CHEMICAL HERITAGE FOUNDATION

ANDREW C. CHAN

The Pew Scholars Program in the Biomedical Sciences

Transcript of an Interview
Conducted by

Helene L. Cohen

at

Washington University School of Medicine
St. Louis, Missouri

on

17, 18, and 20 April 2000

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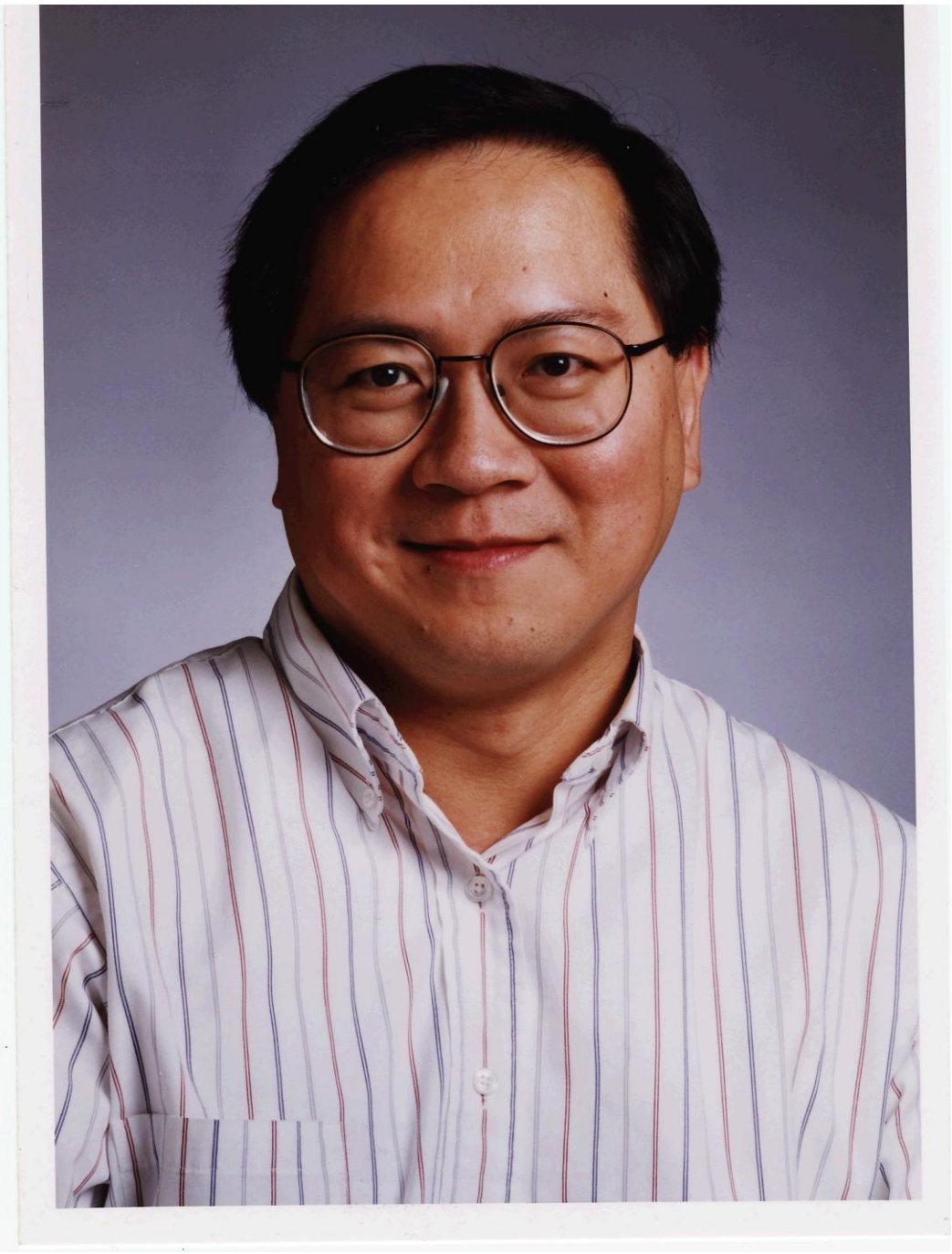

Andrew C. Chan

ACKNOWLEDGEMENT

This oral history is part of a series supported by a grant from the Pew Charitable Trusts based on the Pew Scholars Program in the Biomedical Sciences. This collection is an important resource for the history of biomedicine, recording the life and careers of young, distinguished biomedical scientists and of Pew Biomedical Scholar Advisory Committee members.

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REFORMATTING:

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Interviewee's Name

November 2, 2021

Date

Chemical Heritage Foundation
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315 Chestnut Street
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ANDREW C. CHAN

1959 Born in Hong Kong, China, on 11 October

Education

1980 B.A./M.S., Chemistry, Northwestern University
1986 M.D./Ph.D., Washington University School of Medicine

Professional Experience

Barnes-Jewish Hospital, Washington University School of Medicine, St. Louis, Missouri
1986-1989 Intern and Resident, Department of Internal Medicine
1994-present Attending Physician, Department of Internal Medicine

University of California, San Francisco, San Francisco, California
1989-1990 Clinical Fellow, Division of Rheumatology
1990-1993 Research Fellow
1992-1993 Assistant Adjunct Professor, Division of Rheumatology

Long-Moffitt Hospital, University of California, San Francisco, San Francisco, California
1992-1993 Attending Physician, Department of Medicine

Washington University School of Medicine, St. Louis, Missouri
1994-1998 Assistant Professor, Department of Internal Medicine and Pathology
1994-1999 Assistant Investigator, Howard Hughes Medical Institute
1998-present Associate Professor
2000-present Associate Investigator, Howard Hughes Medical Institute

Honors

1995-1999 Pew Scholar in the Biomedical Sciences
American College of Rheumatology Investigator
American Society for Clinical Investigation

Selected Publications

Chan, A.C. et al., 1983. Identification and partial characterization of a novel form of the fourth component of human complement: Evidence that the secreted form is different from the major plasma form. *Proceedings of the National Academy of Science USA* 80:268-72.

Chan, A.C. et al., 1992. ZAP-70: A 70kD ζ-associated protein tyrosine kinase. *Cell* 71:649-62.

Chan, A.C. et al., 1994. ZAP-70 protein tyrosine kinase deficiency in an autosomal recessive form of severe combined immunodeficiency. *Science* 264: 1599-1601.

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Kong, G.H. et al., 1995. Reconstitution of syk function by the ZAP-70 protein tyrosine kinase. *Immunity* 2:485-92.

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Gong, Q. et al., 1997. Restoration of thymocyte development and function in *zap-* $70^{-/-}$ mice by the Syk protein tyrosine kinase. *Immunity* 7:369-78.

Fu, C. et al., 1998. BLNK: A central linker protein in B-cell activation. *Immunity* 9:93-103.

Bubeck-Wardenburg, J. et al., 1998. Regulation of Pak activation and the T-cell cytoskeleton by the linker protein SLP-76. *Immunity* 9:607-16.

Pappu, R. et al., 1999. Requirement for B-Cell Linker Protein (BLNK) in B-cell development. *Science* 286:1949-54.

Minegishi, Y. et al., 1999. An essential role for BLNK in human B-cell development. *Science* 286:1954-57.

Gong, Q. et al., 2001. Disruption of T-cell signaling networks and development by Grb2 haploid insufficiency. *Nature Immunology* 2:29-37.

ABSTRACT

Andrew C. Chan was born in Hong Kong, the eldest of four children. His father was an engineer, his mother a teacher. When Chan was seven the family emigrated to the United States. His father was able to continue his career as an engineer, but his mother could not teach in the United States. She eventually attended college and became a civil engineer. Though he was young when he left Hong Kong, Chan's studies in Hong Kong were heavily slanted toward sciences and mathematics, but he also had a good beginning in English. He and his siblings did well in their public schools, attending Irvine High School, and all are professionals, Chan and his sisters in science-related fields, and their brother in law. Extra classes at University of California, Irvine; playing violin and accordion; debate; and chess kept Chan too busy to indulge in a very active social life.

Chan dates the genesis of his interest in science to his high-school chemistry teacher. Wanting a smaller incoming chemistry class than would be found in the University of California schools and prompted by two high-school teachers who were alumni, he decided to attend Northwestern University, which he entered with sophomore standing at the age of sixteen. Thinking he would not be ready for medical school at the age of nineteen, when he would be graduated, he decided on a four-year program that included research and granted a master's degree as well as a bachelor's. His desire to become a researcher he attributes to his professor, Joseph Lambert, but for some years he had also wanted to be a doctor. As a result, he applied to the M.D./Ph.D. program at Washington University School of Medicine, a program that he considers excellent.

Youthful allergies led him to immunology; working with John Atkinson and Benjamin Schwartz and his mother's diagnosis with lupus erythematosis led him to rheumatology, so that he did his research on protein processing in John Atkinson's laboratory. He decided to specialize in internal medicine and enjoyed his internship and residency at Barnes Jewish Hospital. After a one-year clinical fellowship at University of California, San Francisco, he began work in Arthur Weiss's laboratory, where he specialized in rheumatology.

Chan then discusses such wide-ranging subjects as parental expectations; his concern over the partial loss of his Chinese heritage; the advantages and disadvantages of pursuing an M.D./Ph.D. program; an example of clinical expertise fostering research progress; his teaching duties; how college students today differ from those of his own day; and patents in science.

Chan then returns to his own career. After finishing his fellowship he became a research fellow, then an assistant adjunct professor, and then an attending physician at University of California, San Francisco. From there he was granted a Howard Hughes Assistant—later Associate—Investigator award and accepted two positions, principal investigator at Washington University School of Medicine, and attending physician at Barnes-Jewish Hospital. He continues in these positions today.

Chan then discusses his lab setup and management; the job market for scientists; funding in general and specifically for him; grant writing; racial and ethnic makeup of Washington University; publishing articles; administrative duties; the physician-scientist program; travel commitments; patient care; clinical literature; advantages and disadvantages of technology; creativity in science; and competitionand collaboration.

Chan finishes his interview by explaining his current research on the regulation of the signaling mechanism of the T-cell antigen receptor; the possible applications of his research;

and his future research goals. He explains how he tries to balance his work life with his family life with his wife, a gastroenterologist whom he met at Washington University, and his two children. He concludes with his appreciation for his family.

UCLA INTERVIEW HISTORY

INTERVIEWER:

Helene L. Cohen, Interviewer, UCLA Oral History Program. B.S., Nursing, UCLA; P.N.P., University of California, San Diego/UCLA; M.A., Theater, San Diego State University.

TIME AND SETTING OF INTERVIEW:

Place: Conference Room, Washington University School of Medicine

Dates, length of sessions: April 17, 2000 (113 minutes); April 18, 2000 (118); April 20, 2000 (149).

Total number of recorded hours: 6.3

Persons present during interview: Chan and Cohen.

CONDUCT OF INTERVIEW:

This interview is one in a series with Pew Scholars in the Biomedical Sciences conducted by the UCLA Oral History Program in conjunction with the Pew Charitable Trusts's Pew Scholars in the Biomedical Sciences Oral History and Archives Project. The project has been designed to document the backgrounds, education, and research of biomedical scientists awarded four-year Pew scholarships since 1988.

To provide an overall framework for project interviews, the director of the UCLA Oral History Program and three UCLA faculty project consultants developed a topic outline. In preparing for this interview, Cohen held a telephone preinterview conversation with Chan to obtain written background information (curriculum vitae, copies of published articles, etc.) and agree on an interviewing schedule. She also reviewed prior Pew scholars' interviews and the documentation in Chan's file at the Pew Scholars Program office in San Francisco, including his proposal application, letters of recommendation, and reviews by Pew Scholars Program national advisory committee members. For technical background, Cohen consulted J.D. Watson et al., *Molecular Biology of the Gene.* 4th ed. Menlo Park, California: Benjamin/Cummings, 1987; Bruce Alberts et al., *Molecular Biology of the Cell.* 3rd ed. New York: Garland, 1994; Horace F. Judson, *The Eighth Day of Creation.* New York: Simon and Schuster, 1979; and recent issues of *Science* and *Nature.*

The interview is organized chronologically, beginning with Chan's childhood in Hong Kong and Southern California, and continuing through his undergraduate work and master's degree at Northwestern University; his doctoral work, internship, and residency at Washington University School of Medicine; his postdoc at University of California, San Francisco; and the establishment of his own lab at Washington University School of Medicine. Major topics discussed include his Chinese heritage, his desire to become a medical scientist, the M.D./Ph.D. program at Washington University School of Medicine (WUSM), his setting up the physician-

scientist program at WUSM, and his current research on the regulation of the signaling mechanism of the T cell antigen receptor.

ORIGINAL EDITING:

Gail Ostergren, editorial assistant, edited the interview. She checked the verbatim transcript of the interview against the original tape recordings, edited for punctuation, paragraphing, and spelling, and verified proper names. Words and phrases inserted by the editor have been bracketed.

Chan reviewed the transcript. He verified proper names and made minor corrections and additions.

William Van Benschoten, senior writer, prepared the table of contents. Ostergren assembled the biographical summary and interview history. Anne Marie Davis, editorial assistant, compiled the index.

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INTERVIEWER: **Helene L. Cohen**

LOCATION: **Washington University School of Medicine**
St. Louis, Missouri

DATE: **17 April 2000**

COHEN: Let's start with something simple, like when and where you were born.

CHAN: Okay. So I was born in Hong Kong in 1959. Basically, I was raised in Hong Kong and we immigrated to the United States in 1967, so when I came to the United States, I was seven years old.

COHEN: Okay. Tell me a little bit about your family, your parents, maybe your grandparents.

CHAN: My parents, who are still alive— My dad [Chiu-hing Felix Chan] is a civil engineer. He actually worked for the Hong Kong government at the time we were there. My mom [Shirley Yin-Yue Lau Chan], in Hong Kong, was a high school teacher. One of the major reasons why they came to the United States was, primarily, because of educational opportunities that were available in the United States as compared to Hong Kong.

COHEN: For you kids.

CHAN: For the kids. So I am the eldest of four. I have two younger sisters [Beatrice W. Chan and Susanna M. Chan] and a younger brother [Vincent C. Chan]. Actually, all of us were born in Hong Kong before we immigrated to the states. So in some ways, I see my parents as sort of pioneers, taking four kids—the youngest at that point was just a little bit over one year of age—

COHEN: Oh my.

CHAN: —to the United States and basically starting totally a new career. My dad continued being an engineer. My mother, because the teaching credential issues were not the same, actually was not able to teach, and actually, you know, was very helpful primarily as— She basically stayed home, taking care of us for most of the time. Then after all of us got out of the

house over the past, now a little bit over ten years, she has gone back and taken on a second career. I think my mom's and my dad's stress for education actually has affected us a lot, all four of us kids, in that while they were working they still continued going to school.

COHEN: They went to school.

CHAN: Right. So my mom, having accumulated probably enough credits for at least ten different degrees, finally graduated—I think now, about five or six years ago—initially with a bachelor's, and is now working for a master's in, of all subjects, civil engineering.

COHEN: Oh my goodness. Wow

CHAN: [laughs] So after all the kids were out of the house, she actually went back and took on a second career. So initially she actually went back to teaching and taught as a teaching assistant at the local high school. Then after getting the degree, she's gone back to work for the Orange County county government in a variety—

COHEN: In California.

CHAN: —in California—of engineering-based jobs. So both my dad and my mom now are engineers [laughs], despite everybody having been grown-up and now out of the house. So that's sort of the background in which you have to appreciate my upbringing, in that education was clearly one of the highest-priority issues. That's sort of where my upbringing came about.

The other interesting thing, really, is that in the transition coming to the United States—which I remember very little about as to what happened, my experiences in Hong Kong—the educational processes were also very, very different, in that the things that were clearly emphasized, retrospectively, in Hong Kong, were really the math and sciences, which, once we came here, we clearly excelled in. Yet the other things, such as social sciences, literature, we were just extremely behind in.

So it led to a sort of a dichotomous achievement rate when we were going to school. We would excel phenomenally-well in certain subjects and not in others. It took us—I would still say, it still has taken us—a lot of time to sort of obtain an even balance between those kinds of topics. I'm sure those things are rather critical in the ultimate determination of how we ended up where we are right now, in terms of our interests, in terms of what kinds of areas of study that we eventually pursued and the way that we think about problems.

COHEN: Well, you were only seven, though, when you came, so—

CHAN: That's right.

COHEN: And you were the oldest.

CHAN: Right.

COHEN: So the younger ones couldn't have been too awfully far behind in their—

CHAN: Right. I think those things are predominantly for me, although the issue of the priority for education obviously permeates through the entire family.

COHEN: Right.

CHAN: And then I think what happens usually is that— I'm a firm believer that what you ultimately become is clearly affected by the factors, or the environment, which you are exposed to. I can clearly [inaudible] or we can get into later, certain individuals or certain sets of situations that clearly affected what I ultimately wanted to be, or the studies that I pursued. So I think from that standpoint, since I was the eldest—and you know these things are rather formative—those things undoubtedly affected my siblings also, down the road. So I think it's sort of a domino affect. It's an environmentally dictated, inherited trait.

COHEN: [laughs] Okay. So what, if anything, do you remember about Hong Kong? You said you don't remember too much.

CHAN: I don't remember too much. Of the few things I do remember, which are extremely spotty, one was the education, that there was still a huge stress on education and most of the things I remember relate to certain aspects of schooling. I remember, you know—I forget exactly which grade this was, whether it was first grade or second grade—staying up very late at night memorizing Chinese poetry. Because that's what was mandated. I went to a Sacred Heart Catholic School, and it must have been extremely competitive. Retrospectively I think, given the two educational systems, it was not a very, very nurturing environment, in that they already set up students competing with each other from grade one. The other things I remember are writing pages and pages when we were trying to learn penmanship in first or second grade, of just O's, of just cursive O's, for pages on end just to make sure that, you know, your Oo's were

between the lines.

COHEN: So you were learning our alphabet—

CHAN: Yes, yes.

COHEN: —rather than the Chinese alphabet? Or both?

CHAN: Right. It was a British-based school, so we actually learned both English and Chinese from—it must have been—at least grade one.

COHEN: I see.

CHAN: So either I would be speaking here with a British accent or, you know, the way I talk and it was determined by the person that taught me English. The teacher that taught me English was either from the United States or from Britain.

COHEN: I see.

CHAN: And obviously my teacher happened to be from the United States. So that actually facilitated the transition from Hong Kong to the United States without any significant amount of difficulty, at least as far as I can remember.

COHEN: So how good was your English by the time you came here?

CHAN: I don't remember any problems with my English by the time I got here, you know, when I was seven, because, again, there was— The schools were extremely academically inclined. We had courses in English, etc., and the expectations were that you had to be fluent, already from day one. So from that standpoint, the larger amount of academic challenges actually paid off, you know, in terms of the transition.

COHEN: Did you speak Chinese at home?

CHAN: I did, but of course this was a seven year old vocabulary. Actually, it is one of those things that I missed, because when we came here, I could still speak, I could still write Chinese, and the first thing to go is the writing.

COHEN: Sure.

CHAN: So now, basically, I can make up certain characters. Actually, the five years that I spent in San Francisco significantly improved my Chinese, because I was, at that time, the only Chinese rheumatologist at the university [University of California, San Francisco] and, boom, I had this entire population of Cantonese-speaking patients. So my Chinese, out of necessity, actually got better. Then, of course, after moving back, it's gotten worse again. But right now, I'm not fluent at all. I mean, I can make out certain characters. I can write my name, but unfortunately that's about the extent of my ability to read and write.

COHEN: So Cantonese is the dialect.

CHAN: Cantonese, yes.

COHEN: Now, once you got here, did your parents stop speaking Chinese at home?

