Childs at Hopkins, and you were elaborating.

DR. NYHAN: Yes. We were trying to do some studies on propionic acidemia, and it’s such a terrible disease as far as recruiting an available subject or subjects to do the kind of tracer study that I had in mind. I just couldn’t find one in the US, and I knew that there were 2 in hospital at The Hospital for Sick Children on Great Ormond Street in London. So I went to London to do these requirements with these 2 kids.

While I was there, I wound up with people and they showed me a kid who was really memorable. He was a kid that had already been studied enough to know that he had an organic acidemia, and the biochemist there had written a paper that was ultimately published in The Lancet, describing him as having an inborn error of leucine metabolism because he excreted 3-methylcrotonylglycine in the urine. But when I saw the kid, I was really
struck. He had a history just like those of kids with propionic acidemia who had developed acidosis that was so intractable that he had been living for months in this hospital and massive ketonuria, but he had this amazing total body eruption. His skin was bright red and peeling. And he had lost all his hair (alopecia totalis); not only on his head but his eyebrows and his eyelashes were gone. I thought clinically he was something really special, so when I was going back to San Diego, I asked if they would let me take a sample of urine and a skin biopsy to set up a fibroblast culture. We had just then developed our own organic acid analyzer, and we had gotten together with people in biology and chemistry to buy our first GC [gas chromatograph] mass spectrometer. When we ran this kid’s urine through the machine, we found just what they found in London, that he had an excretion of 3-methylcrotonylglycine and 3-hydroxyisovaleric acid that you would expect from someone with a disorder of leucine metabolism. But we also found that he had methylcitric acid. And methylcitric acid, we had previously discovered, is the world’s best marker for the propionic pathway; that’s what we’d see in propionic acidemia, so it was clear he also had a disorder of isoleucine metabolism. We then grew out of the fibroblast and were able to show, just as the London people had, that his 3-methylCoA carboxylase was deficient, but so was his propionyl-CoA carboxylase. The other carboxylation is that of pyruvate, and so we did that enzyme, and he was deficient in that one too. So that was fun; we were able to write another paper [Laughter].

We renamed the disease “multiple carboxylase deficiency,” but it didn’t make any sense that you could have a single gene autosomal recessive disease producing defects in 3 different enzymes, each one coded for by different genes. So there had to be a common factor, and it turned out that the basic defect was in holocarboxylase synthetase, which is an enzyme that activates biotin by activating biotin and then hooking biotin onto the carboxylase; so it’s the one that makes these carboxylase proteins into enzymes. That was the molecular defect, but the side issue that’s made it such an important disease is that these patients are exquisitely sensitive to biotin. So as little as a 10 milligram daily dose of biotin is enough to change this disease from something that if untreated is uniformly fatal to something that is really easy to treat. And we now do prenatal diagnosis of that disease, and a family known to be at risk—that small handful of patients—is assigned prenatal treatment if the mother will buy it, so the kid never has a symptom. But I think that was a real success, and rewarding in the sense that it says if you can learn enough about the fundamental biochemistry, it sometimes will lead you to a way to treat the patient.
DR. FINBERG: What’s the mechanism to the alopecia?

DR. NYHAN: It’s biotin deficiency, I think. I don’t know more than that, but I guess the real answer is I don’t really know. The extrapolation of biotin deficiency is that we have studied patients with other enzymatic defects of biotin metabolism and, also, the rare patient who has real biotin deficiency, which we almost can’t produce in man without the avidin protein that is in raw eggs. All those patients have alopecia, but the truth is, I don’t know the mechanism.

DR. FINBERG: Well, that’s 2 major biochemical or amino acid disorders that you were instrumental in describing. Are there others?

