Dr. Irwin Arias was interviewed on September 12, 2017.

Dr. Margolin: I'm Dr. E. Gordon Margolin, volunteer in the Office of the NIH History and Stetten Museum on the NIH campus in Bethesda. I'm here in this audio-visual production area of the NIH Library on September 12, 2017, about to conduct a focused oral history with Dr. Irwin "Win" Arias, regarding his life as an accomplished clinician and scientist, his major contributions to the science and practice of hepatology, and his outstanding involvement in medical education. Thank you, Dr. Arias, for joining us this morning. We're going to pick your brains for the next hour or so. Tell us first a little bit about your background. Where were you born, and where you grew up.

Dr. Arias: Well, I was born in suburban New York in Rockville Center, which in the 1920s was a small town with dirt roads. I went to the public school system there, graduated from high school a year and a half earlier, and went to Columbia College, which after one semester, I joined the Navy. The Navy sent me to Dartmouth College to train for 90 days as a communications specialist officer. At the same time, previously I had applied for and been accepted at Harvard University. And so when I stationed to the Boston Navy Yard, I had a double life, going to school at Harvard and also standing watches on a ship which was undergoing repair. After a brief and uneventful naval career, I returned to college and graduated from Harvard in 1946, officially in the class of 1947. My interests at the time were diffuse. Psychology ... generally I took like two courses in almost every department at the university. And I truly had no idea as to what my future was going to be like.

My best friend played a very important part in my teenage years. He was a clinical psychologist, who was the director of a laboratory that was set up at the World's Fair in New York, 1939, in the Westinghouse Building. It was called Youth of Today, Scientists of Tomorrow. And my good friend Eddie Silvers and I had an exhibit there, which meant we could leave high school, actually, and go to the fair, which we did with considerable regularity. So after the fair, everything that was in that exhibit was set up in a laboratory at 310 5th Avenue. That's one block south of the Empire State Building. It was an amazing experiment in education for young people, and for me was highly motivating.

There were 40 young boys and girls selected on the basis of an original research proposal. There were no classes, no exams. You met at the school weekends, holidays, and pursued your project. My friend Eddie and I were studying light transmission in plastics. So that group of 40 people, when it finally emerged and all the analyses were done, it was the most successful experiment probably ever conducted in a way of educating and exciting young people. There were four Nobel Laureates, 22 members of the National Academy, and when a survey was done 35 years later, it turned out that everyone did something of some significance and excitement in their careers, mostly in science. And that had a profound influence on me.

Well, after Harvard, the director of the laboratory was Henry Platt, and he was a clinical psychologist, and I emulated his interests. So I went to Columbia to study clinical psychology. I became fascinated with the idea that schizophrenia was a biochemical disease and I quickly learned that as a psychologist, I couldn't approach the problem, and I was strongly advised to go to medical school, which necessitated making [inaudible 00:05:39] by taking a bevy of classes which I never had, qualitative chemistry, quantitative chemistry. In fact, I never had had a formal course in biology until this graduate experience. One of the courses was in experimental embryology. Professor [00:06:04 Hoshimi]. That really excited me, as did another course in protein chemistry by Robert Ballantine.

My advisors strongly suggested that I go to medical school, which I had never seriously considered. But my grades were good at Harvard, although quite dispersed, and there was one enigma. I had a D in organic chemistry. And whenever I went for interviews, at all the wonderful places I applied to, that was the only thing they ever asked me. In 1951, I was on the waiting list at five Ivy League schools, and in 1952 ... and one of the schools I applied to was the state university of New York, in Brooklyn. There, professor Sam Seifter became very much an advisor and advised me during the subsequent graduate training that I had. And I think it was largely his influence that I received an acceptance letter to the state university of New York in Brooklyn.

At the end of the second year, I was totally frustrated. I was tired of sitting, listening to lectures, six or eight hours a day. We never saw a patient that I recall, and I decided I wanted to go back to graduate school. Sam Seifter asked me if I had any friends in Boston and I said "Oh, yes." And he said, "Why don't you go visit them because I think you're in the wrong school." So I took a train ride to Boston and on the train, had an experience which taught me that serendipity is one of the greatest things you can follow if you want a successful career in anything. What happened? I was studying diligently on the train all the way to Boston. And a gentleman was sitting next to me, who I thought was old. He was probably about 50. And he was very interested in what I was studying. And we began a conversation in which he asked me all kinds of things, which I had missed in my relationship, or lack of, with the faculty at the state university of New York.