CHAN: No, my parents continued speaking Chinese at home. We still continued, tried to write, but as other things came into play, in terms of academic pressures, of other things that one needs to do, it was just one of those things that, unfortunately, fell to the side. I mean, right now, if I have a conversation with my parents, it's sort of an interesting conversation in that they will speak in Chinese, sprinkled with English words. And for me, I can understand it. I can listen to them and totally understand exactly what they are saying. Whereas, for example, my wife [Mary Finnorn Chan], who is Caucasian, would be sitting there, or they'll be talking to her or talking to me in English, and then in the middle of the sentence, go directly into Chinese. And then of course, she goes, "Wait, wait, wait, wait. I don't understand what you're talking about." And I can likewise converse in it fairly interchangeably, because there are certain words that are just easier to say in English and hence the interchangeability. If you think that way, actually, it's not a problem,

One of the more interesting features is that, actually, I remember doing mathematics. So doing arithmetic as I was growing up, after I came to the United States, I remember distinctly still doing my arithmetic in Chinese and then translating it into English, and it wasn't— I still remember like grade five, grade six, you know—two or three years down the road—I was still doing my math in Chinese and then mentally translating back into English. But now, that's all gone. I basically think, read, and write in English.

COHEN: I actually read an article once about the fact that kids will continue to do math in the language they learned it in for many years afterwards—

CHAN: Right.

COHEN: So that doesn't surprise me. [mutual laughter]

CHAN: It just seemed odd to me at the time; I was going, "Why am I doing my math in Chinese and then translating into English?"

COHEN: Well, now you know you about this study.

CHAN: That's right. I'm one of the—

COHEN: What about your grandparents?

CHAN: Yeah. I remember very little about my grandparents. My great, my paternal great-grandfather, passed away before I was born. He had actually gone to Australia. And my paternal grandmother [Yeung-Cheung Ho] is alive. She is still alive, and she lives in Los Angeles right now.

COHEN: Oh, okay.

CHAN: So I see her the few times when we are able to get back to Los Angeles, which is probably once a year.

COHEN: Now, you said great-grandmother.

CHAN: No, I'm sorry. I'm talking about my grandmother.

COHEN: Paternal grandmother.

CHAN: Not great-grandfather.

COHEN: Okay.

CHAN: My paternal grandfather and paternal grandmother. My paternal grandmother was a typical grandmother who basically raised— I think she had something like twelve or thirteen kids—

COHEN: Wow.

CHAN: —so it was a large family. And then my maternal— I did not know my maternal grandfather, and my maternal grandmother [Anna Lau] still lived in Hong Kong when she was alive and passed away there probably—I forget exactly when, but fifteen, twenty years ago. I've never gone back to visit Hong Kong, so the last time I vaguely remember her was, timewise, when we were still in Hong Kong. So I really don't have any recollection of who she was or what she was like either.

COHEN: That was a huge move for your mother then, because she was never going to see her mother again.

CHAN: Right, right. Well, at that time, you know this was in '67, it was still fairly easy to go back and forth. There was not a threat that the communists were going to come and take over. It was fairly easy to get visas to go back and forth. But you're right, I think, from that standpoint, I really think of my parents as pioneers, in terms of coming to a country— I mean, the only people they knew here was an older uncle—

Well, my dad had an older brother [Wing Chiu Chan] who was in Oregon at the time, and yet we came to California. One of my dad's best friends [Charles Cheung] was already here and was already established. So it wasn't like he was moving, and there was already a huge number of people that he knew in the United States.

COHEN: Yeah, sure.

CHAN: So that's a point. Without a doubt, it was one of those extremely high-risk things that— You know, if you asked me whether I'd be willing to take my entire family and, let's say, move

to, even, Germany, I'd tell you you've got to be out of your mind. But that's the kind of huge change that they underwent.

COHEN: Okay, well, tell me a little about your siblings then.

CHAN: Like I said, I'm the oldest of four. The second oldest, who is my sister Beatrice, she's just, I think, something like eighteen months younger than I. So the family is interesting in that out of the four kids, there were basically two sets of kids that were eighteen months between each other. And between the second and third, between my two sisters was, I think, about five or so years.

COHEN: Oh, okay. So two groups of two.

CHAN: So there are two groups of two, and the two groups of two usually were a little bit closer than the other ones, just, I think, because there was a five-year difference— You would say yeah, it's forty versus thirty-five, but when you're talking about twelve and seven, or sixteen and eleven, that's a huge difference.

So in any case, my older of the two sisters, she went to— She's a pharmacist. Then my younger of my two sisters, who is the third oldest in the family, is a gastroenterologist. So she went to medical school, actually came to St. Louis to Barnes [Jewish] Hospital [also called Mallinckrodt Institute of Radiology] to do her residency, and then went back to California to do her GI [gastroenterology] fellowship. She's in practice. She's in a part-time practice right now. My youngest, the youngest of four, is my brother, who graduated from law school a few years ago. So that's pretty much the four of us.

COHEN: Okay. How did you get along as kids?

CHAN: We always fought. I remember there were always issues of who was going to get what space and whatever. Things like that. I mean, it's always hard for me to guess whether we had a normal relationship growing up or not, just because I don't— That's the relationship that, you know, you had. By and large, I think we got a long fine. There were always fights between brothers and sisters and sisters and sisters and things like that, but there didn't seem to be anything too outrageous or anything like that. So our parents pretty much kept us in line.

COHEN: They were strict?

CHAN: They were pretty strict. I mean, I think again, because we were— Because the environment was primarily so based on education, because that's what my parents came here for, all of us were very geared towards those kinds of activities.

COHEN: Right.

CHAN: And that's where the emphasis always was. So because of that, we didn't have a whole lot of time to actually get into too much trouble. I think the kind of things that, you know, high school kids or junior high school kids could do in those days are totally different than what they can do now. The place that we grew up in, we actually— The high school [University High School] I went to was in Irvine, California. And at that time, Irvine, California, was basically—this is in the seventies now—just the high school, a couple of housing tracts, and farmland. That was it.

COHEN: So the Irvine campus of the University [of California, Irvine] hadn't opened yet?

CHAN: It had opened.

COHEN: It had.

CHAN: But it was the high school. But that was it. You know, over the last thirty, or even the last twenty years, the city has significantly changed.

But the things that kids did in those days were they went to school, you did your extra-curricular activities, and those were about it. We didn't have that many malls. The malls were far away. You didn't have transportation easily and not many kids in those days had cars. There wasn't as much as what is available that kids can do today. So I think it was, in that way, a very, very different world, in that things were probably slower, things were in some ways, you would say, less problematic, in that kids could have a fewer number of things to get into trouble with. So pretty much it was basically whatever you did in terms of your extra-curricular activities or the academics portion. So those two things pretty much kept us totally out of trouble.

COHEN: Okay.

CHAN: Because I just remember, we'd go to school, go to high school, and actually I was initially a part of this— There was an experimental program that was being started between University High School and UC Irvine, where they would take high school students as early as

their sophomore years and we would take classes at the college level. I forget what exactly the program was called, but they started with about, oh, probably, like a half-a-dozen kids from University High School—the program actually, I think, is much larger now—and you could take one to two classes, I think was my recollection. [These were] college level classes with the college students after school.

COHEN: Oh, this was after school. It wasn't part of your school day.

CHAN: Well, it was part of the schooling in that most of the classes we would take would be in the afternoon. So a typical high school curriculum would be six classes. You would take, let's say five classes, and then you would go over to the college campus and take whatever the course is. At this time, the advanced placement courses were also just beginning, so the availability of coursework at the university, complimented by some of these advanced placement courses, were actually two different ways by which one could supplement or complement the basic education. So after a while, you ran out of classes to take, because the high school was not that big. It was two thousand students in total, which meant about four hundred to five hundred students per class.

COHEN: So was it a four-year high school?

CHAN: It was a— I'm just trying to remember now. It was a four year, ninth through twelfth.

COHEN: Ninth through twelfth. Okay. Well, I actually want to spend some more time on your high school years, but to sort of keep the chronology going a little bit, let's back up to your arrival. You came to California—

CHAN: That's correct.

COHEN: From Hong Kong.

CHAN: Right. We came to Los Angeles.

COHEN: Not to Orange County?

CHAN: No, that's right. So we actually— My grade school [Plummer Elementary School] was

in the San Fernando Valley, in a city called Panorama City, which is, again, totally different then than it is now.

COHEN: Yeah, it's not such a great neighborhood now.

CHAN: I remember going there. We rented an apartment building. Retrospectively, I don't remember anything that was so unusual about schooling. You went to school, you walked to school. School wasn't that far away. It was about probably a mile away. Went through third, fourth, fifth, sixth grade. There was nothing that I can remember that was extremely unusual or anything that stuck out that was unusual about it.

COHEN: Did you stick out? That's my question, either academically or in any way?

CHAN: Yeah, I mean, I think like, you know, as I briefly discussed with you before, there were certain subjects that we would just clearly excel in, to the point where the teacher just got bored by us. You know, when it came to math, send Andy out to clean the erasers, you know, because there was nothing— I mean, the system in Hong Kong was a little bit unusual in that, from what I could tell, two grades worth of elementary school in the United States is comparable to one grade in Hong Kong.

So I vaguely remember my parents telling me whether I wanted to skip a couple of grades, because they thought, in the United States— For example, my math, even though it was third grade, was thought to be already at the fifth- or sixth-grade level. We had already done fractions and exponentials and a number of other things that were just being done here. But I think, wisely, my parents decided that socially, it was probably not the best thing for us to do. And there were clearly certain subjects that we just had not gotten a huge amount of education in, such as American history. You know, they had these courses that I vaguely remember, called citizenship. Retrospectively I don't really remember what exactly we learned, but I think things like social responsibility. This kind of thing was not exactly a high priority in the education in Hong Kong. So those classes we took and we did well in them, but it was at least something that we had not learned before. So I remember I spent a lot of time cleaning erasers. But that's— There's nothing unusual, anything else unusual about it.

I mean, I think what was more unusual maybe was— Also, in terms of sticking out, it wasn't that we stuck out, but I think this is just a normal growing-up process. After grade school, we would go to junior high school. We were there for seventh grade, eighth grade. And actually, in the Los Angeles system, I think it was seven, eight, and nine. But then I transitioned into high school in Orange County, because Orange County began at grade nine. I think seventh and eighth grade were just very, very unusual years in everybody's life, in that there was a lot more— You always felt like you always had decisions to make. And that probably is true. Seventh and eighth grade is a different kind of environment. First through sixth, at least where

we went to elementary school, it was a very, very nurturing, yet closed environment, in that you had one teacher, you had one class. You hung around with everybody that was in your class. And immediately in junior high school, it was very different because you had a homeroom, which is what you started with. Then you went and had different colleagues or different students in every different kind of class. And because the school was bigger—because now, you know, I forget how many elementary schools all came together—you all of a sudden met people that you had never met before. During that first year or two, it's not traumatic, but it just increases one's exposure and one's awareness of all the different things that exist within the world. So from that standpoint, it probably was a more challenging time. There was nothing unusual about it, but probably more challenging.

And then, of course, when one gets to high school, I think it actually becomes a little bit easier. There, because there are clearly even greater numbers of diversified groups, I think, in high school, but I think the exposure in intermediate school, or junior high school, sort of readies one for that kind of experience. But in high school, clearly, and I think this is true for every high school and it doesn't matter who you are, you clearly differentiate the certain groups. There were certain groups that were more academically inclined, certain groups that were more sports inclined, and then there is every weird group or unusual group in between. So I think there, clearly, you have more specialized groups or, you know, you had fewer numbers of individuals that you actually specifically interacted with in each group.

COHEN: Now, why did your parents decide to go to Orange County?

CHAN: Oh, it was just primarily for jobs. My dad had a job in the [San Fernando] Valley when he first came and then he had a great opportunity in Santa Ana. The amazing thing again, you know—this is just what my dad does—he commuted for a full year, until the new academic year began. This was in the seventies, so this was good traffic relative to now, and he still had a good sixty-minute commute between Santa Ana and Panorama City. Then we moved down, after the year was over, we moved down. We actually lived in Tustin for a year, and then ultimately we moved to Irvine.

COHEN: So when you were a kid, what did—? Obviously you did very well in school. What did you do for play?

CHAN: That's a good question, because I can't remember exactly what we did for play. I mean, part of it was— At that time computers were just beginning to gain access into even the general population. My mom actually made me, and wisely so probably, begin to take computer courses. So there were a couple of friends that we would actually— We would go to UC Irvine and take these courses, and actually at those times—

COHEN: So this was in high school?

CHAN: This was in high school. We actually spent a lot of time, you know, doing homework assignments and being on the computer. Just to sort of place it, these were the times when computer programs were these huge boxes of computer cards or rolls of tickertape. That's how you stored your programs. So that's one thing. The other things were in terms of things that we did outside of just classroom work, but still we were clearly still academically related, you know? I debated, which actually is a great experience. I played chess. There were a variety of things that they would assemble people for. Like there was this thing called the math team that we would compete for in certain types of regional competitions. I ran track for a couple of semesters, and that pretty much was—

COHEN: What was your—?

CHAN: I hate to run it, but it was the two-miler. I got bored after about the sixth or seventh lap around the track. So that pretty much filled most of what I remember.

COHEN: Did you—? All of these pursuits are sort of organized and academic, in a way. I mean, playing chess and computers and everything. Was there ever a time in your life when you just went outside and, you know, played hide-and-seek with the other kids in the neighborhood?

CHAN: Well, we would play a couple of afternoons, probably during the week. I mean, there were enough kids on our block. We had a great cul-de-sac that was at the very end. But there were enough kids on our block that we would go out and play either football or baseball with a tennis ball; we didn't want to break anything. So there were a couple of people that lived right across from us and enough kids up and down the block. We would say, you know, first down is every mailbox on the right side. Touchdown is the tree down there. But that was probably about it.

One of the things that, unfortunately, I wish that we had done more, but again it's more structured than anything, was that in grade school, in junior high school, I played the violin, and we had great instructors. The junior high school bandleader was the guy that played the tuba in *Mission Impossible*.

COHEN: Oh, okay. Only in L.A.

CHAN: Only in L.A. [inaudible] high school teacher. The great thing was that— But the schedule that I had, I remember, I don't know exactly why— The first year I played in the junior

high school orchestra, and this was a big deal at this junior high school.Our orchestra was probably 150 kids, and the band was easily 150 kids, but for some reason, I don't exactly remember why, I couldn't take the orchestra class. So they worked out a deal, because I really wanted to play violin, that I played violin in the band. [laughs]

COHEN: Okay. Were you the only violin?

CHAN: And I played the flute parts. I was the only violin in the band. I played the flute parts. Then, of course, during the shows and everything like that, I would actually go back and play with the orchestra. But when we moved down to Orange County, University High School was very, very small at the time, to the point where they didn't even have basically an active music department in terms of instrumentals. So that's sort of when I gave that up, but I wish retrospectively that it was a pursuit that I had continued.

COHEN: Now, did you study privately or you learned to play at school?

CHAN: We learned to play at school. There were a couple of summers that we would go off— You know, they have these music camps that we actually had private lessons in. It was nothing that I really took— I was never good enough or took it seriously enough to be really, really quality class.

COHEN: Do you ever pick it up now?

CHAN: I don't. I mean, picking up the violin isn't so easy, whereas the other thing I wish I had gotten into is actually playing the piano, because the piano is a much different instrument. My sister took instructions to play piano, and it's much easier just to sit down and start to play. Although I was actually a serious accordion player. [laughs]

COHEN: Oh really?

CHAN: I was a pretty serious accordion player for actually a number of years. We took instruction, we actually competed, but again, the accordion is not one of those instruments you can just leisurely sit down and play ten or fifteen minutes just to be relaxing about it.

COHEN: But you do know how to do fingering on a keyboard.

CHAN: Oh, yes, right. So that's why actually I can play the piano a little bit. I can pick it up just because I can read the music, but I've never had any formal instruction in piano. That's why all these things now we try and force our own kids to do. It's like, "I know this is good for you, this is what you should do," but they're going like, "No. Why should I do this? I don't want to do this."

COHEN: Right, and then someday, when they're grown up, they come back and say, "Why didn't you make me practice?"

CHAN: That's right. That's right.

COHEN: So what was your social life like when you were a kid?

CHAN: I think my social life was extremely limited in terms of exposure. Again, number one, I think the amount of time we— I mean, if you added up just the number of hours that it took to go to school, go over to the college campus, play chess, debate, etc., it was extreme— I mean, that basically is 80 to 90 percent of your time, excluding homework already. So then the number of hours that we had to interact with people were very limited. They were predominantly either interactions that we had with other people that had either common interests, whether we were going to a tournament for debating, or a math competition, a chess tournament, or just interacting with people, our neighbors. Outside of that, there were very, very few interactions we had with anybody else. It was not like we would— Partly, again, because of the time that we grew up, and probably the suburbanness and remoteness of Irvine at the time, it wasn't like we would go and hang out at the mall, because the mall was very far away. And again, also I think in terms of the kinds of the circles of friends that you had, those people had very similar types of activities that I had. So between all those things, there were very little other interactions with other people, friends at school or in terms of the neighborhood. The only other major things that we would do obviously were all family related. By that time we had a number of cousins who lived in the area, so it was not unusual for us to drive up to Los Angeles when we were in Orange County, or to drive down to L.A. from the Valley and visit, you know, so and so, or so and so, a relative, right.

COHEN: Did you have a girlfriend in high school or junior high?

CHAN: Nope. Neither. I mean, high school was a rather fast-paced type of thing for me. I think there were a number of factors that came into play. One was we had actually moved from L.A. down to Orange County, so I knew no one by the time I went down to Orange County. And second is that I finished one year early in high school, partly because I had taken all the courses.

COHEN: There was nothing else to take.

CHAN: So actually a lot of my time was already spent at the college during my last year of high school. There were probably were maybe a dozen people that I would interact with, you know, thinking back on it, on a daily basis.

COHEN: Now some of the people that I talked to, because everybody's really smart that's a Pew Scholar [in the Biomedical Sciences], they talk about the fact that they felt sort of socially ostracized because they were nerdy. Did you have that experience at all?

CHAN: I think it was— I think yes and no. I think there's always—especially at the high school level and it probably is worse now—a huge difference between people that were sports-driven verses academically-driven, and I think from that standpoint, you are always socially ostracized by the other group. You can flip that around and say the sports people were socially ostracized by the academic group. Now, I think in terms of numbers, you probably— We would have probably felt that we were clearly in the minority, okay, because there were a lot more people that were interested in sports.

Retrospectively, I think that the differences were not that great. There were clearly people that had no interest in academics and there were clearly people that had no interest in sports, but actually I loved lots of sports. I loved basketball, even though at that particular point I was extremely short. So I think the fact that I was younger than most in my class—I was shorter than clearly almost everybody in my class—probably clearly did not allow me to participate in many things that I wish I would have. But I think also, I didn't feel socially ostracized to that degree. I mean, I knew I was different than a lot of other people, but then this may have been sort of a thing that I already accepted, that I was different, because I immigrated to the United States already to begin with, so I always felt I was a little bit different than some of my other classmates. That at least I don't remember it being that much of a factor weighing on my mind.I remember a conversation with one of my classmates with him asking me, "Do you really think this is what you should do?" As in, specifically, was I spending too much time taking certain kinds of classes? Was it really wise for me to take all these other additional advanced classes and have obviously less time to interact with my peers at that particular point? I could see what he was talking about, but at the same time I think, retrospectively again, in the long run, it made no difference. If anything, it was an advantage, because I think again the differences in terms of what one wants to do has a huge impact as to how one interprets it. For my career, or how my life is differentiated, high school was only the beginning of what I wanted to do, and for a lot of people, not to say that that's better or worse, it was the middle if not the end part of their training time, the educational process, before they went out into the real world. So for me, I didn't see it as such, that this was a time necessarily to be able to— I just saw it basically as a springboard to do other things.

[END OF TAPE 1, SIDE 1]

COHEN: So it doesn't sound like you felt ostracized or anything.

CHAN: No, I felt different in that my interests were clearly different than most other students, but I knew there was a certain number of us who had similar kinds of interests. It wasn't like there was only one or two of us, but there were somewhere, probably, between thirty and fifty people that had very similar kinds of goals and very similar kinds of interests that I had. Those clearly were the classmates I had in certain advanced placement courses, the few number of individuals that also would also go over to the college campus and take classes. Maybe that was an advantage also, because I saw all these people at the college, for example, that were much older, and realized, basically, this is only the beginning. This is not anything close to the end. I still have a long ways to go, in which case, whether I went three or four years in high school or whether I did these other extra-curricular activities—it didn't impact on me as much.