DR. NYHAN: Yes. The most recent one is also a wonderful story. Again, it’s not just my work, but the work of the young researcher who graduated from the program. But as we enlarged our clinical spectrum of disease to encompass pretty much the full range of inborn errors of metabolism, I found that we were seeing increasing numbers of patients with mitochondrial disease. I think, to some extent, this is because we developed an experimental treatment and were one of 2 (and now 3) places in the country with Food and Drug Administration approval. But it’s a treatment, so we’re attracting a lot of patients with the kind of mitochondrial disease that wasn’t known before the 1990s as distinct diseases: mitochondrial encephalomyopathy, lactic acidemia, and stroke-like episodes. But, at any rate, it became apparent, particularly to this young fellow who came to us for his training in internal medicine before he was a fellow, that these patients’ clinical manifestations were highly reminiscent of those patients treated for HIV [human immunodeficiency virus] infections with drugs like AZT [azidothymidine]. And you may remember that there was a big a nationwide collaborative trial on the treatment of Hepatitis B CHIMERIC EURO-CELL patients, but it was halted because of people developing what were diseases of the liver and brain, and death. The reasoning was, if these patients who had something wrong with their mitochondria had clinical manifestations like those of the retroviruses, then maybe the mitochondrial DNA [deoxyribonucleic acid] might be made in a similar fashion to the DNA of something like the circular retroviruses, like Hepatitis B. And it has turned out that the mechanism of reproduction of mitochondrial DNA, by an enzyme known as polymerase gamma, can operate as both a DNA polymerase and an RNA [ribonucleic acid] polymerase. The antiretroviral agents are particularly effective against—RNA polymerase activity doesn’t get much activity, it’s DNA
polymerase. So, at any rate, what we have now demonstrated is that, depending on the conditions, mitochondrial DNA will replicate either in an RNA template fashion or a DNA template fashion. Organs like the heart that require a lot of oxygen will function predominantly in the RNA template fashion; whereas, organs like the liver will function in mixed fashion with predominantly DNA polymerase. Further on that, we had a little boy who ultimately died of overwhelming encephalopathy and liver failure. We were able to show first he had a mitochondrial DNA depletion syndrome, and then we were able to show that his fundamental deficiency was in the same polymerase. Now there are a number of enzymes that are capable of causing mitochondrial DNA depletion, but this was the first molecular definition of mitochondrial DNA depletion syndrome.

DR. FINBERG: So your laboratory has moved into the new arena of molecular biology as well?

DR. NYHAN: Yes. Not too many examples of working at the RNA or the DNA level; we’re predominantly still a small molecule laboratory, but we do some molecular work at this laboratory. The other place we’re doing molecular work of course is HPRT [hypoxanthine-guanine phosphoribosyltransferase], the cause of Lesch-Nyhan disease.

DR. FINBERG: Tell me a little bit about that. And who is Lesch [Laughter]?

DR. NYHAN: Sure. Well, that takes me back to Hopkins again. Our first patient with that disease was admitted to the Harriet Lane in, I think, 1972 or 1973. And at the time, Mike [Michael] Lesch was a freshman-sophomore medical student who had come to work in the lab one summer. I was so impressed with his work that we started out our project in a program that was at that time popular at Hopkins, where a student would take a whole year and work in the lab and still graduate with his class. So Mike had launched on that, and we were still doing some cancer research in those days, and I had him working on the problem that I think was probably insoluble in those days and probably easily soluble now. But at any rate, he was doing that when this first kid came into the hospital. Again, our entry into this kid’s story came through the laboratory; he had turned up in the emergency room with blood in the urine. In those days, interns looked at the urine under the microscope. And the intern was really impressed that not only was there blood in this urine, but it was full of crystals. And I remember at that time we called Nan [Nancy] Esterly, who was a resident in pediatrics before she became a pediatric dermatologist. They looked together and looked at
the book in clinical pathology that says how to identify crystals by their appearance under a microscope, and they looked just like cystine crystals. Well, they admitted the kid to the hospital with a tentative diagnosis of cystinuria, and by that time, I had an amino acid analyzer, so the morning after admission somebody came up with this kid’s urine and said to document this diagnosis of cystinuria. We couldn’t find any cystine in the urine or lysine, arginine or ornithine, and while we were doing that, of course, we had to see the patient and that was a very striking experience; maybe even more so than this kid we told you about in London. In addition to his ticket of admission, this was the kid who had severe developmental delay. He had spasticity, movement disorder, dystonia, and he had this horrible self-injurious behavior. His hands were all wrapped up and he’d been chewing and biting his lip, and that just blew our minds. So we took Mike off the project he’d been working on and put him full time on this, and we ended up publishing. We published in the *American Journal of Medicine* because the editor then was Al [Alexander B.] Gutman, the chief of medicine at that time at Mount Sinai Hospital in New York and one of the world’s authorities on gout, and I thought he would appreciate the nature of this. What Mike had shown was that these kids not only have hyperuricemia, which was the real cause of those crystal in the urine, but they also were turning over purine so that they were making inosinic acid and uric acid at a rate that was at least 10 times higher than any of the most severe gout patients that had ever been studied before—again, by people like Schoenheimer at Columbia. Gutman was also back to my time at Columbia. He was my first attending on the internal medical service when I was a third year student, and he was a wonderful connection; as was another guy who worked in the laboratory. So yes, we published it in the *American Journal of Medicine*, and it’s turned out to be a disease that’s caught the imagination of all kinds of people because it’s a very useful enzyme for studies in cell biology.

DR. FINBERG: Self-mutilation is, you know, an obvious major clinical feature of this disorder. Are there other self-mutilation disorders?