As we pulled into Back Bay, he advised me to go see Professor William Castle, who was Chairman of the Department of Medicine of the Harvard Service, at the Boston City Hospital. I went to ... I followed his advice, but I must tell you that when he got off the train in Back Bay, I asked him "Who are you?" I had spilled out all of my story and really knew nothing about him. And he said, "My name is John Enders, and I want you to keep in touch with me." A few years later, John Enders won the Nobel prize, or shared in it, for the discovery of polio virus. And for my subsequent six years in Boston, he remained a friend, an adviser, and I would meet with him three or four times a year and he really expressed great interest in the problems and the questions that I was asking. So

I graduated from medical school and then was accepted for an internship and residency on the Harvard Service at the Boston City Hospital.

The vast majority of patients there had liver disease. This was a high alcoholic population. And we had hands on experience under superb instruction. Professor Castle, Max Finland, Ed [inaudible 00:10:29], Charlie Davidson and many others profoundly influenced my interest in internal medicine and increasingly in liver disease. Parenthetically, at the end of my first year of medical school, I had led a youth hostel group in Mexico and returned with now what we would call hepatitis A but at that time there was no virology known. I was very sick. And I learned that the physicians new little about it other than rest and take some vitamins. But there were many things about having had acute hepatitis that remained in my mind. And that also was a catalyst to push me in the direction of becoming interested in liver disease. But before that came to fruition, I spent a year as a hematology fellow with [00:11:33 Morley] Strauss at the then newly founded Boston Veterans Administration Hospital, which was a mecca of academic hepatologists.

I was unhappy, because the clinic that I ran consisted of about two dozen young men with Hodgkin's Disease. In those days, there was only nitrogen mustard and P32 to treat Hodgkin's Disease. Today, it's treatable, and largely curable. But almost all of those young men died during the year of my fellowship. And I felt that that was not the kind of medicine I wanted to be involved in. And I gravitated back to the city hospital, under the influence primarily of Charlie Davidson, who ran the liver unit at the Thornbeck Laboratory, and others, and spent a very productive two years learning about liver pathophysiology and pathology.

At the end of my training there, I still hadn't decided what I wanted to do, but I thought that perhaps I would go into medical practice. My family lived on Long Island and we used to drive down regularly to visit. And I noticed as one approached the Bronx Whitestone Bridge from the north, that to the west there were new buildings being built. I inquired as to what they were, and I was told it was a new medical school, the Albert Einstein College of Medicine. Furthermore, I was told that the newly appointed Professor of Medicine was Irving London, who had been a professor at Columbia Presbyterian, at Columbia University School of Medicine. And oddly enough, Irving was one of the leaders in bringing the emerging field of biochemistry into hematology. And Max Finland had recommended that given my interest in protein chemistry and all I should really talk to London, which up to that time I had not done.

So this was another serendipity, fortuitous. Irving and I met. He offered me a job as an assistance professor in the department. I was the fifth or sixth member of the department. The school started in 1957 and it was an incredible experience. I remained there for 29 years and it's hard to describe the enormous excitement of a group of brilliant young faculty. Equally brilliant students, many of whom had been denied admission to medical schools in the metropolitan area. In fact,

I would note that in the first third year class, clinical medicine rotation, in which I was the preceptor for a group of ten individuals, nine of the ten became professors of medicine. And one, Jesse Roth, became a branch director here at the National Institutes of Health and played a critical role in the discovery of insulin receptor and other hormone receptors.

So this was a halcyon period. Everyone shared in the excitement of doing things for the very first time. And I remember when our first group of students had applied for internships, the basic sciences and the clinical people all sat and watched as the results came in. Medical rounds consisted of a live patient, a clinician, and a basic scientist. In fact, biochemistry, which was the prevalent advancing science of the time, this is before the explosions in molecular and cellular biology, biochemistry was deeply ingrained in both the clinical as well as the research aspect. The institution flourished and continued to do so. My years at Einstein make me still consider it, frankly, as my perpetual academic home. And I remain a Emeritus Professor and visit there three, four times per year at the request of the Dean, or as an advisor to the Marion Bessin Liver Research Center, which I was the founder of. It was the first NIH supported liver research center in the country.

The strength of it rested on the fact that we, within a few years, had a faculty of approximately 45 individuals from major basic science departments in the school as well as clinical departments. And we sought to bridge the increasing gap between advances in immunology, biochemistry morphology, and human disease, liver disease. And the accomplishments were many. The liver center is now its 35th year, having been successfully funded at each turn, and is currently under the directorship of Allan Wolkoff, who's Professor of Medicine in Cell Biology. The environment at Einstein, which permitted us and encouraged us to be literally living with basic scientists and informing them about major disease problems and in turn collaborating and learning technologies and their potential application. All of that led to major discoveries. The Einstein Liver Center was the first, through the work of David Shafritz, who became the second director, was the first to actually apply molecular biologic techniques in the study of human liver disease, with the demonstration that the hepatitis B virus was integrated into the genome of many patients with primary liver cell cancer.