COHEN: I noticed you were valedictorian of your class. Was that because you were valedictorian of the class ahead of you, actually, because you really graduated—?

CHAN: No, they did it for whatever class that was— No, it was for the class during which I graduated in. So they just amassed whatever all the GPA's were, in total, and picked the people for the— There actually were co-valedictorians. There were two valedictorians.

COHEN: Did you have to give a speech?

CHAN: Yeah, we had to give a speech. This was interesting, because I had debated for a year, and my debate coach, Mrs. Reedy, says, "You better give a good speech."So we worked on it. She helped me a lot in terms of trying to put into concrete wording as to what are the real messages that I wanted to talk about. I vaguely remember what we talked about. We vaguely talked about the concept of "This is only a first step" amongst all of us, whether we were going to go out in the real world, or whether we were going to go on to other educational opportunities. That's a theme of what we talked about.

COHEN: Okay. Now, you mentioned that you started school in Hong Kong at a Catholic school,

CHAN: Yes.

COHEN: But you went to public school here.

CHAN: I went to public school here, right.

COHEN: Okay. Was there a role for religion in your upbringing?

CHAN: I think there clearly was. Is. I mean, both my parents are Catholic, I'm Catholic, and my family's Catholic, but the reason I went to Catholic school wasn't a religious-driven decision. There was a huge dichotomy in terms of the quality of education between public schools and private schools in Hong Kong, and hence the Sacred Heart schools offered certain opportunities that otherwise would not be available in the public schools.

I actually remember vaguely—I don't remember this to any great detail—that we had to take an entrance examination to get into kindergarten. I don't remember exactly what it was. I just remember sitting outside, my parents would go in, and then they would have me go in. Now, I don't exactly remember what happened, but I remember just sitting there waiting for me to go in and take whatever the examination was. So I think the quality of the education also had a huge say into the decision.

COHEN: Were you active in the church? I mean, did you go to church every week?

CHAN: We went to church every week. We still do. We didn't participate necessarily in a lot of the other activities that, for example, our church has now, in part because of the hours. So it was something that was always in my upbringing, although probably not to the same degree of activism as many other members have.

COHEN: Okay. Well one of the things that is interesting to me is how people in science balance the issue God and science, so how do you see the two?

CHAN: How do I balance the two in terms of what I do—?

COHEN: Well, can God and science coexist?

CHAN: Well, I think God and science can coexist. It depends as to whether one takes the *Bible* literally or whether one takes it as a reflection of something that somebody recorded. So whether the earth or the entire universe was actually created in seven days as we know it now, it doesn't bother me whether it was seven times twenty-four hours or seven times twenty-four million years. One can't really, I think in any area, be able to say this is the scientific proof that God exists or anything like that, but actually, even in science, we really never prove anything. I mean, we have hypotheses and we have data that support this type of hypotheses and we think that's truth, but truth is always relative. So we have things that support it, but I don't think necessarily we have— We don't ever prove it. So I think in a way, religion and science can coexist.

Obviously, ultimately, what one believes in, in terms of religion, ultimately comes to an act of faith. So obviously you can't do experiments to be able to demonstrate the existence of God one way or the other. I think from that standpoint, it's an act of faith. In terms of how one applies it to science, for me, I don't— There's nothing that necessarily from my religious upbringing—that I say this allows me to do this or doesn't allow me to do this in terms of science or medicine. Okay? I think we're given certain types of talents; we're given certain types of technological possibilities. We can use those one way or another in terms of either advancing what we presently know about science and hopefully improving life in general, but I don't necessarily see a huge discrepancy between those two types of circles.

COHEN: Well, one of the other things that we like to talk about is how people got interested in science. It sounds like you really started that very young.

CHAN: Well, I think this is, again, one of those things where certain people have a certain impact upon your life. Neither of my parents are scientists. I mean, both of them are math/science driven in that my parents, by and large, are engineers. So during high school, I knew I was interested in math and science, I think, because I excelled in that more than other subjects. At that point, I think also, things aren't so differentiated. At that time I remember you're differentiating yourself, but you really are not. I mean, science in the high school sense is so broad, right? It could be your interest, retrospectively— Now that could have translated into being an astronaut, in becoming a computer scientist, a physician, an archeologist—many things that we would say post-training would be so different. So science and math were clearly very, very related to each other. So it was more math and science, versus social sciences versus arts, for example. And I think that's where most people come into college, as pseudodifferentiated—I'll use that, "pseudodifferentiated"—and that you're interested in either math or science, in that category. So you go to college. You'd be either interested less so in math, but really in biological sciences, physical sciences, versus the social studies, political science, psychology, philosophy, literature, things like that. So I knew I was interested in that.

During high school, one of my most favorite teachers, James Shannon, was my chemistry teacher. He actually was the one that prompted me to take an independent sort of study course with him and try to do different kinds of science projects. That's where, for example, my interest

in chemistry over biology or physics really became more apparent. Then, during college, because I was interested in chemistry already, I was interested in how things worked. And in those days, now we're talking about the late-seventies, chemistry was really one of the physical sciences. You know, you could actually study mechanisms, whereas biology, at that time, wasn't as well differentiated in terms of the things that you could do to manipulate the system. You know, when people talked about biology, it was more observational science. It was comparative anatomy. You couldn't exactly manipulate systems like what we do today, so because of that, I was much more enamored with chemistry and biochemistry than I was with biology. So in college I became a chemistry major, and again, I was— My interest in research was actually also sparked by one of the professors who I had, Joe [Joseph B.] Lambert who—

COHEN: This was in college?

CHAN: —this was in college—allowed me to actually dabble in the laboratory, beginning my sophomore year, which actually I have to confess I didn't get a whole lot done during that time, but I learned a lot in terms of how one approaches science. Because even at that point before my experience in Joe's laboratory, it was very, very clinically inclined. I was basically going to become a physician. At that point, yes, I was interested in medical sciences, but my experience, again in Joe's laboratory, was that he was interested in understanding what the mechanism was in terms of a particular type of chemical reaction. So after two and some years in his laboratory, I mean the questions of why do certain biological processes occur, became more— Those kinds of questions became more interesting to me. That then ultimately led to my application then to medical school, not only just, you know, in the [Washington University] School [of Medicine], but also as a combined program between the M.D. and the Ph.D. degree. In those days—again, we're talking about now the late-seventies, early-eighties—those programs were not huge, were not large. They were not well publicized at the time, but nonetheless, again by concurrence of a number of circumstances, I ended up applying to the M.D./Ph.D. program at Washington University.

COHEN: Let's back up just a step here, because I want to explore how you got— You graduated a year early, so you were probably—what? Sixteen or something when you graduated?

CHAN: I hadn't quite turned sixteen yet.

COHEN: Oh my goodness.

CHAN: So actually I entered— Is that right?

COHEN: Most kids graduate at seventeen or eighteen.

CHAN: Right. So I had turned sixteen; I was sixteen when I entered college at Northwestern [University].

COHEN: So this is really young.

CHAN: Right.

COHEN: It's pretty young, and Northwestern is not in Orange County. It's in Chicago.

CHAN: Right.

COHEN: So how did you come to go so far away? And then after that, we'll talk about how that was.

CHAN: So I think there were a number of factors, again. This is what I am saying: the environment dictates where you go. First was that I was interested in chemistry at that time. The number of choices that I had were, for example, [attending] UC [University of California] schools or some of the smaller schools, one of which is Northwestern. So one of the major deciding factors really was that UCLA's freshman chemistry class is 2,000 to 3,000.

COHEN: I took it once, so I know.

CHAN: Whereas Northwestern's freshman chemistry class is a few hundred, and I had already been through the UC experience when I went to UC Irvine. That is a much smaller school, and their freshman chemistry was already seven hundred, eight hundred students. So in a way, you felt you were just one of the masses. So that was one of the major decisions as to why I ended up at Northwestern.

The second major one is that there were two high school teachers in my high school that were very active in the Northwestern [University] Alumni Association, so what happens, obviously, is that whoever is the most active at the high school level at those times becomes important in terms of a high school kid's world. So I think those were two major factors.

The third factor, I think, is that I had always grown up fairly close to my family, so going to Chicago was going to be totally different. I think that part of me also wanted to test to see whether I could make it on my own. So I think that all three things factored into the final equation and outcome of the equation, which was that I ended up in Northwestern.

COHEN: Now, you had already taken freshman chemistry, though, right? So—

CHAN: Right, but still it was the size of the class. Organic chemistry is a similar thing, just one scale less.

COHEN: Right. Okay, so at sixteen, you packed your bags and went eighteen hundred miles—

CHAN: You know, the funny story is that I had never seen snow for more than twenty-four hours before I went to Northwestern. I remember my parents and I getting ready to ship me off to Northwestern, so we had to— We knew it was cold. So we had to buy a parka, in August, in Southern California. So we ended up going to Sears [Roebuck and Company], and yes, you can order it by mail. So we get this thing, this huge, gigantic parka with this hood that folds out, and I never understood why on earth you would need a hood that folds out about a foot in front of your face until my first winter at Northwestern.[mutual laughter]

COHEN: Yeah, it's cold there.

CHAN: So I got there. It was— I think undoubtedly that I grew up a lot faster than I would have if I had stayed at UCLA or if I was within driving distance or an hour's distance away from home at UC [University of California] Berkeley or something like that. It was actually— Again, I think there are a lot of universities that would have worked out well for me, but it was a good compromise because the school was relatively small. At that time, it had only six thousand to seven thousand undergraduates. My organic chemistry class only had a hundred kids in it.

And it was fairly— It's a very conservative town. Evanston [Illinois], still, I think to this day, is dry. The WCTU [Woman's Christian Temperance Union] has its headquarters there. So it was also a very conservative school, despite it just neighboring Chicago, because it's not actually in Chicago. It's in Evanston. The undergraduate campus is in Evanston. So it wasn't— The transition wasn't all that harsh, except for the weather. You went to class, you know. I lived on campus for the duration for the four years, with the exception of the summers.

COHEN: In dorms?

CHAN: In the dorms. Here, it was actually clearly even a more homogeneous population, in terms of what people wanted to do, as compared to high school. As clearly people here wanted to excel in X, Y, or Z, whether that meant going to medical school, going to graduate school, going to law school. Everybody, from that standpoint, was a little bit more homogeneous than in high school.

COHEN: Now, Northwestern is a state school.

CHAN: No, it's a private school.

COHEN: Oh, it is private? Why did I think it was—?

CHAN: It's the only private school, at that time, in the Big Ten.

COHEN: Oh, maybe that's why I thought so. Okay, so did your parents finance this?

CHAN: Yes, my parents financed it. One of the good things about Northwestern was that they had a significant amount of financial— They granted a significant amount of financial aid, so that actually, relatively speaking, in terms of dollars per year, I think it was pretty much comparable whether I went to UCLA or Northwestern.

COHEN: Now, financial aid nowadays means loans, which you are going to have to pay back.

CHAN: But not in those days. Those days, it was scholarships. I did take out loans, but I think I amassed a total of something like four thousand dollars in loans.

COHEN: For the whole four years?

CHAN: For the whole four years, which in those days were astronomical. Nowadays, you would say that's a year. But I think financial aid was very, very different than it is now. There are federal monies. There were private monies. There were institutional scholarships and institutional funds.

COHEN: Now did you end up spending four years there? You went in with an awful lot of college credit already.

CHAN: Right, so by the time I entered, I had sophomore standings. So what I did was I felt that if I took all four years there, I would have been twenty years old when I applied to medical school, which I thought— Because by the junior year, I had enough credits to graduate, so that would even have been—

COHEN: To graduate?

CHAN: To graduate.

COHEN: Oh my goodness.

CHAN: Because I already had— I started with sophomore standings, so after three years I had sufficient—

COHEN: Oh, okay.

CHAN: Excuse me, three years I had sufficient credits to graduate, but then I would have been nineteen applying to medical school, so I didn't think that I was ready for that. What I ended up doing, because I was already interested in research, was that Northwestern had this very nice program, a four year bachelor's-master's degree program, where you could actually do additional research as part of a thesis for the master's degree.

I had actually entertained a number of different types of options at that point. You know, one of the things I really liked during the first three years actually, I had the opportunity to take a number of senior-level social economics courses, history courses, which to me were actually quite fascinating. So these were great courses, because they were not graduate level, but more junior and senior level courses that had twenty-five, thirty students, and I would obviously be the only science major that's there. But the interesting thing was really that I thought very differently in terms of the way I would attack problems as the other twenty-some students. It was interesting for me to listen to how the other twenty-some students think, because that's an interesting way of thinking about it. I never thought about it from that way. And then when they'd ask me, I'd say, "Well this is the way I would think about it," and they would look at me like, "Work? What planet are you from?" They would say, "Hey, but that's a different way of looking at the problem." So it got to be a very interesting way— A lot of good discussions came from it in terms of how you would resolve a certain social-political situation. How one would

interpret what was the right thing or wrong thing to do in history. So actually, from that experience, I thought a little bit about pursuing a second bachelor's degree during the last year that I was there.

COHEN: Oh. You mean in something non-science?

CHAN: Right. But I ended up for a variety of reasons just pursuing the chemistry aspect of it and still taking a couple of upper-level social science courses.

COHEN: Now, you went into this as a premed. When did you sort of come to the idea that you wanted to be a doctor?

CHAN: I don't know. I think it was probably something that my parents had also contributed to.

COHEN: Subliminal messages. [laughs]

CHAN: Well, I'm not sure subliminal. Because I remember there are these things that your parents always keep, your report cards: on the back you said what I wanted to be, blah, blah, blah. And I remember the first couple of years it was that I wanted to be a shortstop. I wanted to be a shortstop. I wanted to be a shortstop. And then I think somewhere in the later grade school, it was I wanted to be a doctor. But again, I think that is the kind of people that one meets.

One of the worst things I had happen to me was that I had very, very bad—phenomenally bad—allergies in high school, in part brought on by running track, in part because it was Orange County and everything blooms there, to the point where I could not sleep some nights because I could not breathe. So I went to see the allergist and miraculously, three months down the road after some allergy shots, I got better. So you know there's certain things that impress a kid, "Hey, this guy can make me better," that probably even strengthened my desire at that point to be able to become a physician. And that pretty much was what I thought about really as an undergraduate, until I got more interested in, or had a little bit greater exposure to, research.

COHEN: Well it's interesting that you ended up in immunology.

CHAN: Exactly. Well that's—

COHEN: Is that related to—?

CHAN: —also related. That's not just related to my history: so when I was in medical school, my mom actually developed [systemic] lupus [erythematosis]. And fortunately she was able to get over it, and I did my— At that time I did my Ph.D. work with John [P.] Atkinson, who is a rheumatologist. So I think, again, there are certain people that you've been exposed to, that you've had good experiences with, that are extremely formative in one's life. If I had my research with, let's say a cardiologist, I may be a cardiologist today rather than, you know, a rheumatologist or an immunologist. So from that standpoint, it's just very, very— The things that affect you every day clearly dictate what you ultimately become.

COHEN: Sure. Okay, so you got— What did you do in Joe Lambert's lab?

CHAN: One of the major things that he was interested in was— You may vaguely remember in organic chemistry how we had to always memorize which electrons attacked which thing, and one of the things he was interested in was the mechanisms by which certain compounds underwent certain reactions.

The one that I was working on— There are these tricyclic compounds that would become halogenated, so one of the reactions we're interested in is bromination. The idea was that somehow the bromine was going to attack and be attached to the group, and we were interested in understanding exactly how did that occur and in what conformations would that occur. The method that we used at that time was called nuclear magnetic resonance, NMR. Now you have all these other fancy names for it, like MRI [magnetic resonance imaging] and things like that. So we utilized this particular technology to be able to understand exactly what the intermediates are. We attract certain intermediates and see where the bromine was, where the hydrogen was, and what were the relationships between the hydrogens versus all the other atoms within, or the other hydrogens that are within this particular compound. So that's what my thesis was centered upon, to try and figure out exactly the mechanism by which that reaction occurred.

And that aside, the major things I think it taught me were a number of different things. First, that science is hard, but, second, it also taught me to look into problems for a mechanistic basis. And thirdly, again because he was such a wonderful role model, was that you can actually enjoy doing science. I think that really was one of the major experiences I had during my college career, to really develop the love for science.

Science before that was basically you go to class, you do some labs that are already preordained as to what the result was. The only question was whether you got a 95% yield versus a 90% yield, or your reaction didn't work, versus this experience where we don't know what the answer is. This is the question and we want to try to design experiments to try to figure it out. It was really the introduction to the scientific method versus the rote lab classes. I think that's predominantly what I got out of that experience that was so valuable for me, was just an introduction to that method.

COHEN: Did you ever entertain the thought of skipping medical school and going straight to science?

CHAN: To graduate school?

COHEN: To graduate school?

CHAN: No, I don't think so. I was always interested in medicine in terms of how the body works. And again, in the early eighties—no: actually this is the late seventies—there wasn't that much medical research that would break to the newspapers every day. Nowadays, there actually is a science section, but the public's perception of science actually wasn't something that you discussed every day. It was not that kind of general public discussion.

So the general public's perception, basically, of science was pretty much physicians. And hence, I think that was the skewing that prompted me to go into medical sciences. I mean, medical sciences has changed a lot obviously in the last twenty years and surely it will change a lot in the next twenty years, but in terms of exposure, that was predominantly what my exposure was.

My exposure actually was very, very minimal in that nobody in my family, my immediate family, was a physician. Nobody in my immediate family was a scientist, a research scientist. As an undergraduate, we were on the main campus. We were not on the medical school campus. So there was little to no exposure as to what a physician does, aside from when we got sick, and no exposure as to what a career as an academic physician was. The exposure that I had really was what an academic scientist does, like Joe Lambert, but not in terms of a physician-scientist, which is a little bit of a different boat.

COHEN: So I'm trying to figure out how you ended up— What was the thinking that went into going to this combined M.D./Ph.D. program?

CHAN: Again, it was circumstance that led me into this scenario.

COHEN: It usually is.

CHAN: So I had applied to all the medical M.D. degrees and actually I had not known very much about M.D./Ph. .D. programs, so my plan was basically to go ahead and go to medical

school and then maybe, down the road, to come back and reinvestigate potential opportunities in research.

COHEN: But initially, you were just going to become a practicing physician, or—?

CHAN: Right. There were a number of ways by which one can become an academic physician. One of them is to go ahead and do your clinical training first and then, during the latter part of your clinical training, to go back into the laboratory, to go into a laboratory, and then go on to become an academic physician, to do research.

COHEN: But I guess what I am not clear about was, had you already made the decision to be an academic physician?

CHAN: No. In college I remember going through the application process. I was going to become a physician and then potentially go and do some research. The concept of an academic physician really had not been fully— I was not aware, at least, of such kinds of physicians. I knew there were physicians in medical centers doing research. I really didn't have the first iota as to what on earth they did or what their life was, and I am sure— I know that actually the life of an academic physician in 1980 is totally different than what my life is now. So my initial intention was just to apply to medical school, do my clinical training, and then come back and maybe do some lab work down the road. It was at this point that Wash U., among a couple of other places—once you apply for the M.D. program, they immediately send you the information for the M.D./Ph.D. program— So I am looking at this application, and I go, "Hmm. That's an interesting idea. I'll fill it out." [laughs] So again, I sent it in, and that's where the beginning of my awareness of the interest of the program began. If they hadn't sent me that application, I'm sure I would not have the presence of mind to have applied to those kinds of programs. Because again, those kinds of programs were not large programs. They were very small programs at the time. Wash U.'s at that time was the largest and still is one of the largest M.D./Ph.D. programs around the country. So again, it was circumstance—that these things had to fall into place for me to be where I am right now.

COHEN: And how did you end up here? Because my guess is you probably got into pretty much many places you applied to.

CHAN: Well, I got into a number of California schools, because again I wanted to— You know, that's where my parents were. When I came here to interview, I had a fairly positive feeling about the university. I was impressed about its commitment to research and, actually, in comparison to many other physical plants around the country, the physical plant here of this medical center has very few peers. This is now circa 1979. So I had very, very positive feelings

about the university. And, of course, there were a number of factors. At that point, I still did not have a good concept of what a physician-scientist was or exactly what physician-scientists do, because, number one, there weren't a whole lot of them. People still in the late seventies did this sixty-forty or fifty-fifty thing where you spent 50 to 60 percent of the time in the laboratory and 40 to 50 percent of the time doing research. Nowadays, that's not consistent with life.