DR. NYHAN: Yes, but the differential diagnosis is fairly small. Most of the self-injurious behavior you see in institutions is fairly nonspecific and not related to any particular disease. But also, it tends to be different from what you see in these kids in the sense that it’s often low grade and repetitive, so you see hypertrophy rather than loss of tissue. You see kids who bang their heads and cauliflower ears, and the skin becomes hypertrophic; whereas in these kids, the ferocity of the behavior leads to amputations, loss of tissue.
But back to your question, we do see injury of this sort and its sensory neuropathies, but those are quite different too because their injury usually is accidental. We have some patients with dysautonomia, and we have published a few patients with the Cornelia de Lange syndrome, which also has self-injurious behaviors, but it’s a very small list.

DR. FINBERG: Okay. We’ve talked now a good deal about your career and accomplishments as a scientist and a clinician scientist. Let’s dwell a little bit on your career and thoughts as a pediatric educator.

DR. NYHAN: Well, I don’t know that I have it that clearly in my head. I think I alluded to it a little earlier in terms of the relationship to house staff education and medical student education.

DR. FINBERG: Well, in your days at Hopkins, the residents were a powerful group in running what was then called the service patients and had a great deal of autonomy.

DR. NYHAN: Yes, okay.

DR. FINBERG: Much of that has been taken away from them by legislation that insists on having faculty, or at least senior certified pediatricians, being more directly involved. What do you think that has done to the educational system?

DR. NYHAN: I’m not sure, but I think that the Hopkins system that we all grew up with had a dramatic effect; at least on the way I tried to organize both the service in Miami and the service here. The concept we used to use in recruitment of interns was that this was a residents’ service rather than a subspecialists’ service. I think over the years that increasingly there had to be faculty presence. I think that’s not necessarily bad for the patient. The powerful resident who doesn’t think he needs faculty supervision sometimes does need faculty supervision. So I think the patient care has not suffered from these changes, probably it’s improved. I think, over the years, that our emphasis of the central position of the residents and the general services approach to the subspecialty service sometimes fell through because the resident himself really didn’t want the responsibility and would seek out the attending in a subspecialty discipline. And then if the attending isn’t there for him in that situation, he’ll end up just transcribing what the consultant directed, which some residents do prefer.
DR. FINBERG: So you think what we’ll call the older system and the present system sort of come back to the same place, without either of them being superior?

DR. NYHAN: To some extent I think they do. I know our service is much more a subspecialty service than it was in the early days.

DR. FINBERG: Do you think there continues to be a significant role for a generalist in academic pediatrics?

DR. NYHAN: I hope so. [Laughter] It’s certainly the only way to be a successful attending on an inpatient service; I guess even an outpatient service.

[Tape 2, Side 2 of Interview]

DR. NYHAN: I must admit I’ve always thought of myself as a generalist. I had all this training in biochemistry; but as a geneticist, I’m completely self-taught. I’ve never had a fellowship in clinical anything.

DR. FINBERG: And I take it you’ve maintained your confidence to recognize a variety of infectious and neoplastic diseases, so that you can at least begin the initial management of such patients and the supervising of residents in the initial management of such patients.

DR. NYHAN: I think so.

DR. FINBERG: And you would agree then that fostering such careers is still desirable; I think they’re beginning to disappear.

DR. NYHAN: Yes, I know. Well, it’s a mixed bag. I think that as we demand more and more of subspecialty training, we’re not only losing the generalist, we’re also losing the investigator. By the time you’ve put in all those years as a resident and then all those years as a clinical fellow, there almost isn’t any time left for a laboratory discipline. But I think those things are probably going to get worse before they get better.

DR. FINBERG: Yes. I notice that there’s been a recent change in the direction for certifying the subspecialists and that they’re no longer demanding that a research publication be part of the certification process.
DR. NYHAN: Sure.

DR. FINBERG: I’ve looked on that as a good thing that they’ve made the change. What do you think?

DR. NYHAN: I think it’s a good thing, too, in the sense that, to some extent, that publication is often only lip service to research. I think what it needs is a real commitment.

DR. FINBERG: How much laboratory training, in terms of years, would you say the average person needs to become a competent clinical investigator?

DR. NYHAN: Again, I don’t think I really know. But I can tell you that in my case I was at it for 3 years, during which I did nothing but biochemistry. I did take some courses. But you know, the trouble is it has to be a continuum. There are so many hours in the day and years in a life, and I’m not sure I’m too good at the philosophy of what it is you should be doing. But I do, deep down, have the feeling that our emphasis on subspecialty certification is detracting from the investigation of disease.

DR. FINBERG: The other program that’s come along, that you did serially and now is done in a more combined fashion, is the MD/PhD program.

DR. NYHAN: Yes, I would want to endorse that.

DR. FINBERG: Think that might be the way to get good clinician scientists coming down?

DR. NYHAN: Yes, get him trained in research before he gets down to the hospital.

DR. FINBERG: Then he can build on that subsequently, yes.