The Center has a long and distinguished record of accomplishment in this bridging between basic scientists and clinical activities.

Dr. Margolin: Dr. Arias, you told me that hepatology as a subject of study hadn't been developed early in your life, career. When did that really come into being?

Dr. Arias: Well, it happened primarily as I mentioned at the time when I became frustrated with hematology and was at the city hospital where there was an abundance of liver disease. It was very interesting that a very famous pathologist, I think it was Tracy Mallory, had convinced the city of Boston authorities that alcoholic liver disease was a toxic disease. This meant that all

patients who died who had liver disease fell into the domain of the medical examiner. In other words, autopsies were performed on virtually every patient. 85%, something like that. So the accumulation of pathologic information actually was extremely valuable in defining the course of chronic liver disease, discovery of the pathology and like Wilson's disease and others. So this was environment in which I became interested. And when you added to that the biochemical interests that I acquired, was influenced by at Einstein, it seemed challenging to bridge these two, which is exactly what we did.

Dr. Margolin: It seems to me by recollection that pathology was really the basic science of the day before the biochemistry came in, and that's exactly what you just said.

Dr. Arias: I think that's true.

Dr. Margolin: Yeah.

Dr. Arias: And that has a very interesting historical basis.

Dr. Margolin: Yeah. Exactly.

Dr. Arias: The great medical centers of the late 19th century, and early 20th century, were Vienna, Glasgow, Berlin. And what they had in common was for the first time trying to relate pathology to symptomatology of a disease, the signs and symptoms. That had never been done before. And the tool that was used to do that, was pathologic examination. Now in the case of the liver, it's interesting that the workhorse stain that was developed in the late 19th century and is still the workhouse, is the hematoxylin and eosin stain. And in our present work, dealing with polarity of hepatocytes, one of the reasons why no one has ever commented about this in any textbook or anything ... I've never seen the word polarization used in a liver biopsy report in all my career, nor have my other colleagues. And the reason is because pathologists still rely to a great extent on hematoxylin and eosin stain, which does not visualize the portion of the liver cell that is the polarized domain. But that came many years later.

Dr. Margolin: Did you use an awful lot of liver biopsies during those period of time for part of your studies at Einstein?

Dr. Arias: Did we use liver-

Dr. Margolin: Liver biopsies.

Dr. Arias: Well, yeah, liver biopsies were first developed, my recollection is, perhaps in the fifties and sixties-

Dr. Margolin: Yeah. Before maybe-

Dr. Arias: There were different kinds of needles, and veins connected with it. But that became ... You see, there were no real liver function tests in those days. They were very indirect, until Arthur Carmen, who was a medical student at NYU, he discovered the amino ALT and AST, as enzymes in the liver and other tissues, and he developed a rapid test. And it turned out to be useful initially for diagnosing myocardial infarction, but then it was realized that most of this stuff came from the liver. So those two enzymes still are the workhorse today identifying damage to the hepatocyte. Before that, we had a whole collection of things which nobody understood mechanisms that were involved, and they were very imprecise. And none of them are used anymore.

Dr. Margolin: Let's move on to your move to Tufts and tell us about that.

Dr. Arias: Well, okay. So when I ... I was very fortunate in my era and given my interests, to have taken five sabbaticals in my career. Each one was in a basic science environment. Each one was a full year with outstanding people, and they profoundly influenced the nature of our research, which we have not gotten to. The first was at Stanford in 1970, in the Department of Pharmacology, with [inaudible 00:25:07] Goldstein and Bob Schimke, who had just gone from NIH to join that department. We met, became colleagues, friends, and I worked with Bob in the general problem of protein turnover and degradation of organelles within the liver. In those days, this was really avant garde, and Bob became very famous for his pointing out that degradation was a major factor in controlling the presence of various proteins, all proteins.

That was a highly productive year, which greatly influenced our work. The second one was seven years later at UC San Diego, where I was with Nate Kaplan, who was a leading biochemist, Gordon Sato, an incredible cell biologist, and Jack [00:26:16 Kite], a protein chemist of considerable renown. And during that year, as with all my sabbaticals, I met incredible people, established close professional and personal relationships, and they were highly productive. And as I said profoundly influenced what the next steps were in our research. The third one was here at the NIH, where I was fortunate to be appointed as a Fogarty Scholar and I studied for a year with Bob Adelstein learning about cytoskeleton.