COHEN: Not compatible with life.

CHAN: At least not fundable life. So when I weighed all the factors, this came out ahead, and one of the major things that came ahead, obviously, was the M.D./Ph.D. program is fully funded. So when you came to medical school, your entire tuition was paid and you were paid a stipend for the entire duration of your medical school.

COHEN: And this is not an inexpensive place to go.

CHAN: Right. I mean, many other programs have that, but this program probably was the best of all of the programs in terms of commitment by the university. In many of the other programs, you had to pay for your first two years of medical school or they'll pay for your research years, but then you were sort of out on your own in your final year.

COHEN: Now, was this the only combined program or did you get into another one somewhere?

CHAN: No, this is what I am just trying to remember. I think I applied maybe to one or two other programs. Once I became aware of this program, then I went back and did additional research on the other programs. I'm trying to remember back as to what other— I don't remember exactly which other programs. I think this sort of tells you how difficult it is to predict on paper. Actually, retrospectively, I can honestly say for myself, I probably was one of their higher-risk picks—

COHEN: Oh, really?

CHAN: —in terms of people that were going to be physician-scientists. Because, one, I had no role models as to what a physician-scientist was. Two, I came from a background which was— The research was not biomedically related. It was a basic science chemistry laboratory, whereas a lot of the other applicants, my colleagues, had been doing research in the medical school, had a very good idea of what physician-scientists do. So I think, without a doubt, I had to be one of

their more high-risk picks as to whether I was going to ultimately stay in academic science.

COHEN: So you came here.

CHAN: And within the first week, I was ready to leave. [laughs]

COHEN: Really? Oh!

CHAN: So this is the summer of 1980—

COHEN: Well it was August, yes.

CHAN: —when seventeen people died—

COHEN: Oh my goodness.

CHAN: —in St. Louis—

COHEN: Of the heat.

CHAN: —because of the heat. And my electrical system in my old Ford Mustang got fried by the heat. So the first week I got here, I remember calling my parents and going, "I'm not sure if this is the right place for me. You know, there are people dying here. Blah, blah, blah, blah." I had never been in St. Louis previously. And my parents said, "Stick it out. You'll be fine. You'll be better. It'll be better." And they were right.

But it was a good introduction. Because again, I think the place is very different than other medical places—and I can say this now having been here for so many years now—in that it's probably more collegial than many other major medical centers. There's a great emphasis on teaching. There's a great emphasis on training M.D.'s, M.D./Ph.D.'s, and the Ph.D. students. The M.D./Ph.D. program is clearly one of the gems of the university. It's the first one, or one of the first, that was introduced into the country. It's the largest program. It's one of the programs that has had one of the best track records in terms of training physician-scientists. So all the faculty are always looking out for the students at this particular institution.

So from that standpoint, actually, it was one of the best environments I just lucked out into having. Because everybody was always concerned about what you were doing, how you were, if you were having any problems. They cared about the students. So from that standpoint, it was a great environment to shift into, because again, I was not as savvy as some of my colleagues were in knowing exactly what it was that I had to do, or wanted to do. And it was a phenomenally good infrastructure whereby they told you exactly what you had to do. You rotate through these labs, you go to medical school, then you choose a lab and you basically work as a graduate student during those laboratory years.

COHEN: Now, did you do the whole four years of med[-ical] school first?

CHAN: So the program is divided up so that you do the first two years of medical school first, then you spend three-plus years in the laboratory, and then you do your one clinical year as the final year of the program. You don't do the equivalent of a fourth year of medical school within this program.

[END OF TAPE 1, SIDE 2]

COHEN: We were talking about the way the program worked. You were saying you only had one clinical year.

CHAN: That's correct, which is a little different than many other programs and obviously different than the traditional medical training, even for our M.D. students here. There are advantages and disadvantages of the program as it is designed. The advantage, obviously, is that you finish in a much shorter— You finish one year earlier than if you had to do two full years of clinical work.

COHEN: But it's six years for the whole—

CHAN: It's a minimum of six years. When I went through my training, the average student probably took six and a half years, so half of us did graduate in six years and the other half took seven years, by and large, to finish. The program actually has changed over the years, because the requirements for the graduate portions of the curriculum actually have greatly increased, so that now it's not unusual for students to finish in seven-plus years. But then if you added on another year of clinical work, you're talking about eight to nine years for the combined degree program and that's even before you begin your intensified clinical training, which is your residency and fellowships. So the other disadvantage—

The disadvantages then of just having one clinical year—this has been debated back and forth for many, many years now—is whether the trainees are adequately trained to become M.D.'s. Do they really have significant disadvantages, let's say, as an intern? I think that this is clearly very individual based. Part of the difficulty, obviously, is that you've been out of medical school for three-plus years and you've got to come back and you have to remember all the stuff that you've forgotten from eons ago. But I think on the whole, the students catch up very, very quickly.

Having the graduate training actually I think, helps one. Some people have argued that it is a detriment. I think it teaches one to think in a very, very objective manner and to prioritize what the major problems are. If you go in the laboratory, you've got ten different things to do. Immediately you have to prioritize. What experiments are there to do first in the morning so that you'll be ready by the afternoon? And if one is very good about doing that, then clinical medicine in many ways is very similar. You know, most patient's problems are very complex. They may have eight different co-morbid states and, yes, you have to take care of each one of them. But certain ones become much higher priority than others. So if you have that kind of skill, then once you understand what problems are more detrimental than others and which ones you should address first, it actually becomes a huge advantage. And I think that most house staff directors would agree that while many M.D./Ph.D.'s have more problems at the beginning, as in the first months of one's training, by about three months, six months down the road, they actually are very, very outstanding.

I actually had, again, certain advantages because, again, I had a great Ph.D. mentor. John [P.] Atkinson was the division chief of rheumatology at the time, and he dragged me on rounds for three straight years. I would attend clinical rheumatology rounds every Thursday during the academic year, probably two out of every three weeks.

COHEN: So you really weren't out of the clinical—

CHAN: It's partly the vocabulary and the jargon, and I didn't understand a lot of the stuff that was being spewed around. But again, you get accustomed and not get intimidated by the jargon, and you develop a certain way of thinking about problems, so for me actually, it wasn't that bad of a transition. It was actually a pretty natural transition from the laboratory back into the clinics. And partly, I also like clinical medicine. There are people that just don't like clinical medicine, but I like clinical medicine and I like taking care of patients. So for me, it was actually very exciting and a challenge to do this.

A lot of people tell me I'm crazy, but you know, I loved my internship. Internship was one of the greatest times of my life. It was a fun time. Residency was a great time. But I think that's the difference between the one year clinical work and the two year clinical work that most other medical students, as well as a lot of the other M.D./Ph.D. programs, have.

COHEN: Okay. Well, we'll get to your internship. But tell me a little bit about what you did in Atkinson's lab.

CHAN: John was interested in a family of proteins that make up a critical arm of the immune system, called the complement proteins. So there are basically two general types of immune responses that one can classify. The immune response into one is called the innate immunity, which is the nonspecific immune response, which you and I have, flies have, worms have, etc. And there's the adaptive arm of the immune response, which takes over after a few days, which becomes specific to certain organisms or certain types of antigens. So he was interested in the complement system, which at that time was appreciated to be the innate part of the immune response.

His laboratory fell upon two major topics. One was the proteins themselves, the complement proteins themselves, that circulate in the serum and are a critical component of the activation cascade. The second component of his laboratory was interested in the receptors that bind these particular proteins. So I was in the first camp in trying to understand one component of the human complement system, the fourth component of the human complement system. But even though it was immunology, the central project basically was a cell biological question, which was, "How is this particular protein synthesized, regulated in the cell; how is it secreted? And upon secretion, how is its activity regulated?"

So during the three years I was in John's laboratory, we described basically how this particular complement component, *C4*, which in its mature form in the serum consists of three different polypeptides that are all bonded together by disulfide bonds— But nonetheless, this particular complex protein is actually synthesized as a single chain polypeptide. And we described certain types of proteolytic cleavages that occurred within certain compartments of the cell that altered or broke it from a one single chain polypeptide into the three chain protein. And upon secretion, we further described an additional cleavage event in the carboxyl terminus of one of the chains, the α chain, that further allows the protein to now be increasing its enzymatic activity, because these things are enzymes of themselves. So it's a very, very cell biological type of question. We really didn't deal with— at least my project didn't deal that much with—the immune function of these particular proteins. We were interested in using this particular protein as a way of studying how processing of proteins occur.

So in that thirty seconds, I've summarized three years of my life. [laughs]

COHEN: Well, you wrote six papers while you were at it.

CHAN: I was again very, very fortunate, and, again, [I was] stepping at the right time in the project. John had some inkling—based on other studies and other systems—that there was going to be this proteolytic cleavage in the human *C4* chain. The laboratory had spent a year trying to find a good cell line that would make the uncleaved form, as compared to the mature form.

So I remember when I entered the laboratory, John suggested, "Well, after all, complement proteins are made in the liver." At that time they predominately looked at monocyte macrophage cell lines, which also secrete the protein. There was another laboratory, Arnie [Arnold W.] Strauss's laboratory, who had been working with this liver cell line, Hep G2. So that was the first line I examined, and within two weeks I sheepishly came into John's lab and I said, "I think this is the right cell line. I think this is the right cell line for which it's making the proform." I showed him the data in which the precursor was migrating higher and the cleaved form is lower, so after almost one year of hard work by a number of individuals in the laboratory, I—in two weeks—had lucked out basically in choosing the right cell line. Once you had the cell line to make the protein, the rest actually becomes extremely easy. I mean, not easy, but it becomes much easier in describing a number of those other cleavages.

So that again, partly, is the luck of just stepping in at the right time and having the luck of having the right collaborator at the university that happens to have the right cell line. I mean, otherwise I could have spent easily another year or more trying to find the right cell line. Again, another matter of circumstance.

COHEN: [laughs] Well, we're going to spend some time, probably tomorrow, talking about serendipity, so we'll revisit this one a little bit. You know the thing that strikes me when I listen to the way this program was outlined, it seems like if you weren't a very flexible person, this would be a little schizophrenogenic, because you're a med student, then you're a graduate student, then you're a med student, then you're a resident, then you're—you know? But you seem to have been able to kind of flow along through it.

CHAN: Well I think it's not— I think good medicine and good research are not that dissimilar. A lot of it obviously is recognizing the problem, trying to amass the data to be able to support one particular hypothesis versus another hypothesis, and then figuring out what to do thereafter. So if somebody comes in with chest pain, you need to figure out whether this is a cardiac problem, pulmonary problem, musculoskeletal problem, GI [gastrointestinal] problem. Based on the clinical history and some preliminary tests, you set out additional, basically, experiments to test each one of those hypotheses. So the approaches that one takes in both camps, I think, are actually very, very comparable, in terms of being able to diagnose things and being able to treat them.

The flexibility issue I think is true, no matter what you do, whether you're in business—especially as we are scientists—because the technology and the approaches that one takes this year versus ten years ago or ten years from here are going to be very, very different in terms of what's possible. So you always have to be very flexible as to what challenges you're willing to take, what kind of approaches, technically, that you're willing to take, so you have to be adaptive. I think if you don't, you fail basically in many, many different forums. So I think that's just the personality of the individual and the way that they've been trained. I've been very, very fortunate, because in each arena that I've had training in, I have had really outstanding mentors

that have had certain strengths in certain things and strengths in other things. On the whole, I've had role models for different kinds of things as represented by different individuals.

So, for example, Joe [Joseph B.] Lambert was really an outstanding role model in terms of stressing teaching, in terms of balancing life and work. Every summer, he goes on another archeological dig. That's his hobby; that's scientifically based. So you know, he tries to also work on methods of dating certain archeological objects.

John Atkinson is a physician-scientist. He's an outstanding physician and he is a very caring individual. He is an outstanding physician and scientist. So there are a number of things that I've learned from him that I had not learned from other individuals.

And then my postdoctoral mentor, who I am sure we will come to, Art [Arthur] Weiss, is a brilliant scientist. And he has certain insights into scientific problems that otherwise, if you don't withdraw yourself from the problem and look at it from the whole, you just don't appreciate. He taught me really how to appreciate a problem from the beginning to the end.

So I've taken the strengths of all these mentors as valuable experiences in shaping, obviously, the person that I want to be. And it still— This is what goes back to the beginning of the conversation we had this session, which is training— I still feel I'm in training. That's really one of the wonderful things about science, is that you are always learning something new. And hence, if one is able to adapt to that kind of philosophy and say, "Okay. I am not the world's expert in this, because if I were the world's expert in this, the answer would be already known and there's no reason for me to ask any more questions." Or at least put it this way: You can't say that I know everything about this field, because that never is the case. And if one takes that kind of philosophy into either the medical side or the research side, then I think actually you get the most out of both.

So I think there are lots of people that say you cannot be a good physician and be a good scientist. And I don't think that's true. I think the reality of the thing is that you can not necessarily spend as much time as you would want to as a physician and a scientist. I think that's true, but I still think you can become an outstanding physician and an outstanding scientist in terms of applying each one of those types of skills.

COHEN: Let's do one more thing, and then I know we have to break. Your residency— How did you decide on internal medicine?

CHAN: I think many people go through the following procedure. See, first of all, you eliminate everything that you don't like to do. Okay? So in the end, for me, it was either medicine or pediatrics, internal medicine or pediatrics, and that was even till the beginning of the year that I actually had to choose the residency. So I did medicine and it was as I thought it was, because I had been around all the medicine people anyway. I did pediatrics. I actually liked pediatrics, but there were a couple of reasons why I chose medicine over pediatrics.

One was there are lots more social issues that one has to deal with in pediatrics than in internal medicine. So that was one factor. A second factor, in part, was adults make the choices and they have to live with the consequences of those choices. Children don't make choices. The parents make the choices, and yet the children have to live with the consequences of their parents' choices, which actually many times makes it extremely hard for one to become a pediatrician, I think, because you have no control over the situation. You just can't say, "If you don't take the medicine, you're going to have a heart attack. End of story." And that I found actually more difficult to accept, because there is nothing I could have done about it, or very few things I can do about it, to control not only the patient's behavior but the parents' behavior.

The third thing is a very minor issue. You always worried about exactly what the weight of the kid was being in pediatrics, right? All the pediatric house staff would sit there with these calculators. Everything was mgs/kilo/day [milligrams per kilogram per day], whereas with adults I'd say, "Give them 40 milligrams of lasix. That's fine." There are very few things I actually need to calculate per meter squared with. Cytoxan is probably one of the few things, but I have a pretty good idea as to— Big person, you know—? But here: "How much?" Two point two kilos? Twenty kilos? That was something I just didn't like.

But the science behind pediatrics I thought was actually at the time extremely interesting, because one of the areas I thought about actively going into was pediatric hematology/oncology, which was, and still is, having huge amounts of scientific success in terms of diagnostics, therapies, as well as in the molecular pathogenesis of the disease. But in the end—I think also influenced by the people I've been exposed to, like John Atkinson— I ended up choosing rheumatology and internal medicine in particular.

COHEN: And how did you happen to stay here, because many people leave?

CHAN: So at that time, I think this was, in part, the one less year that I had in terms of the clinical training. So I felt comfortable. But you know, when you go from medical student to intern, it's actually very frightening when you just think about it. So, one, I felt comfortable within the confines of Barnes [Jewish Hospital, also called Mallinckrodt Institute of Radiology], because I knew where everything was. I didn't have to go through, "Where's radiology? How do I get an X ray?" This kind of thing. Two was, I liked the setup at this particular residency program at the time, which was one resident, one intern. The resident's always there.

I looked at the [Johns Hopkins] program, I considered the Hopkins program seriously, but the Hopkins program was— It was similar, one resident, but the resident goes home. I want the resident there. [laughs] And, you know, these were the days where the resident would tell you as he's leaving the hospital, she's leaving the hospital, "Feel free to call me, but calling me is a sign of weakness." All right, so you're saying, "Okay, should I call the resident? Should I shouldn't call the resident?"

So I think that was one of the factors, just the way that the resident intern system was set up. Two was, Barnes Hospital was and still is a very, by and large, a very supportive kind of hospital and it has a number of ancillary services that you just didn't have to deal with at other places that were more city hospital based. We still had to do a lot more scut work than the interns have to do now, but it wasn't to the same degree as other hospitals. You knew approximately how many patients you would admit per evening, on call, and it would be somewhere around seven patients. So it was not too outlandish.

I mean, I looked at the [University of Texas] Southwestern [Medical Center] program, and I was walking through the emergency room and they are telling me, "We see twelve hundred patients every twenty-four hour period."

I said, "Well, how many interns are there?"

"Well, there are three interns."

Just doing my math, I said, "This is not the place." So I think from all those factors and the fact that I only had one clinical year, I felt probably a little bit concerned about my ability to just be able to step in and be able to run the show by myself. So I felt more comfortable within this particular confine and hence, I stayed.

[END OF TAPE 2, SIDE 1]

[END OF INTERVIEW]

INTERVIEWEE: **Andrew C. Chan**

INTERVIEWER: **Helene L. Cohen**

LOCATION: **Washington University School of Medicine**
St. Louis, Missouri

DATE: **18 April 2000**

COHEN: In reviewing the work that we did yesterday, I was reminded of a few follow-up questions that I wanted to ask you, and one goes back to the issue of this expectation that your parents had that you would all achieve in the educational field. You know, there are many forms that can take, from overt pressure on kids to just setting an example. And I was wondering how that was— How did you know that—?

CHAN: I think probably it was both by example and by actual active things that my parents did on their part as well as for us. So as I mentioned yesterday, you know, one of the major things they have done is that they have gone to school basically forever, as far as I can tell. It actually took a huge amount of effort to convince my parents to stop going to school over the last few years.

The second thing was that pretty much throughout our schooling, we were pretty much always participating in some academic aspect of schooling, whether that was courses at the— You know, a number of the junior colleges had courses for children over the summertime, whether they were painting, art lessons, music lessons, music camp, art camp, math camp, etc. So we always participated in something every summer, which always meant that we were always, quote, in school in some form or another. So I think that kind of active planning on their part probably sunk in, that you always try to better yourself whether it was in a structured manner or by yourself, in an unstructured manner. So I think it's probably a little bit of both.

COHEN: Were there any particular expectations about what you would do?

CHAN: I don't think so. I mean, I always thought— My interests, again, were predominantly in the science field and science/math field. I think that's always been reflective in part of where we sort of excelled in and, I think, in part, where you excel in becomes sort of the aspects that you have a greater interest in. Number two is that, you know, both of my parents were also in fields that were more based on math and science. So I think it was a combination of those things that pushed us in one particular direction, but I didn't feel like there was any particular expectation as to what field, per se, we did.

Again, I think also that the exposure even that my parents had to a variety of fields was somewhat limited, and that while I didn't know what a physician-scientist was, what an academician was, I think similarly my parents didn't have a very good concept as to what that also entailed. The closest interaction we had was that I have a cousin who is also a physician-scientist, but he wasn't that much further in terms of his training, so it wasn't like I already knew what a physician-scientist did based on what he did.

So again, I think all of us were sort of in the dark as to what kind of careers we were pursuing, and that actually came multiple times home, because my parents would always wonder when my training would end, because it always seemed I was going to another additional level of training. Because again, training in both clinical and laboratory science, you know, obviously takes a huge amount of time.

COHEN: Did anybody in your family ever entertain the idea of not going to college?

CHAN: I don't think so. That was clearly, I think, an expectation, and I think also it was an expectation based on the general circle of individuals that one is acquainted with. So again, in high school, you know, you have a particular circle of friends and all of them have the similar kinds of expectations, so it wasn't anything unusual. I don't think it ever dawned on us that we would consider not going to college.

COHEN: The other thing that I was wondering about was— We talked a little bit about you, how more or less your Chinese got arrested at the age of seven and that you lost your ability to write and that sort of thing. One of the things that I think is interesting about all immigrant cultures here is that the next generation loses some of that identity. First of all, how connected do you feel to being Chinese?