Okay, let’s turn a little bit to student education. When we went to medical school, the format was pretty much the one that [Abraham] Flexner described after his 1910 report, in which he spent 2 years doing exclusively the underlying sciences and then 2 years clinically. It was leading to a lot of frustration in some medical students; they didn’t like those first 2 years. What was done to adjust to that, was putting some clinical experiences into those first 2 years. What do you think of that movement, which has now become just about universal?
DR. NYHAN: Again, my experience with it is so limited that I don’t really feel adequate to comment.

DR. FINBERG: Did you do that here at San Diego [University of California, San Diego]?

DR. NYHAN: Again, I’m distant enough from that, I think, that I can say yes, but I wouldn’t be able to tell you how we did it. I’ve done regular teaching in what amounts to the physical diagnosis boards. So I think I really plead ignorance. I mean, I’ve been highly involved in teaching and the clerkship, but other than that, I just haven’t really had the experience.

DR. FINBERG: Have you talked to students about it? Or do you have any feeling about their reaction to the present state of things? Obviously they can’t compare. [Laughter]

DR. NYHAN: No. Again, I have talked to students. Over the years, I’ve had quite a record of people telling me they’re spending extra time with us, but I get the feeling that, pretty much, they’re still dying to get through those first 2 years and get onboard.

DR. FINBERG: What about recruitment into pediatrics these days? What do you see as the present and potentially the future of that endeavor?

DR. NYHAN: Well again, that’s something that during my years as chair I was intimately involved in. I’ve kept quite a low profile here since I’ve stopped being chair. But I don’t honestly know any problem in recruiting to pediatrics.

DR. FINBERG: Are you currently involved in committee work with the NIH or with other national organizations that are sponsoring and funding research?

DR. NYHAN: Yes and no. I did a lot with the NIH over the years. I was on 2 different study sections, and I was on the council of NICHD [National Institute of Child Health and Human Development]. But I think they’ve retired me by now [Laughter]. And I was on 2 committees for the March of Dimes for birth defects. I have been working with the new genetic mitochondrial disease foundation [United Mitochondrial Disease Foundation] and reviewing things for them and a small local foundation.
DR. FINBERG: What else would you like to talk about in this interview that we haven’t covered?

DR. NYHAN: I’m not sure that there’s anything left. [Laughter] Well, actually there’s one thing that might be fun to mention: I don’t know if you saw this book. Probably not.

DR. FINBERG: No.

DR. NYHAN: Richard Preston is an interesting author who writes about science—sort of—as mystery.

DR. FINBERG: The book is entitled?

DR. NYHAN: I’m sorry. *The Cobra Event*. He came up with it, and he came up with one award-winning book called *The Hot Zone*, which is about Ebola virus. But anyway, in this one he writes about germ warfare, including some of the US files before the ban was set, and some of the things that probably were still going on in Iraq before our latest adventure over there. In the context of a sort of viral warfare, he writes about a mystery in which the terrorists have developed a virus that contains the DNA of a worm everybody uses because it replicates a lot; they hook it onto a virus that will penetrate the mucosa and target the brain and, ultimately, hook it onto a mutated HPRT [hypoxanthine-guanine phosphoribosyltransferase] enzyme so that somebody infected with this will indulge in mutilative behavior, either to himself or to somebody else. [Laughter] That’s sort of the theme of this thing. And actually, they’re making this germ in New Jersey, in a factory that’s masquerading as a gene therapy laboratory.

DR. FINBERG: Were you consulted on any of these books?

DR. NYHAN: No. He’s consulted me since.

DR. FINBERG: Ah.

DR. NYHAN: But I think he clearly got a transcript of one of the lectures I gave in New Jersey at the Matheny Institute [for Research in Developmental Disabilities], so he knew even some of the wording I’ve used. But we hadn’t met on that until after he published it.

DR. FINBERG: And why would he consult you after he had published it?
DR. NYHAN: I think because he became interested in the disease. He’s thinking about writing a book on the disease.

DR. FINBERG: All right. Anything else?

DR. NYHAN: I don’t think so.

DR. FINBERG: All right. Well, thank you very much. It’s been a great pleasure for me to do this. I learned a good deal about your career, which is certainly a fascinating one. How long do you think you’ll continue to work, or do you ever plan to retire?

DR. NYHAN: I don’t plan to. I’m having too much fun. I’m long since over the time that it used to be mandatory to retire.

DR. FINBERG: Okay. Well, thank you very much.
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Government and other Appointments:

Academic Appointments:
The Johns Hopkins University School of Medicine, Asst. Prof. of Pediatrics, 1958 to 1961, and Assoc. Prof. of Pediatrics, 1961-1963; University of Miami School of Medicine, Professor of Pediatrics and Biochemistry and Chairman, Department of Pediatrics, 1963 to 1969; University of California, San Diego, Professor, Department of Pediatrics, 1969 to present and Chairman, 1969-1986.

Publications:
Books, chapters and original papers, 633; abstracts 214.

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