And during that period of time, another serendipitous event occurred which profoundly influenced what we've done. I went to a seminar where Mark Willingham from Ira Pastan' lab, I'd known Ira for a long time. He talked about the multi drug resistant proteins and they had developed antibodies and were staining them in different tumor cells. And I asked, are these proteins, is this protein, MDR1 or PGP as it's known, is it present in normal tissue? And I was given the surprising answer, we don't know, and they didn't have much normal tissue at the NIH, and it had to be fresh. I went back to Boston, without killing anybody collected a bunch of fresh normal tissues, came back in a week, and we identified for the first time the presence of this PGP molecule on apical domain of hepatocytes.

I'm getting ahead of myself as to what that apical domain means, but it was that discovery that opened a whole new paradigm of how things are secreted from the liver into the bile. The fact that they use ATP hydrolysis and specific transporters had not been considered at all because in those days, ATP was for driving ions, sodium, calcium, potassium. Not organic molecules. I've often reflected that if we ever had the conversation about biliary secretion with a microbiologist, they would have told us to add some ATP to these vesicles we were studying, because in microbiology ATP was known to drive organic molecules, but that knowledge had not been transferred into mammalian physiology. It's really kind of interesting.

Then the fourth sabbatical was at Harvard, with Guido Guidotti in the Department of Molecular Biology and Biochemistry. Guido, like all my mentors, is a most remarkable person who is an expert in membrane structure and function, which is what we were involved in. So while I was there in Boston, a dear friend was the chairman of a search committee at Tufts, in physiology. And they had not been able to recruit anybody for a period of several years. So I was asked to come over, take a look and advise. I had no ideas. My plan was to go back to Einstein where I was happy and productive and have a lot of activities, etc. Well, at the end of my visit, it was apparent that the department consisted of three people, and they were teaching morning, noon and night. It was not very productive.

So the president of the university, whose father had been a famous French physiologist, Sir Jean Mayer, he called me in and said "Look, tell us what we should do to make this a first rate department." I really think he wanted to compete with Harvard, that was always his ambition. So I wrote down a bunch of things, some of which were quite ... I'd never heard of being accepted before. At any rate, I received a phone call from him and said "Look, if we accept all of this, would you think of coming to Tufts as the chairman of the department?" Part of this deal was to recruit 11 faculty who were to be paid fully by the university, and to re-equip and revise, I think it was about 4,000 square feet of space for the department. Furthermore, and this was extraordinary, this faculty was largely going to be doing research, and they were going to be highly productive. And they would be attracting grants and other funds.

So the money that would be used to offset half their salary was to remain within the department as a rotating fund. Jean Mayer, the head of the school, accepted this, and we were off to the races. This was in an era long before the extensive requirements that exist today to recruit a faculty. Some people refer to it as benevolent dictatorship. Now being in Boston and having strong contacts at Harvard and being in Guidotti's lab, I was very fortunate in that people like Lew Cantley came to our department. Ellen [inaudible 00:32:44], Michael Forgac. Within two years, we had recruited eleven faculty plus many others. And the total size of the department had swelled to something close to about 50 or 60 with graduate students, post docs, and it was incredibly exciting and highly productive.

At that time, having come from a medicine department, I was intrigued by the fact that when I talked to graduate students, with whom I'd had very little experience, of why are you a graduate student in a medical school, rather than in the biology department or chemistry department, and they all would say because we want to do something that influences human health. Now the truth is in that day, and I expect today largely as well, a lot of these students may be across the street from a major medical center. They might as well as be on the moon. Because their knowledge, their experience, their contact with medicine, per se, is negligible. And they become frustrated. So we set up a program at Tufts, pathobiology for graduate students and post-doctoral fellows. The program was rather simple. It met twice a week for two-hour sessions. The first would be in the hospital, where being also a professor of medicine I had access to what was going on there.

And so if we ... take for example, a topic would be liver death and regeneration. Now these students and fellows, most of them didn't know where the liver was let alone what it looked like or what it did. And they were very bright students, they were very outstanding, and they've had very careers. So we would give them three livers. One like jello, one like leather, and one ... and ask them just to push at them and describe what they feel. And then they would look under a multi-headed microscope and they would see necrosis, fibrosis, and normal. It didn't matter that they couldn't name the cells or anything else. In a brief exposure, they had seen the essentials of pathology and realized that these things happen in every cell in the body, not just the liver. And then they would see a patient who ... well, each one was a unique experience. Two days later, they would sit around a table, no lecturers. They were given things to read, references to look up if they wanted to. It was all Socratic, and with an outstanding person knowledgeable in liver cell or any cell growth maturation and so forth.