CHAN: I think that is a good observation. I think I don't feel that tied in to my heritage, okay, because I think what happens is that, especially, the first generation immigrants come over and the major thing usually is to strive for something else that we didn't have before—in this case it was educational opportunity—in which case, I think most, if not all of one's energies are put into those directions. The things that you obviously have you really don't think of as things that you would potentially lose, but obviously that's what happens. And as you pointed out, I think most of the immigrants do lose a lot of their own heritage because of the goals of trying to attain certain other things. So from that standpoint, I feel that I have lost part of my heritage, and I think in the whole aspect of things, I would like to have not lost that part of the heritage. But again because of the things that we do on a daily basis, I also find myself not having sufficient time to go after and regain some of those aspects of my life.

COHEN: Was that an issue at all for your parents?

CHAN: I can't tell. I'm sure, rationalizing it, I think they would have liked to have seen me retain probably more of my heritage. But I think they were also involved in the same kind of issues that I just discussed, which was they wanted us to obtain a certain degree of excellence at certain levels and with this, of course, was that one loses certain aspects of what one had already. So I don't think that they're that concerned about it. I think they're more concerned that we work too hard than necessarily that we've lost these particular aspects of our history. I think, you know, if all things were equal, they would say absolutely I wish that we hadn't done this in terms of losing that part of our culture, but it doesn't seem to have bothered— At least I can't tell whether it bothers them a lot.

COHEN: A colleague of mine who is Chinese told me was that there was a lot of pressure on her. She was born here, but her parents were from China. There was a lot of pressure on her to marry somebody Chinese. I know you mentioned that your wife [Mary F. Chan] is Caucasian. Was there any pressure by your family or difficulty about that?

CHAN: I mean there wasn't any pressure from my family, maybe again because Hong Kong is not quite like China, in that it is clearly a very westernized city. My parents have never commented on it. I'm not sure whether they would have, but they have never commented on it. I think, again, that it's just one's environment as to who one is exposed to and things like that that leads one to a certain particular situation, but that again wasn't a major factor in my decision making.

COHEN: Okay. Well, I want to also go back and touch on a little bit more about M.D./Ph.D. program, because I've heard lots of different comments from different scholars about the value, or relative lack thereof, of having an M.D. degree if you're going to be a basic scientist. I'm wondering what your perspective on the advantages and disadvantages of doing something like what you did is.

CHAN: Well, let me just discuss the disadvantages first. I mean, a disadvantage obviously is just the time issue in that one goes through a variety of additional durations of training into a certain aspect or certain career path. One probably does not utilize it to the fullest extent, but again the M.D./Ph.D. program is only one facet of the training, and again many individuals, depending on what their interests are, may go into different directions at a variety of different points in their career. So, for example, my training was to finish with the M.D./Ph.D. degree, complete my full clinical training before going back to the laboratory. Other individuals would just obtain their M.D./Ph.D. training in school and really never obtain additional clinical training and actually go directly into the laboratory. So again, there are many different lengths of training and different kinds of training that can result from this kind of path. So the downside, of course, I think, is just the time issue.

The advantages, actually, I think, can also be judged depending on what one's view is. If one values the clinical knowledge that one obtains— And I agree to some degree that not all the training is absolutely required, but nonetheless, I think an appreciation of what human disease is and what the different aspects or subtleties of human diseases are actually allows one potentially to have certain insights based on one's basic science research. Okay? So, for example, my research has been primarily in immunology and my clinical training is in rheumatology, so this is clearly one of the aspects whereby I can many times easily relate what some of the basic science observations are in terms of the pathogenesis of the disease. That clearly is what has lead to—not from my experience, but based on other people's experience—a variety of different insights that have lead to products or to new discoveries in terms of the pathogenesis of disease. So I would agree that, yes, you don't need to be there, for example, to take care of patients being on call every third night or fourth night, depending on what one wants to do, but yet at the same time, I think having that type of insight is helpful if one wants to be able to tie the clinical aspect of the disease into their basic science work.

In terms of the clinical training, I think the other advantage is that you're probably one of the few people that's going to be able to meld or be able to walk between the basic scientists and the translational medicine or clinical scientists and that, I think, is extremely important. Just like, you know, a good scientist should be able to meld between or be able to take observations from one field and be able to cross-fertilize another field, an outstanding physician-scientist or well-trained physician-scientist should also be able to bridge the bedside aspects of medicine and the bench sides of medicine. If one basically just continues focusing on one aspect or the other, I think then we would be missing a lot of the interplay between the two fields or between the two disciplines, which I think is important.

So without saying that, you know, this is clearly what everybody has to do, I think it's still a wonderful opportunity to allow one's self to go between both fields. Now, you could make an argument as to whether it's worth all the time in terms of training, but again it also depends on whether one enjoys doing that kind of work. Some people don't like taking care of patients, others do, so I think it's very much based on what one wants to do eventually, what kind of research that one wants to do, and what other kinds of interests one has. I think that the position of the physician-scientist is important in that one has to be able to relate to both aspects of science. Hence another important role for why we need physician-scientists is really to train additional individuals who can do that. So I think the teaching responsibilities and the mentorship of those individuals also likewise becomes extremely important, because again you are then the basis for the teaching and hopefully the next generation of scientists.

So I think for me, I'm biased obviously because I like doing both, but I think those are the advantages. The disadvantage is that you just don't get to sleep as much because of the clinical responsibilities and the time issue.

COHEN: Well, the example that springs to my mind about being able to sort of see the basic science side and the clinical side is the work that you did with the SCID [severe combined

immunodeficiency] patients missing the *ZAP-70*.

CHAN: Right. So again, that's a lot of serendipity. We weren't in the position exactly to go out to screen children with immunodeficiencies, but we happened to be in a situation where we actually had those cells sitting in the freezer and that initial observation sort of taught me a lesson as to how to approach the next time that we would be in a similar position. So having described the children with mutations in the *ZAP-70* gene that have severe combined immunodeficiency, the next time, which was now 1998, when we cloned out and discovered the *BLNK* linker protein, it was obvious to me that that was a disease to look at for a counterpart in human disease. Now, that's not to say if I didn't have it the first time—and obviously I'm not trained in pediatrics—we wouldn't have done it. But I think having the clinical training, one at least sees or increases the potential importance, or recognizes the potential importance, of understanding that kind of phenomenon and hence, one puts probably a little bit more effort in trying to attack questions of that type.

So I think that's basically the insights that one takes. I think the question in the end is whether that should really require—or whether that is worth—you know, five or six additional years of clinical training. I think with that you've seen the aging of the young scientist. Young scientists aren't young anymore when they start, [mutual laughter] but this has been the progressive increase in the average age of PI [principal investigator]s for their first RO1.

COHEN: Well, some of that has to do with not being able to get jobs, but we're going to discuss that in length. One other thing you mentioned yesterday was that you loved your internship and residency, and that's not everyone's experience. So tell me what you loved, how you loved it.

CHAN: What one hears is always that the internship and residency is sort of a drudgery, but I think that in part depends on how one approaches it. So when I began my internship, maybe this was just naivete or the fact that I had only one clinical year versus two clinical years—and I think it also depends on what one's previous training is— So actually, I found internship to be less challenging than my graduate work in the laboratory.

COHEN: Less challenging mentally or timewise?

CHAN: Clearly both. Now, while I spent more hours physically in the hospital, it was less mentally challenging, because when you were done at the end of the day or at the end of the rotation, you were done. You signed out. You pretty much had some idea that all your patients had been taken care of. You may go home and look up certain aspects of things, which were already known. So you were basically looking through differential diagnosis just to make sure you hadn't missed something or reading up on the proposed pathogenesis of a certain disease. But it was not the same kind of thinking that one does in a laboratory where at the end of the

day, that's the beginning of the day, which is yes—you've finished the physical aspects of your labwork—but now you also have to contemplate, "Well, what does that result mean? What new types of experiments should one think about in terms of developing new paradigms for your field?" This is just not reading and learning. This is reading, synthesizing, and reinventing. So from a mental standpoint, it was much more demanding in the laboratory than it was during clinical training.

Physically, it was more demanding as an intern, because you had to stay up more number of hours. You know, you would get interrupted. You would be called at two o'clock in the morning, four o'clock in the morning, five o'clock in the morning, because somebody had a temperature or somebody wasn't feeling well, somebody was having chest pains, etc., but you knew how to take care of those kinds of situations. It was very straightforward things that you would think about. You know, somebody spikes a temperature. You know, What are they in here for? Are they infected?

Do they have another source of infection? Are they not responding to the antibiotics? Is this a drug fever? Is this some connective tissue disease? The workup was very, very standard, and you could pretty much do it by rote memory. So from that standpoint, it was much more mentally challenging in the laboratory than it was as an intern. So hence, the internship was easy, relatively speaking. It was physically demanding, but in terms of mentally challenging, it was not mentally challenging.

The other thing was that I liked taking care of patients. Okay? I liked interacting with the patients. I liked trying to figure out what the patient had. So from that standpoint, it was fun, it was challenging. You interact with the people all the time. You interacted with your colleagues all the time. The internship, actually, while it was physically challenging, wasn't as demanding as previous times and I was doing something that I enjoyed.

Then during your residency, it's less physically challenging, because now the intern's doing basically all the scut work, but then you have the responsibility of teaching and I enjoy teaching also. So from that standpoint also, it was an additional responsibility that was thrust upon you that I enjoyed. So every single point in my training, they were giving more things to do that I enjoyed. So I enjoyed all of it.

Now, if you told me to go back to becoming an intern, I don't think I would be physically capable at least of being an intern again—you know, the kind of hours that people were spending in those days. I mean, it's actually interesting, because during my internship, we had to fill out these time cards to estimate the number of hours we actually had spent in the hospital, for Medicare reimbursement or something like that. And typically we would put anywhere from 80 to 120 hours per week. I mean, hundreds of hours per week was not unusual. And by and large, people just didn't complain. This is the expectation, this is how you worked, and that's what you did.

So I enjoyed it for a variety of different reasons, but part of it probably was the novelty. Part of it was that I was doing things that I liked to do.

COHEN: Well actually, I'm trying to remember who it was that said it about— You know I read your recommendations for the Pew [Scholars Program in the Biomedical Sciences] from different people, and I think it was John [P.] Atkinson who said that you were a legendary figure among the house staff. [mutual laughter]

CHAN: I enjoyed my— We enjoyed our work.

COHEN: Yeah, yeah.

CHAN: It's an experience. It's actually a very binding experience for everybody that's involved, because, you know, these are people that you spend all your life with basically. This was your social circle in part.

COHEN: Right. Now, had you met your wife by this time?

CHAN: No. Well, I met my wife during my residency. So she was from Alabama, from UAB [University of Alabama], came up here and began her residency the same year as I.

COHEN: Oh, so she's a physician also.

CHAN: She is a physician, right. So both of us were interns together.

COHEN: I see. In the same— ? Internal medicine?

CHAN: In the same class. We got married during our junior resident year.

COHEN: So that would have been two years later.

CHAN: We'd known each other for two years. Right. She actually jokes to this day. She can't quite figure out how it happened that we ended up married, because we were on call every third night and we did not have coordinated calls, so one of us was always post-call, the other one was pre-call.

COHEN: Right.

CHAN: But it all worked out.

COHEN: So what does she do now?

CHAN: She is an academic physician, also at Washington University. She's in the division of gastroenterology, and she has pretty much 85 percent clinical responsibilities, about another 15 percent teaching and administrative responsibilities. I don't know why, but she enjoys that combination also.

COHEN: Well, luckily there's a place for everybody and everybody's personality, right?

CHAN: [laughs] Absolutely.

COHEN: Well, actually, I'm going to spend some time talking about all these things that you do now, these PI responsibilities—and there are many, I know. Let's start with teaching, because you already alluded to the fact that you enjoy teaching. How much teaching do you actually have to do here?

CHAN: Well, I mean, I think teaching is a very, very general and loose term. So there is classroom teaching and this, actually, I do a very few number of hours. I teach in the classroom probably no more than a total of about twelve hours a year, twelve lecture hours per year.

COHEN: This being to medical students or graduate students?

CHAN: It's predominantly to graduate students. So these are either just lecture courses to immunology students, graduate students, and/or discussion in advanced topics, lecture type—Not lecture, but faculty sponsors of journal clubs. So those are sort of the didactic type of sessions. There are also teaching responsibilities when I attend on the medicine service as well as the rheumatology service. While part of my responsibility obviously is to ensure that the care that's being given by the house staff and the fellows are outstanding, part of the teaching responsibility is also to relate not only the diagnostic and therapeutic implications of the patient's case, but part of the responsibility also relates to trying to discuss basic science

developments as they relate to the case, or basic science developments as they relate to general medicine, depending upon how much time that we have. Those are the two most straightforward types of teaching responsibilities that we have.

And then to a more looser extent, teaching occurs daily. So for example, I mean, I have graduate students, rotation students, postdoctoral fellows, clinical fellows in my laboratory. So there part of it is a teaching responsibility, because we have to discuss, you know, "How does one interpret experiments? How does one evaluate data. How does one evaluate other people's published data. What are the implications of other published data in terms of your studies?" So I think that's also a teaching responsibility.

And then there's also, for example, teaching by example, and that is when one is at seminars, one asks questions sometimes just because one wants to know the answer, but one also asks questions, even though it might be a stupid question, to make a point that asking stupid questions is not a bad way of trying to think. So many times we have seminars which are very informal, for which everybody's just sitting there like a log and just to instigate discussion at some level, one either takes just an unusual stance on a particular situation, not necessarily that one believes in it, but so that one can instigate some sort of dialogue or discussion amongst the group. You know, teaching can have many, many different types of connotations and I actually see— I view, actually, many of the things that I do on a daily basis as sort of a teaching exercise. So that depending upon how you define it can range from only 20 hours, 24 hours a year, to 365 days a year.

COHEN: When you do the more formal type of teaching? What kinds of preparations do you have to go through for that, or do you anymore? I mean, sometimes the first year it's a lot, and then after that it's—

CHAN: Yeah. I'm fortunate enough to— Actually, in most of the formal teaching responsibilities that I have, they're pretty much in my area of expertise, so that you're absolutely right. The first two years of teaching was a huge amount of work just to prepare all the handouts, the transparencies, to be able to synthesize and present a particular topic in a logical and concise manner. Then the subsequent years, you know, for me to give a— For example, for the four one-hour series on T cell receptor activation in immunology, I probably spend an additional four to eight hours redoing the handout and redoing the talk based on additional information that has been obtained over the past year.

COHEN: This is a one-hour talk.

CHAN: This is a four one-hour lectures, a series that I give over a-week-and-a-half. But in doing so, of course, one has to think about, "Well, what are the major messages that I want to put through? Because otherwise, I could just accumulate four hours one year, eight hours one

year, twelve hours one year." So one has to come back and say, "Okay, what are things I'm going to take out? What are the things I'm going to put in? And why is it that I'm going to put it in this particular way,so that at the end of the four hours, at the end of each hour, the students have a concise view as to what it is that I tried to teach them." I think teaching is an extremely demanding and exhausting task. I mean, after I give every lecture, I am just exhausted for the next two hours because you're always thinking, "Okay, what is the next major topic that I'm going to talk about?" and be sort of two steps ahead . Because again, you only give this lecture once a year.

It's actually easier, for example, for me to give a standard research talk, because I give that three or four times a month. I can basically go on autopilot sometimes and just come back at the end of the session and answer questions. But it is a huge endeavor and I think it's important, not only to teach that section, but it also gives an example to the students of how to teach, which is something that we're not taught as a postdoctoral fellow. There are lots of things that I've done as a PI in the last six years for which we have no formal instruction in. And each one of those takes a huge amount of time to do it correctly.

COHEN: Well, you mentioned earlier that this idea of mentoring other students who are on the same path you're on was very important to you.

CHAN: Yeah. I think mentoring, you know, especially students, as well as trainees that are in my laboratory, as well as other individuals that are interested in my input are all important. One of the major things that I've learned in the brief six years that I've been around is that not everyone is built in the same mode nor do they hold the same goals as you do. So coming out of a postdoctoral fellowship, you had an extremely focused view of what one should do. And in part, I happened to be in a laboratory where everyone in that particular laboratory had very, very similar goals. I mean there were twelve of us there, all of whom felt that what we're here to do is outstanding science and none of us complained. None of us thought about anything else except for the science. When you train in a place like that for three to four years, that's what you expect everybody to be at, and once you remove yourself from that group, I soon realized that, well, that's not true for everyone. That actually is probably only true for a very small minority of individuals amongst even the general scientific population. So that I think was one of the startling things that I discovered soon after I became a PI. One of many. [laughs]

COHEN: Well, actually, I was going to ask you if you think students have changed over the years. You know you're getting older when you start saying "Boy, students have changed. When I was a student—"

CHAN: No, I've said that for the last six years that students have changed.

COHEN: In what way?

CHAN: Students have changed, and I don't necessarily think this is good or bad. It's just different. First of all, students actually are much more aware of the real world than we were when I was a graduate student. For students now, there is always an agenda. And again I'm not saying that that's necessarily good or bad, but there's always an agenda aside from science. It's not just whether this is a good question and you want to know what the answer is, but it's what is at the end of the pay line. Not scientifically, but in terms of potential personal gain. So I think students nowadays weigh much more these issues that we never thought about as students.

I mean, when I was a graduate student, you know, I lived with two other graduate students at the time. All of us were in the M.D./Ph.D. program. We would come to the lab, we would do our work, we would think about what the next sets of experiments were, and at a certain time your boss would say, "It's time for you to graduate." And we said, "Okay, it's time to graduate."

Now the students are very much different. I'm generalizing again, but there's a greater concern of, "Well, if I do this experiment, what is it that it's going to afford me after I do the experiment? If I undertake this higher risk project, how might it pay off for me five years from now?" So I think they're much more aware of what the consequences are, which is good as well as bad, because I think what it does— The good side is that they're always thinking about what the consequences are. The bad side then is that they don't take the risks, because the risk is too high. But I think that becomes the major difference.

There are also a lot more opportunities for students now than there were, you know, ten, twenty years ago, in that they can go and join an analyst group speculating in stocks and make more than an assistant professor. So why should they go on to another three or four years of postdoctoral fellowship? They can go to law school and then become a biotechnology advisor or whatever advisor to a law group and make substantial amounts of money. So what I see is actually the— I mean this is happening in science in general, you know. This is the commercialization of science as it has occurred over the last ten to fifteen years, that everybody wants the patents, everybody wants the starter companies, everybody wants to be a millionaire, and that clearly has affected the way that students as well as trainees think about their own training, sometimes for the better and sometimes for the worse. It's just different.

COHEN: Well, it actually brings up an ethical question, one of many, which is "Should people be able to patent scientific ideas?"

CHAN: I mean, I think the issue of patenting relates to drug discovery. If we didn't have patents, the argument has been made, then there would be no development of drugs, and that may well be the case. Clearly the United States has a huge lead in terms of drug discovery as compared to other countries. So from a purely ethical view, I would say no, they shouldn't do

that. From a purely realistic view, I think you have to give them certain patentable ideas or certain patent rights so that they will take the risks in developing the appropriate drugs or testing which of the targets may be reasonable targets for drug discovery. If we didn't have that, I think the drug discovery, at least in terms of the private sector, would be very, very different, and the academic sector is not in a position to develop drugs. A few universities have tried, but usually that has not been born out in anything that's been successful. So I think out of necessity, realistically, we have to have those kinds of opportunities for drug companies to patent ideas and to patent molecules.

Whether academicians should do that, I think, is a different issue. That's a harder issue to address. You know, one argument that's been made is that if the academician discovers a molecule, patents it, or if they don't patent it, then obviously somebody else is going to patent it. In a purely academic lab, that really shouldn't make a big difference, but again in reality, in most situations, it's a huge difference. One can probably, in a way, justify it by saying, "Well, you know, if a drug company is willing to pay a certain amount of licensing dollars or royalties to a laboratory for the use of a certain type of reagent or a certain type of knowledge, then if that money goes back to the laboratory, that probably is a good use of funds." But I think there are a zillion types of individual situations that we could discuss endlessly, which we have done in many of our ethics courses.