And that was the basic nature of the bridging for about 15 to 20 topics were covered in that course. Well, this program attracted enormous attention. We received funding sequentially from four different foundations. The last was the [00:36:39 Markie] Foundation, who became so excited by us that they put it on a national level and funded approximately two dozen such programs, each one different from what we were doing, but on the basic theme of teaching pathobiology and exposing basic scientists, not just students and fellows, to what are the real problems. What do they look like? What do they feel like? What is an MRI? And this also attracted the attention of Michael [inaudible 00:37:19], who became a good friend. We met at the MDR meetings, because of Michael's work in multi drug resistance was similar to what we were doing in the normal liver. And we had long conversations.

And that formed the basis of my coming down here for second sabbatical because at this time we were doing advanced imaging analysis of the liver with Jennifer Lippincott Schwartz and so I was appointed a second Fogarty with Jennifer, and at that time Ruth Kirstein became very interested in this whole

educational business, and was very influential in helping us to set up what is the demystifying medicine program here. Given the huge size of this institution and the fact there are something like 4,000 or 5,000 post-doctoral fellows, and patients can't ... these are research patients, you can't take patients, students and fellows easily. So we had to change it. So what we did was reinvent the wheel. We reinvented old fashioned brand medical runs. In today's medical centers, I have yet ... in many years of giving grand medical rounds in the largest places in the country, many of them, there has never been, to my knowledge, a live patient ever presented.

Dr. Margolin: You're right.

Dr. Arias: And so we reinvented old fashioned grand medical rounds, a topic, maybe HIV is an interesting one just for illustrative purposes. So I'll never forget this. We had a 35-year-old gay male nurse who presented his story in unabashed English that people could understand. Nothing had been watered down. People were shocked, because most of the audience here at NIH, they didn't know much about HIV at that time. They knew what was in the newspapers, which wasn't very much, and a lot of it had been watered down. At any rate ... And then a clinician discussed the HIV epidemic and so forth and so on. And then a leading retrovirologist discussed what do we know about this, the virus and how does it work and what are the problems. And the audience has swelled. We have about 800 or 900 NIH people who sign up each year for the course. On site there's between 80 and 120, sort of fills the room. There were between several hundred up to 400 or 500 watch online, and then a few days later every program goes on YouTube or on the NIH video archive, which is available around the world.

And the program and its contents are replicated now in 18 different countries and over two dozen major North American institutions. All of the programs for the past 14 years are accessible online to anyone. And the people who participate in this are largely the NIH clinical and basic investigators. So this is really material that's truly at the crest of the wave. So that's how I got to Tufts.

Dr. Margolin: Well, now, I want to clarify. You were at Tufts for a goodly period of time, and then when did you transfer to NIH and begin to spend a full time here?

Dr. Arias: Yeah, I was at Tufts for what, 18 years, I think? 17, 18 years. Wait a minute, I-

Dr. Margolin: I had you from 1984 to 2002.

Dr. Arias: Yeah, that's right. And now in 2000, when I first came to NIH, it was under a program where I was officially a faculty member at Tufts, but my support came from the NIH, and I was here virtually full time, with a laboratory as part of Jennifer Lippincott Schwartz's lab, and a group of fellows and students which was an incredible experience. I was the only medically trained person in that laboratory of really brilliant young people. And they profoundly influenced me,

and we to some extent influenced them in terms of the important problems and sort of being a benevolent grandfather to them. And that has been a great experience. At any rate, so I was in that, I think it's called an IPA program, until 2007. So in 2007, by Congressional limitation, that IPS was limited, and so I was given a choice. I should point out that during the time that I was both at Tufts and here, my research grants was still operable. It was first awarded in 1957, and continuously funded until 2007.

Dr. Margolin: That's very remarkable, and probably set a record of NIH grants.

Dr. Arias: So we had a laboratory in Boston where we could do some things that were not so easily done here legally. And at the same time had the support and working in Jennifer's domain. And this was really an incredible, highly productive arrangement. So in 2007 I had to make a decision. I either went back to Tufts permanently or became a senior scientist here. So I chose the latter, became a government employee, and that lasted until ... for five years. And at the end of the fifth year, I was given another choice. I was a rehired [inaudible 00:44:50] for another three years, and then that program ended, and I became a contractor. And in the meantime, my responsibilities were divided between a research operation and so forth. And then being a member of Michael's staff as an assistant to the director of the intramural program, I was responsible for the Demystifying Medicine course. So it's been a little bit of a delightful mix-up and all of it to the good. All of it challenging, exciting, and-

Dr. Margolin: So with all these changes you've still been able to run a laboratory and develop new ideas and new thoughts?

Dr. Arias: Oh yes. Well, so you want to hear a little about our research.

Dr. Margolin: Yes.

Dr. Arias: Okay. So in the days when I went to Einstein, oddly enough bilirubin was a hot topic. Bilirubin is the breakdown product of [inaudible 00:46:08] that makes people yellow, jaundiced, and it happens through the liver disease, blood disease, all kinds of things. But nobody really knew about the chemistry of bilirubin. Why was it sometimes secreted in the urine and other times not? And it was research done almost simultaneously in England, in Czechoslovakia, and that Rudy Schmitt did here at the NIH that identified the water-soluble bilirubin that came out of the urine and bile, was actually a glucuronide conjugate of the bile pigment. Well, and that was the state of affairs when I went to Einstein. Well Bilirubin is somewhat related to hematology, and Irving London was a hematologist, so he was very happy and very supportive of this. And the question was how do you form a glucuronide?

And in the literature, I came upon the work of Julius Axelrod, who here at the NIH had developed methods for measuring glucuronides and their formation. It's an interesting story. I tried, I was very clumsy in the laboratory, particularly

the first year or two there I was terrified at Einstein. And I had trouble, I couldn't repeat Axelrod's assay. And I went to Irving and I said "Something's wrong. Should I write to him?" And he said "No, call him up." I'm a young assistant professor calling up this famous scientist, Julius hadn't won the Nobel prize yet, but he was very famous, and he went, he said "Irwin, call him." So I called him, and he said "Look," he said. "I can explain it to you, but you better come down here." And that was my first visit to the NIH. That was about 1958 or 9.

So not only did I come down here and spend two days, but Julius invited me to stay with his family, and we became friends, and for the rest of his life, later when we came here to NIH, Julius was a frequent visitor at our home [inaudible 00:48:40]. He was an amazing man who also had a great influence on me. I have been fortunate to have a list of mentors in science and in medicine that have all had profound influences not only on work but life and the way you think, for which I am very grateful.

At any rate, we took the assay back, modified it for bilirubin, and we worked out on enzymatic assay for an enzyme called UDP glucuronyl transferase, which transfers the glucuronic acid from a donor molecule, which had been discovered by a Scottish colleague, Geoffrey Dutton, from that donor molecule to bilirubin, and that enzyme is only found in the liver. Well, that was our first big science thing, was a paper in Science. Well, one of the people in the lab, Victor Herbert, who has a very illustrious career, Victor belonged to an Army Reserve group where there was a famous physician named George Jervis, who was in charge of the state asylum in New Jersey, where they had a patient who was deeply yellow all of her life. And it was not with this water-soluble bilirubin. So we thought ah, this patient must be missing the enzyme.

A liver biopsy was obtained. We demonstrated absence of this enzyme, and this was a paper in Science that attracted a lot of attention. And then we discovered each one of the these ... this is a long and interesting story, but I'll be brief. We discovered all kinds of animals that had inheritable jaundice. Rats, mice, later sheep, the golden lion, tamarind monkey in the National Zoo. Many have inheritable jaundice. And people. And this led us into a whole world of pediatric hepatology, genetics, and some of this bilirubin damages the brain, so we got involved in kernicterus or brain injury. And the pathways that we described for bilirubin going into the cell being conjugated and being secreted turned out to be far more important in their application to drugs and to endogenous things like hormones, than even the bile pigment.

But knowing that people who have mutations in these processes were going to be yellow, for the most part from birth, provided a marvelous phenotype which we could exploit worldwide and met all kinds of interesting colleagues, important colleagues and friends when we discovered inheritable jaundice in two small towns on Greek islands, in a family's ... in a distant area of Puerto Rico, in South America, in Asia, and through this a collection of nine inheritable disorders was described. And as I said, each of these, like with bacterial

mutations, provided a key to what the normal processes were. And the next step was their application to acquired diseases, drugs, even viruses. So the bilirubin has long since dropped off the scene. Nobody does research on bilirubin much now. Except pediatricians who are still concerned about how bilirubin damages the brain and produces kernicterus.

So that was our first big area of research, inheritable jaundice and mechanisms of bilirubin and so forth. The second big area spun out of the serendipity of PGP, of the experience here. The discovery ... it had been thought that things like bile acids, phospholipids, various organic molecules, bile pigments, that they were all secreted into the bile by energy from the sodium pump, which is on the other side of the cell. Somehow, we all knew that minus 35 millivolts from the sodium pump was insufficient to create these concentration gradients, but for the reasons I mentioned before, nobody got too excited about just adding some ATP.

Dr. Margolin: You're fine.