[END OF TAPE 3, SIDE 1]

COHEN: Well, you know, one of the questions is, for example, if Celera [Genomics] finishes the genome first, which they probably will, do they have a responsibility to share that information with people like you, for example, who don't have a profit motive involved? And I don't, you know—

CHAN: Well, I'm sure that they probably will, but of course they will hold certain patent rights probably to all of the information that they're releasing, because by themselves, if there were no other investigators, they really couldn't do anything with that information. They do not have the manpower nor necessarily the ideas to be able to go and attack every gene there is within the database. So they are dependent upon the general community, the general scientific community, to be able to ultimately make money for them. Now, in terms of what percent rights they want at the end is probably going to be a huge issue of discussion, but this is not without precedent. I mean there are companies—

For example, there's a company that has utilized random insertion to make knockouts, and depending how much you're willing to pay, you can get those knockout mice at different prices so that— I don't remember exactly what the numbers are, but—for example—if you're willing to give up 90 percent of the rights of the mouse, then that mouse only costs you ten thousand dollars. If you want to keep 90 percent of the patent rights and the company has 10 percent, it may cost you fifty thousand dollars for the same mouse. So it always comes down to,

obviously, what the costs of the reagents are, which is, I think, a reality. It's unfortunate, but it's a reality of the market.

COHEN: Do you hold any patents or have pending patents?

CHAN: We hold one patent based on the identification and discovery of the *BLNK* gene and the protein. It was an interesting learning experience just to go through the entire patenting process. It's probably not a process that I would want to undergo again, and I don't know what the implications of having a patent on that particular protein is at this point. I mean probably ninety-nine point nine percent of all patents filed probably are going to be meaningless. Not that they're not important discoveries, but in terms of clinical applicability, they are probably going to be no products ever made from those particular things, but nonetheless the technology transfer office and obviously the companies basically try to patent everything that comes out.

COHEN: Usually, when you're on a faculty, you have to— It really belongs to the university.

CHAN: Right. Right. I mean basically the university owns x percent of the patent.

COHEN: Yeah, okay.

CHAN: But it was an interesting experience.

COHEN: In what way?

CHAN: Just going through it. I mean, the technical aspects of what one has to go through in terms of filing a patent is just in many ways painful. One can think of a lot better use of one's time scientifically.

COHEN: We got sidetracked off the business of teaching, so we're actually almost done with that, but I have one more question about it and that is—we talked about how students have changed in terms of attitudes, but what's the sort of gender and ethnic makeup of the students here at Wash U. [Washington University School of Medicine]?

CHAN: Well, it's very program dependent. I actually don't know the specific percentage of the breakdowns, but if it's— For example, some of the fields—such as structural biology,

biophysics—tend to be more male dominant than female dominant. Many of the engineering subspecialties obviously tend to be more male dominant than female predominant. But in actuality, I think that in the majority of the other programs, such as neurosciences, immunology, molecular and cellular biology, at least at the graduate student level, there is an equal representation, if not a greater representation, by women over men. Now, that is an interesting discussion as to why that percentage is not equally represented at the higher levels of academics. But at least at the graduate student level at Wash U., and I know for many other universities as well, it is equal if not greater representation of women over men.

In terms of racial representation, it's pretty evenly distributed in terms of its distribution of Caucasian and Asians, at least within the university. I mean, clearly there's certain minority groups, such as Blacks, which continue to be totally underrepresented amongst the graduate school programs—I think, basically, in all subspecialties across the board.

COHEN: Even in medical school?

CHAN: No, not medical school. I'm classifying medical school now as a professional school rather than graduate school.

COHEN: Right, it's different. Okay.

CHAN: In medical school, again, I don't know what the percentages are, but I think this year I vaguely remember the women also outnumbering men. The racial makeup there, Asians again, usually are overrepresented. Other minority groups, such as African Americans, are better represented amongst the medical school than, for example, the graduate school. So that's the makeup of our graduate program. I mean, I think in certain programs, Asians probably are even more overrepresented, depending what the geography is. So certain California schools, there's clearly even a greater overrepresentation there.

COHEN: So let's go ahead to that other question which is, why aren't the women represented at the higher level? First of all, what does the faculty look like here in terms of gender?

CHAN: The faculty here—I can't tell you the exact numbers. I would not be surprised if it's something on the order of probably 85 percent male and 15 percent female. That may be an overrepresentation of the female faculty. Now, it also depends on which faculty you're talking about. So those percentages— I'm only considering people that are in basic sciences.

COHEN: Okay.

CHAN: If one were to take the full faculty, I think there the percentage of women probably would be higher, because I'm including a variety of full-time clinicians. But in terms of the basic science faculty of people running full-time labs, I would probably guess it's going to be 15 percent women and that may be an overrepresentation of the actual numbers. This is a huge issue as to why women are not better represented at the higher level, you know, at the professorial level or associate professor levels. Without a doubt it's multifactorial, some of the things which we just can't change.

One factor obviously is the issue of family. The scientific environment is not conducive with somebody taking nine months off or three months off, especially during the early years when you are doing the work. I know of no competitor of mine that would say, "Oh, my competitor is on leave. Therefore really, to even the competition field, I'm not going to do any science for the next three months." That just doesn't happen. So I think that's one factor.

I think by and large, this university is by and large very supportive of the faculty, of the women faculty. I know of very few examples— In terms of people that have come in and terms of the success or failure rate in terms of obtaining tenure and things like that, my guess is that, based on the very small number of individuals that I have known, the percent of women and the percent of men that failed probably are comparable.

COHEN: Percent based on the number in the bigger picture.

CHAN: Right. The number of assistant professors that are hired at Wash U.

COHEN: But if it's a percent of the number, then the women have a higher failure rate, because there are fewer of them hired.

CHAN: Right. So I'm saying that if out of the fifteen women assistant professors versus the eighty-five men as assistant professors—the percent failure rate is probably comparable between those two groups. There's a difference clearly in the absolute numbers that go on. So we actually—

I was discussing this with one of my friends about six months ago. I think one of the differences which needs to be actively worked on is the perception that women cannot succeed in academic science. So again, as I told you before, there's greater than 50 percent of our graduate classes are female. Less than 50 percent, but still a substantial percentage of our postdocs, are women, and yet when it comes to posthiring, there's, I think, the greatest discrepancy. So, one, it's clearly partly an issue with the search committees. And, two, you know, when I've talked to some search committees, they have expressed that we just don't get

that many applications from women. The question is why is that? And when I ask a variety of the trainees, postdoctoral fellows or senior students, I have a perception, or they have expressed certain perceptions, that they don't think that they can do it. They don't think that they're quite up to the task. Okay? So I think this is an interesting perception. It's not that they're going to fail, because clearly the people that have done it succeed just as well as their male colleagues, but it's the perception that they won't succeed and hence they don't apply. That's one possible hypothesis to test. I have no data to necessarily to support it one way or the other.

COHEN: Do they think that they won't succeed at doing the science or they won't succeed at getting the job?

CHAN: They don't think that they will be able to succeed in combining family, doing the science, and being tenured. So it's not necessarily one aspect, it's just the entire, overwhelming aspect. I was actually at a retreat where we had a faculty panel discussing husband/wife dual career type of things, and one of the women there expressed that her perception was that the men were just smarter—

COHEN: Oh really?

CHAN: — and they were going to succeed, which totally shocked me. So I related to them and said "What is the basis of your statement?" And you know, "Well, just look at these classmates, these classmates, and these classmates," but then at the same time, they don't realize that there are an equal number of women classmates that they have that are equally qualified. They probably just don't toot their horn as much.

So I think that becomes an important issue. The only way I can think of trying to at least partly remedy that, I think, is basically we need more role models of women academicians and women physician-scientists. So I think we need to be able to mentor the women physician-scientists, as well as the men—but the women in particular—to impress upon them that if they just continue doing good work, in the long run, everything will work out. Okay, yes we understand the need for family. We understand the time constraints that one puts on them, but they have to take the risk . This is where I think human nature comes in, as people don't want to take the risk on things that they think they may fail in. Because, without a doubt, it's going to require hard work. For them to accept that risk and to take that type of career choice means that they're going to basically put away probably six to eight years of their lives. That's a long time, especially already post-training, you know, at a time when your parents are still asking you, "Why are you still in school? Didn't we pay already for your college career, you know, eight years ago?" So I think that is still a perception thing. I think the women clearly are well-qualified and they can do it, but it's partly a mental thing of, I think, getting certain students to overcome that particular hurdle.

COHEN: Now, some of the universities give you more time to tenure if you're having children in this process. Does this place do that?

CHAN: I think they take it in consideration, but you know, one of the things that determines tenure is national and international perception. Okay? As in reputation. And of course, the international reputation or national reputation is based on your productivity per year. People read your papers and they go, "Oh, so and so is again doing good work." If you fall off the face of the earth in terms of productivity for ninth months or whatever amount of time, it clearly affects it. You know, nobody's going to say, "Well, the national reputation needs to be corrected for X." So I think that becomes a difficult part, because you know, I think this is most important especially to the early part of the career where yeah, the university may well do that. But one's reputation, scientifically, clearly will be affected one way or the other. I don't see an easy solution to that problem.

COHEN: Well, now, I know because I saw pictures in your office of your two cute little kids [Michael A. Chan and Jennifer C. Chan], so obviously your wife, Mary [F. Chan], who is in academics, had to deal with this issue. I think you told me your children are seven now, so she must have been in the early part of her career when she had twins, which is a lot of kids to take care of all at once.

CHAN: Right. And I think— No, absolutely. I think, you know, it's a huge responsibility. It's a huge amount of effort and a huge amount of time, and I think she has done a phenomenal job in balancing all those things. But at the same time, I'm not taking anything away from her, she's not a laboratory based individual—

COHEN: Right, right.

CHAN: —so many of her tenure decisions were based on the amount of clinical work that she does. And that's easier to measure, I think. When one takes in the context of children and leave and things like that, then it is productivity in terms of papers, because people don't quite see that kind of relationship when one evaluates a scientific career. You don't see the— You know, when somebody goes and gives a distinguished talk, visiting professor. You know, there are lots of distinguished women professors who have given talks, and to this day I have yet to hear that when the person introduces them, that they are also the mother of blah, blah, blah. So while I value it, you know, just from an individual and person type of view, it is very hard to integrate that into evaluating the scientific productivity of a person—

COHEN: Sure, sure.

CHAN: —and I think that is just a difference in the two cultures. Again, I don't see how one is going to be able to resolve those kinds of paradoxes between the two types of— Because you're really talking with two different types of language.

COHEN: Sure. So I actually usually get to this question a little later, but it's a natural progression here so— You are in that field where you have to have your productivity measured by numbers of papers and what not, and having children affects men too, not in the same way, but it does. So how has that impacted your career? We'll get to how it impacts your personal life eventually.

CHAN: I think— I mean there are clearly certain things that you would rather do because of the time issue. On the whole, I think it's positive. I'll just give you that first. Okay? So obviously once one has a family, there are certain constraints in terms of the hours that one can spend in the laboratory. You know as a graduate student, it wouldn't bother me to spend eighty to a hundred hours in the laboratory. That's the way you can function. Once you have a family, obviously, that entire equation changes. So here I've been very, very fortunate to have a very understanding wife and we have a great nanny and we have by and large very, very healthy kids. So one sort of divvy's the time mentally as to what one can do and hence, I still—

During the regular week I spend most of my time in the laboratory. Usually I won't get home until between seven o'clock or eight o'clock in the evening. So at most, I probably have two hours with my kids. Actually, now that they're seven, they don't really care about me anyways, and they just want to go out and do their own thing, which I'm sure will only continue in this vein as they get older. But, you know, the number of hours I have with them during the evening is extremely limited. We may read together, play one or two games together, and that's about it.

One thing I do do differently is that whereas before the kids, actually I would spend a lot of time over the weekends in the laboratory. What I do now is that at most, I will spend Saturday mornings in the laboratory, at most, and then basically all Saturday afternoon and all day Sunday I spend at home with them. I take my work with me to home. Sometimes I can get to it, but usually out of procrastination I don't. But I think that's one way I try to balance between the two.

It's not ideal. You would like, obviously, to spend more time with the kids, but then other things would suffer, and then if you spend more time with one, then that takes away from the other. I think you just have to sort of figure out a happy medium for yourself to try to balance the two. And there's no strict equation. It's not necessarily just the number of hours. It's actually what you do with them that I think that's extremely important.

COHEN: Sure, sure. Okay. Since we talked about women on faculty, let's go ahead and talk about the faculty again from the ethnic point of view. Does the faculty—other than women which we know are underrepresented on the faculty— How does it look ethnically compared to the graduate students?

CHAN: Compared to the graduate students, it's probably very similar in that, again, African Americans are underrepresented, Asian Americans are typically overrepresented.

COHEN: Asian Americans or Asians?

CHAN: Asians.

COHEN: Asians, okay.

CHAN: Asians as well as Asian Americans are overrepresented. Even in St. Louis.

COHEN: Even in St. Louis, okay.

CHAN: You know, the overrepresentation becomes even worse when you go to a place on the West Coast or the East Coast. So I think it's a reflection of the makeup of what you see in the graduate student class, aside from the gendered issues.

COHEN: One of the things, you know, people— I haven't heard too much about it lately, but I know that I read something in *Science* six or eight months ago. It was an editorial about whether having so many foreign students was good or bad for American science and in most labs, there are many foreign students, I think, mostly from Asia.

CHAN: Well, probably foreign postdocs. It's probably more postdoctoral trainees, rather than predoctoral trainees. So our predoctoral trainees are still pretty much U.S. citizens. It's the postdoctoral trainees that clearly are overrepresented in terms of non-U.S. citizens. And again, I think it's a reflection of the things that present day graduate students are worried about. If you just take a look at *Science, Nature, Cell,* etc., you know, in terms of the premier journals, you take a look at who the authors are. I will be willing to bet that the overwhelming majority or a significant percentage will not be, in terms of first author papers, U.S. citizens. Now, that I think is just the nature of that particular position in that it is not easy to find individuals who have finished graduate school training here that want to go on to do postdoctoral work, who want to

take those three to five years to do postdoctoral work and work at a certain level of efficiency, creativity, you know, of that stature.

Again, this is something I learned during the beginning part of my being a PI which was, you know— I was very fortunate to be trained in an outstanding environment, and I just thought you assemble that kind of team and boom, off you go. And you know, you always see these huge laboratories, these outstanding laboratories like David Baltimore's, where basically he creates a particular type of environment and the people basically are totally independent and they do their work and they have these phenomenal observations. But I think in reality, probably ninety-nine point nine percent of the laboratories in the United States don't function that way. The overwhelming majority, over 90 percent of the laboratories, probably function based on the PI's own ideas, the PI's insights, and basically just directing people of what experiments to do.

Very few labs— You know, it may be once in a blue moon that you have a postdoc who comes in, has some phenomenal idea, takes it upon himself or herself to do those experiments, have it all laid out beautifully, and be able to carry on a certain type of conversation at a certain intellectual level with them. That is a very hard thing to find in most normal laboratories, with the exception with those handful of very, very special laboratories.

So basically, what it comes down to then is that you need people that are willing to work hard. You need people that are willing to think. You need people that are willing to troubleshoot and hopefully by that three to four year period of osmotic learning, that they will hopefully become independent. Now, that was really one of the shocking things for me when I became a PI, because then, again, when I was a postdoc, every one of the individuals from our laboratory became an independent investigator. I mean Art [Arthur Weiss] had a batting rate of about over 90 percent in terms of generation of independent scientists and, in reality, it's probably less than 10 percent in terms of turning out individuals who have the intellect, the drive, and the patience to make it. I've seen many individuals, many of whom are in my lab, that have one of the three or maybe two out of the three. And it's hard to predict what people will do, but it's very rare to find the combination of all three.

It was pointed out to me that, you know, even in outstanding graduate programs like Wash U.'s or Harvard [University]'s or Stanford [University]'s, odds are of the entering class in any graduate program— It's probably only 15 percent or 20 percent of those students that will become independent, that will clearly become independent investigators at an academic institution or one of the leaders in the field in a biotechnology or pharmaceutical company. The others really are not going to become that independent.

COHEN: Is that because of the quality of the students or because of the availability of positions, because I know most search committees, you know, they'll get three, four hundred applications for every job.

CHAN: Yeah and usually after about two hours, they can throw away about 80 percent of the applications, because the quality of the people just aren't there. Even in the most difficult times, there have always been positions open. It's just that, you know, institutions were not willing to take the risk. If they saw an individual that had outstanding credentials, came from an outstanding lab, there was no hesitation ever to hire them. But when funding levels dropped to single digits or the low-teens, institutions became more reluctant to hire some of these individuals, because to hire each individual, it usually costs the university somewhere on the order of three-quarters-of-a-million dollars for an assistant professor, because you're getting them a starter package, you're covering their salaries for X number of years, and it all adds up probably to somewhere between a half- to three-quarters-of-a-million dollars. So if you have somebody that is good, but not great, in a shaky funding environment, universities wouldn't hire them. If they had that same position, same funding environment with an outstanding individual, they would hire them instantly.

So I think the opportunities have always been there. It's just that the number of really outstanding, qualified individuals haven't been there. But this is sort of the hierarchy that we built ourselves. Okay? You know, the top journals can only publish a certain number of papers per month. That's part of the reason why they are the ones that we, all of us, want to publish in. I think outside of that, there really is nothing that is necessarily better about those particular places. But as such, there are only a limited number of individuals that are going to have that kind of quality paper. I mean, just for example, here at Wash U., for the last six years that I've been here, there have been multiple searches by multiple divisions, programs, and departments for a variety of positions in immunology. Again, there are lots of applicants, but I would say that the number of really outstanding qualified applicants in all the positions that have been available over the last six years I can probably count on two hands.

COHEN: Really?

CHAN: You know, to be able to point to somebody and say that this [person] is a no-lose situation. The majority of applications are like, "Well, they've done okay. They've done a good job." Is this something that makes you excited about hiring them? No. You know, when the individual comes and gives a seminar and they themselves aren't very enthusiastic about their own work, how can one be enthusiastic about their work? So again, it's very hard to find the individual who's accomplished, who clearly shows the drive, shows the spark, who wants to have colleagues to collaborate with, who's willing to contribute to part of the community, and who's bright and has a great system to work on and looks like that they're going to be a winner. When you put all those factors together, you're talking about a handful of individuals every year.

So I think the positions have been there. There are probably more positions now than there were before, and it always looks like we're hiring more. That's not necessarily true. Again, I think there may well be more positions, but I think what happens is the bar becomes lower, because funding opportunities become better. So now the university says, "Well, this is still a risk, but it's not such a risk when we consider now the funding pay line's the twenty-fifth

percentile" All right? So when you go from a pay line that's 12.5 to 25 percent, that's not a difference of 12.5 percent. That's a 100 percent increase in the percent of investigators that are going to be funded.

That's why it was so devastating when they went from funding lines from the low twentieth percentile to the low-teens, because again it wasn't 12 or 10 percent that were being cut off. Half the investigators were being cut off and actually, in those cycles for study sections, the number of grants actually continued to dwindle for a number of years to the point where I remember sitting in study section and going, "Well, we have half the grants." Usually we take two days. After one day we're going to be done, just because the number of people that have stayed in science had dwindled.

So I think it's a combination of having the well-trained and well-qualified individuals as well as having their own spark, and depending where the funding bar is, it increases or decreases the reluctance of the university to take certain risks. I think it's that combination.

COHEN: Well, actually, since we've come to funding and grants, let's talk about that a little bit, because that's—for most PIs—another huge chunk of what they do, either chasing money or renewing money or whatever. First of all, how are you supported here? Is your salary— Does it come from grants or do you have hard money for your salary?

CHAN: In the [Washington University] School [of Medicine], there's no such thing as hard money, okay? Which means that we're expected all to bring in 100 percent of our salary, one way or the other. Now, I actually have been very fortunate, because I'm a member of the Howard Hughes Medical Institute, so my salary's fully covered by the institute, but my colleagues, they're expected to bring 100 percent of their salary in, in the clinical departments, based on grants. So whether it be in a— You know, they're all extramural grants or American Cancer Society, American Heart Association, Arthritis Foundation, etc. So those are the expectations. So to be able to cover close to 100 percent of one's salary, what that entails is probably getting funding from two RO1 grants and one other non-NIH [National Institutes of Health] grant or part of a PPG [program project grant] or something like that. So that pretty much is a full-time job. Again, the NIH has gone through huge swings over the past decade. Now is actually a great time. Eight years ago, wasn't such a good time.

COHEN: Right. Now, tell me a little bit about the Howard Hughes, because I know that these institutes exist in various academic sites, but how does it work exactly?

CHAN: I don't know. [laughs]

COHEN: You don't know.

CHAN: No.

COHEN: They just pay you, right?

CHAN: The institute itself has undergone some changes. As of prior to six or seven years ago, about 1993 and previously, the way the institutes worked were that there were institutes at various medical centers, because, after all, Howard Hughes initially granted the monies to be funded for medical sciences and hence it began in medical schools. And each university would have x number of positions they could nominate into and, upon approval, would appoint those individuals to the institute positions.

Over the past six to seven years, that entire strategy has changed, so that now what happens is that when a certain number of positions open up, there is a call by the institute to all the universities—not all the universities: a selected number of universities—and I think it's based on the degree of NIH funding. Each one of them are given a certain number of slots to nominate into, and then there's a national competition to ultimately select, again, x number of new investigators that will then go into the Hughes institute. As a member of the Hughes institute, depending on the level that you're at—assistant professors are assistant investigators, associates are associate investigators, and full professors are full investigators—you're given different levels of funding, but the salary of the investigator is fully covered by the institute. So from that standpoint, it is obviously a huge relief for one not to have to go and get the multiple RO1s or the other extramural sources to get 100 percent of the funding.

COHEN: Now, is this for a period of time or just indefinitely?

CHAN: It is for a period of time, so assistant investigators now, as well as associate investigators, they go through certain— You're appointed for a certain period of time. That typically is around a five-year period. Okay? So it's equivalent to what an NIH grant, probably, period is. Then you're subjected to review after your review period to determine whether your funding will be continued at that level.

COHEN: So was it the decision of Wash U. or was it the decision of Howard Hughes that you got that appointment?

CHAN: It's both. The institution has to nominate you. So there is an internal competition for the number of people that they would nominate and then it would go to the Hughes institute and they have their own selection committee.

COHEN: I see.

CHAN: Now, when I joined the university in the Hughes institute, I was right around the transition between the old rules and the new rules. So at the time, I actually came in not through the national competition, but because there was a position available within the Institute and they submitted my name then to the national committee who then decided, based on whether I was qualified or not for the position.

COHEN: Okay. Could you conceivably stay in this institute for your whole career or is there an exit time?

CHAN: There is no particular limitation on the time that one can remain with the institute. It's based on the quality of work. Hence, the reviews become extremely critical in, obviously, determining whether one is permitted to stay within the institute.

COHEN: So given that you probably need one less RO1 than everybody else to stay afloat, how much of a commitment of your time is given over to trying to obtain or keep money? That is, writing grants, schmoozing.

CHAN: Yeah. I mean I think— Well, with the Institute comes certain expectations. These aren't written down anywhere, but the expectations are that you have to be one of the leaders within the field. Okay? And the idea, I think, in part with the Institute is that it allows one to spend less time on writing grants and more time to thinking about the science. And that undoubtedly is true.

Now, most Hughes investigators also hold RO1 grants, but again the expectations, I think, have become a little bit different. I hold as many RO1 grants as probably a non-Hughes investigator would anyway. Okay? So right now, by certain strokes of fortune, in addition to my Hughes funding, I have three RO 1 grants. So it just happened to be, again, a certain fluke in the timing of the grants that this came about. But because of that, there's a certain expectation that one does work that's comparable to that particular level of funding, so I think the expectations always increase. The bar always gets raised with everything, and that's always true about science. Whatever you do or what you did technically has to be more advanced the next time around, otherwise you're not going to get your paper published in the same high-quality type of journal.

[END OF TAPE 3, SIDE 2]

CHAN: So again, I think the approach to science actually becomes maybe a little bit different in that the quality of the science becomes extremely important. It's not necessarily the numbers of papers that one publishes, but the major advances that one makes over a certain period of time. So in the end analysis, I think what one has to ask oneself when one is undergoing review then is, "Well, over the part five years, what are the major advances out of my laboratory that have really advanced our understanding of the biological questions that we have asked?" Not necessarily, "Well, how many papers have I published?" That then takes it to a new standard, because most papers, I would say, if you take the average papers out there, really don't add that much to our understanding of biology or the questions that are being asked. That's not to say that they're meaningless. They clearly provide some information, but the amount of information may well be very incremental.

COHEN: So let me go back to my original question which is, How much time do you spend grant writing?

CHAN: I don't spend—- Well, I spend probably still a significant amount of time in grant writing, but it's hard to average it out, because the NIH [National Institutes of Health] grants run to every five years, so if you caught me in a year that I was writing my renewals, I would probably be spending a significant amount of time. Now, when I write grants, it actually is not that time demanding for me. That's not necessarily because I write it well, but probably because I start early enough. [laughs]

COHEN: I see.

CHAN: I start typically six to seven weeks before the grant is due, and I usually have a first draft within four weeks before the grant is due. So then I actually can take it pretty leisurely over the ensuing two, three weeks in terms of touching up the grant, getting comments on the grant. So it's not as probably harried a process as many of my colleagues who wait three weeks before the grant is due to begin writing the grant. Some people just like it and do it that way, because they feel that they can work better under pressure. But I just don't like to work it that way.

I think it also depends on how one perceives the grant writing. Again, I have the luxury of having the [Howard] Hughes [Medical Institute grant], so most of the grants that I write, at least with the Hughes funding, are not the grants that I absolutely have to have. They're grants that would facilitate our being able to do a certain high-quality work, but it's not like I'm going to go starving the next day. So from that standpoint, it becomes probably a little bit more of a luxury and not as much of a drudgery or a pressure situation where I know I absolutely have to get this grant. Otherwise my position at the university becomes tenuous.

COHEN: Now, I have heard some people say that they feel the pressure not so much for themselves, but they don't want to have fire anybody, and if they don't get the grant or get the renewal, they're going to have to let people go and that feels like a big sort of personal burden.

CHAN: Well, it is a burden from that standpoint, especially if you've had people for long periods of time. That becomes problematic. Maybe it's partly St. Louis, but you know, we have a pretty continued turnover of personnel. So people usually don't necessarily stay in a particular position for more than five or six years. They decide to go do something else. We hire people right out of college, and they may want to do this for two to three years. Then they want to move onto something else. So I think all those things are true. I mean, I think losing funding or losing a position is a fact of academic life and people in those positions realize that. For me it's usually—

Outside of the funding issue, actually, I'm more concerned about whether one of my postdocs or my graduate students who have worked very hard on a project is going to be able to get that paper published in the best journal possible. Because in part, you know, I have a job already. Having this other paper, yes, it would be nice. It would be another feather in the cap, but again, I'm not really put in the position whereby I'm not going to have a job if I don't have that paper. I may lose certain lines of funding, but that's a different story, whereas for the postdoc or the graduate student, getting that particular paper published is extremely important to them in terms of their careers. So actually, I have more fear or I have more concerns about those kinds of situations than the funding situations.

COHEN: Well, we're going to talk about paper writing in a minute so— But just to finish up on the grant thing. Has there ever been a time when you thought you might be short of funds or have you always been in pretty good shape?

CHAN: Well, by and large, we've been in pretty good shape. There have been times where it was clear that we were overspending what we should be spending, you know? It would be like, "We spent like ten thousand dollars this past week. How did that happen?" But with the Hughes so far, it's been a pretty easy time to make ends meet.

COHEN: Now, the Hughes, I would— I don't know if I'm on the right track here, but I would call that philanthropic funding, kind of like the Pew [Scholars Program in the Biomedical Sciences] is philanthropic funding, as opposed to the RO1s are government funding.

CHAN: Yes, right.

COHEN: And then there's also the possibility of commercial funding.

CHAN: Right.

COHEN: Do you have any commercial funding?

CHAN: I don't have any commercial funding. I mean, getting commercial funding in combination with Hughes funding is a huge conflict. The Hughes institute, by and large, does not permit strings-attached funding from commercial sources. You know, if a company wants to give us funds with no strings attached, that's fine, but most companies won't do that. And again the degrees of funding, you know, one has to sort of measure what is the payoff in terms of this particular line of funding versus the amount of work that's required to get that kind of funding. So every week there's some other internal type of granting or other external type of funding agency for a total of twenty thousand dollars. Well, for twenty thousand dollars that I'm going to have to write five even or ten pages for, it probably is not worth the effort. So you know, again, we've been very fortunate, because we've had the Hughes. We've been fortunate with our success in getting extramural funding from the NIH [National Institutes of Health] and other sources that we, by and large, have not had to worry about those kinds of factors.

That doesn't mean that— I mean, I still right now keep tabs pretty much on where the money goes. I have to think about who's being paid off what grant, you know, those kinds of things, but not so much in terms of finding ourselves a hundred thousand dollars short here, a hundred thousand dollars short there.

COHEN: In terms of what you can do with the money, what are the differences between say government and philanthropic funding?

CHAN: The Hughes funding basically allows me to do anything I want, scientifically. Okay, you know, if tomorrow I decided that I have this phenomenal idea and we're going to study worm development, I can do that. The NIH grants' granting mechanisms have obviously a little bit different of a responsibility or guiding rate, because the Hughes—primarily they just want to see cutting-edge science done. So if you go back and you work on worms and you come up with some phenomenal discovery, they'll be very happy, I would think.

Now, in a way, the government funding does and does not allow you to do that. So if you present a grant on the immune cell system, the immune system, you're expected to be able to finish that particular grant. Now, you want to renew it five years down the road. Well, you better have shown that you have completed all the things that you proposed to do and have been successful and have published papers. This then becomes extremely subjective in many ways, because I've sat in study sections and there's always a debate on productivity of the individual

versus the quality of work that the person has done. Some people count papers independent of the quality of papers. Other people say they've made significant advances in the field and big deal, they've only published three major papers in the major journals out of this particular grant and those three papers have clearly made greater advances in the field than another grant that has published forty papers with incremental advances. So this becomes— I mean there's no hard line here, but nonetheless, I think with the NIH, you're held to much more so in what you propose and whether you've accomplished it or not than, for example, other sources. Because actually you know, aside from philanthropic, but let's say the American Cancer [Society], the American Heart [Association], the Arthritis Foundation. Those particular grants usually are nonrenewable. Not all, but most of them are nonrenewable. So there is really, from that standpoint, less accountability in terms of ultimate completion of what one initially proposed.

I think in some ways it's hard, because it's hard to predict where the science goes. How can I predict every result that's going to happen in the next five years and know whether it's interesting or not? If I can predict every result that's going to happen in the next five years, odds are the experiment probably is not worth doing. Okay? Because it must probably be so incremental that I could predict what the result was going to be. So I think those are the differences in terms of what one can do and can't do.

COHEN: Well, it sounds as if the Pew money was kind of a hybrid of those two things, because you were expected to have a proposal and yet the funds were unrestricted.

CHAN: Right. I think that's really the beauty of the Pew funds, that you proposed a particular project based on, obviously, what you've done before. From what I can tell, the selection was extremely keen, because the competition between the last forty individuals were extremely close. I mean it was very hard. You know, many of the advisors said you could have just flipped a coin, but at the same time, the funds allow you to take whatever high-risk kinds of experiments one wanted to do. If you wanted to change the direction of your science because of a particular opportunity, you had the opportunity to undertake that transformation.

I think that's one of the real beauties of science, and that actually is what many times distinguishes an outstanding scientist from a good scientist, is that you're going down a certain path and you have an unexpected result. The good scientist will continue going down the original path and the outstanding scientist will say, "Hey, this doesn't quite make sense" or "This is not what I expected" and totally reroute their thinking in pursuing an entire new direction. And hopefully, it's those kinds of unexpected results that will allow you to make a particular observation.

I mean this has happened to us, for example, in my first few years when we were looking at a particular interaction for one particular project. As it turned out, it was a total artifact. At the same time we were studying interaction with another protein, and it turned out the first protein was actually the correct one that interacted with the protein involved in the second project. If you weren't thinking, you wouldn't have tied the two together. We were lucky that we were able

to tie the two together and the subsequent studies were made very easy, because we already had made all the mutants of the first protein. So I think one has to be able to redirect one's science, and having the funds to redirect one's science becomes a huge advantage.

COHEN: Now, in terms of the Pew money or the Pew scholarship—which is more than just the money—when that came along, where were you in your career?

CHAN: Let's see. I started '94 through '99, so it was my first year as an assistant professor.

COHEN: Oh, okay. And you already had the Howard Hughes, though, at this point, right?

CHAN: Right.

COHEN: So what, if anything, did it mean to get the Pew?

CHAN: I think the major impact that the Pew had, scientifically now—I mean it has a lot of other impacts, but scientifically—was the availability for me to have colleagues that I can discuss issues that I wouldn't discuss with my division chief.

All the things that you don't learn as a postdoc about— How do you motivate people? How do you deal with postdocs or students or technicians that spin their wheels? How to focus one's attention in terms of trying to deal with all the nonscientific issues that clearly directly relate to your science was a huge advantage, because all of a sudden you realized you weren't alone. All of these other people had similar problems and this is what they tried and it didn't work. This is what this person tried and that did work. So, number one, it gave you a perspective of all the problems that one can run into which are fairly common.

Second, the diversity of the science was obviously a huge advantage, because it made me appreciate a variety of the sciences that were not the science that I typically read or individually interact with on a day-to-day basis. So those were clearly two of the major advantages for the Pew scientifically. I mean, there were obviously other things, you know, social policy, scientific leadership, the role of the scientist in terms of the world, all these other issues. One increases their awareness of all these other issues, and I think in the long run, that's going to be important. I mean, the money, per se, is a small chunk of money. It allows one to basically take off on different tangents.

So for example, one of the things that we have done recently is we were interested in this relatively new methodology of being able to identify proteins using proteomics and large two-dimensional electrophoresis and the entire setup cost about thirty thousand dollars. I mean, no

NIH grant's going to allow you to do that and even the Hughes funding is not going to allow you to do that on a whim. But it wasn't on a whim. It was after months of preparation that we decided this is the way that we were going to do it and, you know— Yes, I could have written for an equipment grant from the NIH, but the problem with the equipment grant from the NIH is that it's going to take probably a cycle. You'll get the equipment, if you're lucky, after about a year. I could have applied from the Hughes, but then I may get it in six months. Well, I want to do the experiment in the next month. In six months I may not necessarily want to do the same experiment, so the funds from the Pew allowed me at least to purchase that equipment to then go in this particular direction. If it works, it's going to change drastically the way that we pursue our science probably for the next five to ten years. So it's having the opportunity to be able to do that that is the huge advantage.

COHEN: Now, in terms of this kind of sharing of ideas about lab management and science and that sort of thing, was that what happened at meetings. Because you know, everyone loves the Pew meetings; did you actually find yourself communicating at other times with—?

CHAN: It's predominantly at the meetings. I would say probably 80 percent of the discussions are there, but out of those meetings you develop a certain relationship with a small number of individuals. Over the years I may have some crazy idea or I have a question about a field that I know little in and I'm just lazy and I don't want to go investigate the entire ten years of literature. So then I just E-mail so and so and I say, "Listen, this is the crazy idea I have. What do you think?" Just a few weeks ago, I noticed that in one of the genes that we had had a particular sequence that one of the other Pew scholars actually wrote a paper in 1986 on and subsequently a review in 1996, so I just ended up calling him and saying, "Hey, this is Andy. Yeah, yeah, how's everything going? Oh, it's fine. You're the expert in this field. What do you think about so and so?"

So the networking also is advantageous, you know, during the year outside of the Pew meetings, because you know, these people know who you are. It's not that they would be any less agreeable if I wasn't a Pew scholar, but you've already established a certain relationship with them. It doesn't make you any smarter or any less smart, but they've seen you as a person, which may be good or bad. In any case, I think it allows one to just get on the phone and say, "Hey, what do you think?" And just bouncing certain ideas off other people who are experts and have a different view on it actually is very, very valuable and very helpful. Whether anything comes of it is a different story.

So the Pew has— You know, there are multiple facets of the Pew program that I think have enriched my scientific life, my view of science and the world, my view of my colleagues, and my appreciation of all of those.

COHEN: Okay. Well, as I promised you, we'd come back to writing papers and—[tape recorder off] Actually, because of some time constraints, we're going to leave writing for tomorrow. Let's

just talk briefly about lab management, which is something else you're not trained for before you have to do it. You talked about it just briefly before about how do you motivate people and that sort of thing. But first of all, who's in your lab? How big is your lab?

CHAN: Small lab right now. It usually is around a dozen people, myself included, which includes usually anywhere from two to three students. So I have two thesis students and usually one to two rotating graduate students. There are four postdocs and there are four technicians.

COHEN: Okay, that's a pretty good sized lab.

CHAN: So that's about the size I like it, because I can't keep track of more projects than that. The way that I run the lab is from a day-to-day level: I meet with my graduate students once a week formally. So I set aside an hour-and-a-half to meet with them, to discuss their data, and I tell them the meeting may last five minutes, the meeting may last an hour-and-a-half or longer.

COHEN: An hour-and-a-half each one.

CHAN: Each one.

COHEN: So that's six hours a week that you spend meeting with—

CHAN: With just the students.

COHEN: Okay.

CHAN: I also block off an hour-and-a-half for the technicians.

COHEN: Each technician.

CHAN: For each technician. Usually the meetings don't usually run an hour-and-a-half. Usually they run maybe an hour, depending what the need is that particular week. Sometimes they may only last five minutes if we really don't have anything to discuss, but I think it's important, because it blocks off that hour-and-a-half and tells the student if you have anything to discuss—You don't want to talk about science; you want to talk about what you want to do as a postdoc.

You want to talk about what your future is going to be like twenty-five years from now. You have that hour-and-a-half of my undivided attention. And I think that's important, to set aside time to be able to discuss those kinds of issues. Most of the time it's basically just going over the data, figuring out what kind of experiments we need to go over next, try to troubleshoot for the student. What things you can try to do to clean up all these dirty gels, dirty blots, you know. Why a certain type of ligation in molecular biology is not working, how to interpret the data, and things like that.

Then I meet with my postdocs once every two to three weeks. Again, the same kind of hour-and-a-half. And then during the week, I always bug people. "What happened to such and such?" [laughs]

COHEN: So you wander in the lab.

CHAN: I wander sometimes. And then we have lab meetings twice a week with journal clubs at eight forty-five in the morning on Monday followed by two half-an-hour talks by two individuals in the laboratory on their science. And then a second journal club on Friday where we do a second journal club, in addition to all the other department seminars and division seminars that we have. So each individual has usually one to two projects. Usually one, their major project, which is probably the higher-risk project, and sort of a second backup project, and they usually try to balance the two depending on how each project is going. The technicians likewise also have some project or projects of their own. Either some crazy idea I have and they're just testing it out to see whether there's anything to it, or they're actually— There are certain projects that have been going on a while in the laboratory that are fairly straightforward that we just need to crank out the data for. So that's pretty much how I run my lab from week to week.

COHEN: And what about this business, because you know, you get twelve people together and there's going to be all kinds of politics and things going on, so—

CHAN: I have two rooms. [mutual laughter]

COHEN: So you just separate warring parties or what?

CHAN: No. I mean, I think by and large, this has happened where clearly there are certain personality differences that just are never going to get resolved. And usually what I end up having to do is sit both of them down and say "Look, you're both professionals. You're both adults. This isn't grade school so either, one, you act professionally or, two, you're going to have to leave." Because, you know, somebody like that can be extremely detrimental to the entire

laboratory. So that's the way I try to handle it. It's not easy, because you really don't want to interfere with certain— Because lots of times certain things will take their course. And you hate to have to intervene with every single incident that happens. But when it starts affecting the general morale or the general operation of the laboratory, then you have to intercede.

COHEN: So this will be my last question for the day. What kind of a boss are you? [mutual laughter] You have thirty seconds now.