Dr. Arias: Once we did that, we discovered functionally that there were at least three ATP dependent processes in the polarized apical domain, the part of the liver cell across which bile is secreted. And functionally we defined them and showed their absence in one or more of the mutations. This now occurred at the period of time when molecular biology was beginning to have an impact. And within a short period of time, the genes responsible for these individual transporters were cloned, the proteins were largely sequenced, and much was known about them. And this of course spread widely around the world. Many laboratories in the liver world were becoming interested in this. The next thing that happened was, people wondered as did we, what would happen if any of these transporters were mutated. And when we looked, largely in the pediatric liver population, we and others discovered six inheritable diseases due to these transporters, in their primary sequence, their folding or their release. So that was the second big area of our research.

The third spun out of the linkage between those discoveries and cell biology. The question was, why are these transporters only in apical domain of the hepatocyte? How did they get there? Where do they come from? Why don't they go to the other places? And what determines their steady state? These are all basically profound cell biologic problem. And the relationship and collaborations in working with Jennifer's group have provided answers to that. And so the next ten years was spent delineating the cell biological roots by which these transporters are made, processed, secreted, go to the apical membrane, recycle, are degraded, come back, and in other words defined this whole area. And we're still doing that. We've identified close to 20 major components of the complex system that causes this. The trafficking system. And this is where the cytoskeleton gets involved, and the tight junctions, and these are basic cell biologic problems, which we are relating.

And it was during this that we began to utilize the newly developed techniques of silencing RNA or have knocked out experiments with mice and so forth. And beginning a few experiments with [inaudible 00:57:20] technology more recently. And so the question was what happens if we knock out one of these 19 guys? And low and behold, when we began to do this, an amazing thing happened. It wasn't just that the transporter didn't get to the apical membrane, it's that the cell was no longer polarized. The whole apical membrane structure didn't occur. Wow.

This introduced us to this whole area of polarization. And it's fascinating because in hepatology, it's totally neglected. There's only one text book, the one that we had, that mentions the word polarity. Of all the major ones it doesn't exist, and even in the pathology books. Why? Because it's all based on this hematoxylin eosin stain, which doesn't see that structure. The structure of the bile canaliculus wasn't appreciated until electron microscopy was developed on the fly. So the other thing that's unique, the hepatocyte is the only cell in the body where two cells come together and they form ... part of their structure comes together and they form a tube. And that tube is the smallest branch of the biliary system and connects eventually to the common bile duct. Very unique. And every cell may have two. Or sometimes three. Very complicated cell biology to cause that kind of a structure. And then it turns out of course that it's polarization is very complicated. And we've discovered it involves four major complexes. The tight junctions, the cytoskeleton, the trafficking pattern, and energy.

And that is the third big serendipity. It was actually at a family party in Boston, of a mutual friend, when Lew Cantley and I were wandering around, just catching up, and Lew said to me "You know this molecule AMPK, adenosine monophosphate protein kinase, it controls everything. It even controls polarity." "Polarity, how does that work?" Well, Lew had discovered that AMPK plays an important part in the polarization of tissue culture cells. So we wondered if the same thing happened with hepatocytes. And it does. How? So the past seven or eight years, we have focused on the utilization of energy within the hepatocyte as influencing all the components of polarization and what happens. And the bottom line is, when a cell is depolarized, its programmed for death. Now, we have now identified nine inheritable diseases previously unknown, rare, in children, where depolarization is the phenomenon.

The interesting question is now, okay, what can we learn from the rare ones that applies to the common ones, like hepatitis, drugs, viruses, liver damage? Because those cells are depolarized too. Now how does that happen? And that's what we are actively exploring at the moment in conjunction with a lot of other people.

Dr. Margolin: This has been quite a tour and quite an opportunity to hear all this, in a brief way, considering the many years that you've put into all these studies. And they're very, very exciting to listen to. I'd like to take the last five or ten minutes

of our discussion and have you comment on what happened to the physician scientists, which you were and still our, and which is rare bird these days. And why did they disappear and why were we taken over by PhD's, and exactly what is happening in the world of medical science that you've been so involved in all these years.

Crew 1: Okay.

Dr. Arias: Well, believe it or not, at the time when I was a beginning medical scientist, believe it or not, what was rate limiting was ideas, and not money. If you were a bright student, if you'd worked hard, if you showed you were deeply interested, and you had a good sponsor and an interesting idea, you would be funded with a fellowship or a grant. It wasn't that difficult. I don't know what the figures are, of the proportion, but what I'm saying is quite true. That what was limiting was ideas and not money. As science advanced, beginning with biochemistry, then the explosion, development of molecular biology, cell biology, which continues, these are not like one tidal wave. This is a continuing thing. More has been learned in the past I don't know, 20 years, than in the past hundreds of years. So I think of it as a logarithmic explosion.

And the problem is that its linkage to human disease, you can think of it as arithmetic. So the gap gets bigger and bigger and bigger. Well, what caused the gap in the first place? Lots of things happened. For one, it no longer became an attractive career. Well, in my day you could do three things. You could be a pretty good scientist. You could be a clinician. You could be a good teacher. You really could wear all those hats and still fly around on airplanes and give talks and do every other thing. I don't think that's possible anymore. It hasn't been possible for a long time. For a few exceptional individuals, it's quite possible. But medicine has dramatically changed. It no longer ... our patients, you know, would be in a hospital for a week, 10 days, you really get to know them. Then it all changed. People would come in for a procedure with a chart that's two inches thick. It's rushed, it's movement. It's movement. So there isn't that pace has changed. And it's all related to the healthcare issue and funding and all that sort of business. So science has advanced tremendously.

The opportunities for young people have diminished in that regard. More and more physicians are required in an academic setting to basically earn their salary, or a large part of it, by taking care of patients. How can they compete in the contemporary world, let's say of the past even 30 years or 40 years? They're going to compete for grants with people who are really at the forefront of training in these new technologies which are providing answers. The problem is what questions are they answering. And this is a manifestation of the gap. Somebody once said that it's more likely the academic physician who knows what the questions are, and it's the basic scientist who knows the answers, but they don't communicate. And I think that is ... even that today is more of a problem than it has ever been.

But it began about 30 years ago. Jim Weingarten, when he was director of the NIH, wrote a very important paper in the New England Journal, of the disappearance of the physician scientist. And it was because of all of these factors. Then you have to add other things. If you're a physician, the requirements to be certified in any given area, you know, they keep adding years and years on, it becomes impossible. People also want to live somewhat of a reasonable life, and that becomes difficult to do under all of these pressures. So much has been written about this. This one of the reasons ... I think it was, I forgot, in the late 80s I wrote an article in the New England Journal talking about training of PhD's not to be alternative physicians, but the role of the PhD in helping to bridge this gap.

It's very simple. Tom Cech said it's so simple that everybody should believe it. But nobody seems to buy into it. The simple thing is, why shouldn't PhDs know something about medicine. Not just somebody give a lecture but let them see what a patient looks like. Let them hear what a patient experiences. Years ago I once asked a group of our students at Tufts, "Give me an example of a molecular disease that you could cure." And they all said sickle cell anemia. And I asked them well, what is a patient, what does it look like? Well, they knew something about it. So the next day they came in and we introduced them to three patients. They all had homozygous S sickle disease. One had impossible bone pain. The other had major hemolysis. The third one had major thrombosis. They all had the same genetic disease. Now please explain that to me.

They didn’t know that. They didn’t realize that medicine is much more complicated than a black box with arrows going in and out. And you can only get that if you have some exposure to what a patient feels. Isn't it ... It seems to me incomprehensible that at some point, hundreds of people were working on HIV virus, and frankly most of them didn't have a clue as to what the disease was like. Now how do you know what's important. Some things are, some things aren't. And I think that the real problem is for physician scientists today, it's very difficult to compete. There's been a surge to where translational medicine. To me translational medicine is the same terms that we used 40 or 50 years ago, like bridging or communicating. But it's this idea that yes, you should learn something about clinical trials and all of that, and that's important. But that in and of itself is not the whole picture. You have to know where did these clinical trials come from? People have to get together and talk.

The reason why places like Vienna and Glasgow and so forth were so successful was because in those days, people from many different areas of arts and sciences would have coffee together. They didn't drink themselves into oblivion as we do today. And they talk. So Freud learned from Klimt, Klimt learned from Freud, everybody learned from everybody. We don't do that anymore. Everybody seems to be talking their own language. And to me this is one of the biggest problems that we confront. And I don't know any simple answer to it. There have been many efforts to increase the physician scientist training. And I guess to some extent they've been successful. The MD PhD programs I think are

limited and it's very difficult to wear both those hats today. But it shouldn't be difficult to facilitate communication.

Dr. Margolin: Which is what you try to do with your Demystifying Medicine as a demonstration of what could be done.

Dr. Arias: That's right.

Dr. Margolin: Absolutely. Dr. Arias, your whole life experience and your behavior as a physician all through it and still thinking like a physician are very remarkable for me to sit and listen to. I thank you very much for this exposition of your background all the things that you've brought to this world, and really praise you for all your contributions to medicine and to the education. Thank you very much for this. All this information is just fascinating. Thank you.

Dr. Arias: Thank you, Joe. Can I take you to lunch?

Dr. Margolin: It was an hour and a quarter.