CHAN: I'm an extremely demanding boss.

COHEN: Are you?

CHAN: I expect that certain things be done at a certain pace. I expect people to be able to think about what they're doing, to be able to troubleshoot what they're doing, and be able to plan the experiment beforehand, to walk themselves through the experiment, to be able to come out with a reasonable experiment. Okay? Now, that's not to say that I expect them to do that from day one. You know, graduate students are graduate students. Postdocs still require training, though I expect them to be a little more advanced in their ability to go through this kind of process. For the graduate students, it's extremely important to me that by the time they finish, that they're going to be outstanding and rigorous scientists. As I tell them, I don't want the person they're going to end up working for calling me and going, "Who is this that you sent me? They're not trained." So it's extremely important to me that my students, as well as my trainees, know how to do that. And I will tell, you know—

I've told the students and trainees that I will tell whoever calls me that I'm going to tell it as it is, because it's not fair to the other people that can do that for me to cover for them or to not exactly tell them exactly how good—or what their strengths and weaknesses are. So from that standpoint, I'm extremely demanding.

I think I am supportive. If they have a certain situation, I'm more than happy to listen to it and try to help them come to some resolution how to get around or how to resolve the problem, whether it be a personal problem, whether it's an academic problem, whether it's a scientific problem. I'm willing to expend whatever energies, monies, or anything else to try to help them in any one of those capacities, because I think from an ethical and moral view, I have taken them under sort of— They're my responsibility, but at the same time I expect them to uphold their part of the bargain that they will make themselves as good of an individual that they can be. So from that standpoint, I'm extremely demanding.

[END OF TAPE 4, SIDE 1]

[END OF INTERVIEW]

INTERVIEWEE: **Andrew C. Chan**

INTERVIEWER: **Helene L. Cohen**

LOCATION: **Washington University School of Medicine**
St. Louis, Missouri

DATE: **20 April 2000**

COHEN: Yesterday we got sidetracked, or maybe I got sidetracked, into starting to talk about being a PI [principal investigator] before we finished talking about how you got to be a PI. So I wanted to go back. We had pretty much talked about your internship and residency, but then we didn't talk about your fellowship/postdoc, which you did in San Francisco. So how did you come to end up there?

CHAN: Again, based on the people I had been exposed to, being John [P.] Atkinson and—Actually, my thesis committee chairman at that time was Ben [Benjamin D.] Schwartz, who's also a rheumatologist. Those two individuals clearly had a significant impact as to the type of physician-scientist I had wanted to be, I think further compounded by the fact that my mother had [systemic] lupus [erythematosis] and I was interested in immunology. All those things, I think, contributed to my ultimate decision to do rheumatology, although it's sort of a strange dichotomy. The two subspecialties I had debated about were actually cardiology and rheumatology, which are probably as diametrically opposed in terms of subspecialty that one can do. In the end, I think because I was interested in doing basic science research and also because of the undoubtedly greater demand in terms of one's time in terms of clinical responsibilities, if I went to cardiology, I ultimately chose rheumatology and, hence, I did a rheumatology subspecialty.

The selection of UCSF [University of California, San Francisco] at that time was primarily, again, asking a variety of individuals where they thought probably the strongest rheumatology subspecialty fellowship programs were and my need at that point to at least leave Washington University [School of Medicine], because I had been there for six years of graduate training and also three years of postgraduate training. And after entertaining a variety of different programs, UCSF was the program I ultimately chose. So I went there in 1989 to begin my clinical fellowship. It was a one year clinical fellowship, and then I began doing lab work in the laboratory of Art [Arthur] Weiss at UCSF, working on T cell receptor activation. I was in Art's laboratory for about three and a half years before coming back to Washington University [School of Medicine] in January of 1994.

COHEN: Now, I don't know whether things have changed since I knew a lot of people going through fellowships or whether you just had a different experience, but it seemed like

fellowships used to be about three years—a clinical year and two years of research. So you had kind of a long fellowship by that standard.

CHAN: Right. So that's what the fellowship program is. Usually it's one year clinical work and two to three years in the laboratory.

COHEN: I see.

CHAN: Realistically I think— And that's the end of your fellowship, but I think most people who want to continue on in science in terms of an academic career undoubtedly will require probably a total of anywhere from three to five years of laboratory training. So for me the three-and-a-half years was probably a little bit on the short end, in terms of the general experience. Again, you think about it, you know, in three-and-a-half years; that means you probably have to start looking for jobs at two and a half years in the laboratory. That doesn't give you a huge amount of time to really get a sufficient amount of work done. Again, I was fortunate to have sort of stepped into a project that worked, not immediately, but fairly quickly. So from that standpoint, three and a half years is probably—by today's standards, when one actually considers the total amount of time—a little bit on the short end. What you may in part be referring to is also the titles that people hold, so I consider my entire three and a half years as part of my fellowship, when in fact probably on paper, the last two years— Actually, I think I'm listed as an adjunct-assistant professor at University of California, San Francisco.

COHEN: Oh really?

CHAN: So I still consider that part of my fellowship, because responsibility-wise, my primary responsibility was to do my laboratory work despite the titles. The title permits one to obtain funds for the university, to get a variety of funds to fund your research, but in terms of training-wise, it was really in that mode as a postdoctoral fellow.

COHEN: You had mentioned, I think it was yesterday, that everyone in that lab went on to become an independent investigator—this was while we were talking about the quality of the graduate students and postdocs now—and I wonder if you have any ideas about what that was about. I mean, there are many possibilities about why all those people went on to do that and maybe now they don't or whatever, but what went on there that created that?

CHAN: I think first of all, the PI of the laboratory, Art Weiss, was clearly a very, very accomplished investigator, and as such he was able to attract individuals who also wanted to

achieve a certain degree of excellence, rather than just seeing a postdoctoral fellowship as a job. Hence, the individuals that he recruited, whether be it graduate students or postdocs, went into the laboratory with that goal in mind. They weren't going into the laboratory saying, "I have to get a Ph.D. Well, I'll just go into here and spend my five years in the lab here and I'll come out the other end with a Ph.D." The graduate students that were in Art's lab, by and large, were extremely driven, in that they wanted to accomplish something, not just necessarily just get a Ph.D. And it was one, I'm sure by chance, that he had recruited a group of individuals that, by and large, got along with each other extremely well, had very common goals, and who worked well together. So that in itself made the environment better than each one of the individual parts. There were a lot more discussions than I've seen in most other laboratories.

So I think in part it was Art and in part it was the recruitment of a certain set of individuals that just clicked. Then the final thing, I think, it was San Francisco. I mean everyone wants to obviously go to San Francisco at some point in their lives. So I think all three factors created that particular environment for those particular years. Once those individuals left the laboratory, obviously, the environment of the laboratory changes. So even though Art was in San Francisco, we're still constants in that equation. Clearly, it was an unusual circumstance that all those individuals happened to be recruited there in a particular group within a particular time.

COHEN: Sure. So how did you like San Francisco?

CHAN: Well, San Francisco is a wonderful place. When we started there, my wife [Mary F. Chan] was a GI [gastroenterology] fellow.

COHEN: So she was able to get a fellowship also.

CHAN: Yeah. She was able to— We co-matched in rheumatology and GI. We didn't have kids at the time, so our expenses were by and large just real estate for renting the apartment and paying for the parking space. Those were our two major expenses. We didn't really have any other really expensive vices per se. So we lived comfortably on fellow salaries, when you had two fellow salaries combined. But it was a wonderful time.

COHEN: So when you look at— You know, the whole medical thing is different, obviously, than just going through a Ph.D. program. So here you are finally at this fellowship/postdoc level. How does the path that you took for this period of time compare with just doing a regular postdoc?

CHAN: Are you asking for, in other words, an M.D./Ph.D. versus a Ph.D. postdoc?

COHEN: Right. Well, a fellowship versus a postdoc. A subspecialty fellowship versus a postdoc.

CHAN: Oh, I see. A clinical fellowship versus a postdoc.

COHEN: Well, the fellowship is part clinical and part research, right?

CHAN: Right, but really I think the only major difference there, for a fellowship that includes certain clinical years and certain basic science years— So the clinical years, obviously, are very different. It's basically continuing in patient care and learning about the rheumatology subspecialty, but then the research years are pretty much similar. You participate in the same kinds of journal clubs, seminar series. You do your labwork and you are measured in the same way as a Ph.D. postdoctoral fellow who is also doing the postdoctoral fellowship. The only additional responsibility that usually one has is that you still have one half-day clinic per week. So I mean those are required for you to be able to get board certification in certain subspecialties, but otherwise the other four and a half uncommitted days were totally committed to my research. So from that standpoint, the other 80 percent remainder, nonclinical time was basically the same as a postdoctoral fellow.

COHEN: Did you have to pull any sort of on-call rotations as the—? During your lab years, you know, for the house staff if they needed a rheumatologist—

CHAN: No. During the second and third years of my fellowship, which equate to the first and second years of my laboratory experience, the program is set so that you are spending 90 percent of your time doing basic science laboratory work. The on-call rotation, at least at this particular program, was set up so that the first-year fellows had their full year of clinical work. Now, during the last year that I was at UCSF, because I had this adjunct-assistant professor position with my own grant funds, I did have to attend on rheumatology one month out of the year, but that's the only additional clinical responsibilities that one had during that time.

I think this is an important thing. This particular concept of protected time is extremely important. I was fortunate to have mentors, Art being one of them, who were extremely protective of the physician-scientist mission, of the academic-scientist mission. He, as division chief, also realized that one cannot be spending x number of additional weeks or months or be pulled away because somebody happens to be sick onto the clinical service, and that you'll really have to dedicate your life and your time and your focus onto the basic science research. That is not a universal finding across divisions at almost every medical school in the country and that actually has led to certain things that I have helped develop subsequently here at Washington University, which we can come back to and discuss later, which is the physician-

scientist training program that tries to ensure that the research mission during the postdoctoral research years are totally protected. But I was fortunate, again, enough to have the mentors that I have been exposed to to realize that and protect me from those other issues during my training time.

COHEN: Okay. So I was trying to do some mental calculation here on how old you were by the time you finished—

CHAN: Oh, ancient. [mutual laughter] Um, let's see.

COHEN: Comes out about thirty-four in my head.

CHAN: That sounds about right. Before I took my first real assistant professor job.

COHEN: So how did you end up here?

CHAN: Back at Washington University [School of Medicine]? I had entertained a couple of possibilities. Clearly I wanted to be at— You know, by the time I finished, I wanted to be an academic physician. I wanted to be in an institution that valued basic science research, that had strong basic science immunology. I think as one trains further, one realizes there are fewer and fewer numbers of institutions in the country that would make it possible. Wash U. [Washington University] at the time had very, very strong basic science immunology, and based on my previous experiences here, I knew that it was extremely supportive of junior faculty. Sort of the odd thing is that when we left, post our clinical training, at that time it never dawned on me that I would even consider coming back to Washington University.

COHEN: Oh really?

CHAN: But nonetheless, you know, after taking a look at a very, very small number of positions, I ended up deciding that Wash U. was the right place, because of its commitment to junior faculty, its strong basic science immunology, the respect as well as push in commitment to physician-scientists. A lot of the outstanding basic sciences that are done at Washington University are actually done in the clinical departments, and that's not true for many other institutions, where most of the basic science research is done in the basic science departments. And finally, you know, I had known lots of people here, and the department chairman at that time was my thesis advisor, John Atkinson, so it was sort of a very comfortable place. A place where I knew that I would be taken care of and a place that I knew that I would be given the

resources to flourish. Then with the birth of our twins [Michael A. Chan and Jennifer C. Chan], that also totally changed the things that we were looking for in terms of a city. So we had our twins six months before we moved, but we knew we had— By ultrasonography, we knew we had twins already, you know, obviously six months previous to that. So it was that constellation of resources and observations that made us come back.

COHEN: Okay. Now, you mentioned the other day that they have a startup package here that they invest—what—a hundred thousand dollars or so in a new junior faculty member. So what kind of a deal do you get when you come here?

CHAN: I mean, that's clearly dependent upon who you are, what division you go into, and things like that. And inflation clearly has affected that.

COHEN: Sure.

CHAN: At the time, in 1994, I think a reasonabe startup package probably would have been on the order of somewhere between three hundred to four hundred thousand dollars total, exclusive of salary for the PI. The way, you know, that many— At least I discussed it over in terms of the resources I needed, which weren't necessarily in absolute numbers and dollars. It was more of a description of what kinds of resources I needed in terms of equipment, access to equipment, and what kind of support for students, postdoctoral fellows I needed over a certain amount of time.

While all this was going on, all this was sort of made moot because of my appointment to the Howard Hughes Medical Institute, because that allows me to have certain number of positions from the institute. So not only does it pay my salary, they pay the salary of a certain number of postdocs and a certain number of technicians and there's a supply budget and equipment budget on an annual basis. So all of that sort of— While we had gone back and forth a number of times on discussing the resources that would be committed to me before the Hughes appointment went on, retrospectively, [we had discussed this] needlessly. The point became moot once that happened.

COHEN: Okay. So you ended up with a joint appointment. You have an appointment both in [the Division of] Rheumatology, which is I assume the Department of [Internal] Medicine—

CHAN: That's right.

COHEN: —and also [the Department of] Pathology [and Immunology].

CHAN: That's right.

COHEN: So how does that work?

CHAN: Washington University runs its graduate program through the division of biology and biomedical sciences. It's one large division, and graduate students that come in enter that division and actually can participate in any program, whether it be immunology, biophysics, neurosciences, molecular cell biology, etc. That's actually, I think, one of the beauties of the system, because I think it's very hard for graduate students to know when they're twenty-one, twenty-two years old, to know exactly what it is they want to do. And hence, this actually gives them opportunities to be able to investigate different avenues or different fields of investigation.

For one to have access to the students, one has to be in a basic science program. The Department of Medicine is considered a clinical program at Washington University, but the Department of Pathology is considered a basic science program at Washington University. Actually a lot of the programmatic interests in immunology are based in the Department of Pathology, which most recently actually has been changed to— The name of the department has changed to the Department of Pathology and Immunology. So given those particular types of interests, one always has to decide what kind of co- or joint appointments one requires and, hence, I picked pathology of the various departments. I mean, most of the faculty here have joint appointments between medicine and some other department, whether it be Department of Genetics, Department of Cell Biology [and Physiology], [Department of] Molecular [Biology and] Pharmacology. It doesn't matter, because once you have the appointment in the basic science department, the graduate students pretty much can cross between programs. It's pretty seamless. So that was the basis for my co-appointments in both departments.

COHEN: Well, the thing that occurs to me, though, is that then you have, or maybe you might have, double kinds of meetings and double— You know, if you're serving two masters in a way, do you have twice as much?

CHAN: Again, Wash U. is probably a little bit different than many other universities in that, again, one's everyday life is more dictated by their programmatic interests, so while I am a member of the Department of Medicine and I am a member of the Department of Pathology, ninety-nine percent of my interactions are primarily with people through a variety of departments but whose research interests are common to mine. So for example, I know there are about a zillion business meetings for both the Department of Medicine and pathology, which I never attend.

COHEN: You don't go to any of them.

CHAN: I don't go to any of them. So there are these aspects that— I mean, the Department of Medicine is very large. The Department of Medicine probably is somewhere between 250 to 300 faculty members. The medical school, I was just reading the other day, numbers around 1,200. We actually double the size of— The School of Medicine makes up half the size, in terms of faculty, of the entire Washington University campus. So a lot of the meetings— I think there are only like 2,200 or 2,400 total faculty in the entire university.

COHEN: The whole campus?

CHAN: In the whole campus, main campus and the medical school campus, of which half of them are in the School of Medicine. As such, a lot of the business meetings basically aren't really forums for discussion. They are forums for announcements, which I can spend my time better off doing things more directly related to my research. I can read the minutes much faster than I can sit there for an hour-and-a-half sitting through a meeting.

COHEN: Sure. Now, you are an associate professor now, right?

CHAN: Yes.

COHEN: And do you have tenure?

CHAN: Yes.

COHEN: So tenure is at the associate level here.

CHAN: Yes.

COHEN: It's always curious to me what tenure means if you have to bring in all of your salary. Now, you don't, because of the Howard Hughes—

CHAN: No, well I do.

COHEN: But you could lose the Howard Hughes.

CHAN: Right.

COHEN: So what does tenure mean here?

CHAN: Tenure, I think in general, is probably an outdated term. Tenure, I think, for the medical sciences in particular, is an outdated term. I mean that tenure traditionally has been primarily to protect the faculty so that they have freedom of expression, which I think historically has been especially important in the non-biological sciences or non-science fields, like humanities, because obviously somebody may be expressing a point of view that may be contrary to whatever the in-fad view is of the university.

So tenure at the medical center basically means that— I mean, there are a number of criteria all of which boil down to: one, have you been able to establish an independent research program? Has that research program resulted in advances as measured by publications and international reputation? And third, has one been able to obtain funding for your research program? Then, of course, there are a number of other factors that could factor into it, like service to the university, teaching responsibilities, and contribution to the community. So it is—

The way I have always felt about it, it's one of those things that one absolutely has to have, because if you don't get tenure, then you have to leave the university. But having tenure, to me, actually doesn't mean a whole lot after one gets it, because you're exactly right. You still have to be funded and you're still going to be judged in terms of your scientific accomplishments. I use this great quote, and I forget exactly where it came from, and that is, "You're only as good as your last experiment."

So from the standpoint of longevity and tenure, I don't think the tenure issue is any major factor. It is obviously a major thing when you're an assistant professor because you know you have to get it, but if you are a well-accomplished individual, there's no doubt that you should be able to get tenure. If one is looking to achieve and attain a certain degree of excellence and if you're not able to achieve that degree of excellence, then it's time to move on to do something else, then the decision of tenure isn't such a major stage or major issue that affects one's life. In the future, I think, there probably, undoubtedly will be a time where tenure is just gotten rid of.

COHEN: Gone.

CHAN: Yeah. I mean, many institutions now actually go on three- to five-year rotating contracts—again, with funding issues, scholarship issues contributing to the decision of renewal or nonrenewal.

COHEN: Well, I guess that's they way most people in the world live. They either do a good job or they're gone, right?

CHAN: That's right. Many of the universities actually have gone to a salary system that basically does the same thing. So many universities, this one included, have gone to these salary scales, which they call the XYZ at this particular university. So X is basically a base salary, which is usually pretty low, which would be the salary that you're guaranteed even if you lost all your funding and you're tenured. The Y component usually is the remaining component. The X and Y represents the total of most people's salaries right now. The Z component is predominantly for more clinically based individuals. It's actually a bonus. So what will happen is that if you lose all your funding all of a sudden, you will then only draw your X salary. And most people won't tolerate being paid an X salary indefinitely. That in essence gets rid of tenure.

COHEN: Okay. A lot of places, though, if you lose your funding, they'll fill the gap for you for a brief period of time until you can get funding. Do they do that here at all?

CHAN: That is a very— They will, and the usual variable is how long that period is.

COHEN: Yeah, sure.

CHAN: As an M.D./Ph.D., the one thing that they can always do is give you more clinical responsibilities. So you can always make up the difference by doing more clinical work, but then that basically is saying you're going to give up your laboratory-based research operation.

COHEN: All right. Well, let's go back to all of your PI responsibilities where we left off yesterday. We had covered quite a few things, but we didn't get to the writing of papers, because of time constraints. Obviously that's a major component of your work. So tell me a little bit about the writing process for you or your lab.

CHAN: The writing process really is dependent upon the project. There are certain projects that are extremely competitive, in which the paper has to be written in forty-eight hours. In those situations, I take an extremely active role in writing the paper, because the paper has to be sent in primarily because of competition reasons. In most other cases we actually have quite a bit of time, so usually the way I go about doing this is that the postdoc or the graduate student and I sit down. We actually outline what all the figures are first, and we actually have the data, hopefully, sitting in front of us, knowing what missing pieces of the data still need to be

completed. Then I tell the student or postdoc to go ahead and start writing the paper in whichever order they want. And then I say, "Okay, I expect a rough draft in two weeks." Or if they just want to write a section of it, I'll tell them I expect a rough draft in a week. They'll give me a rough draft and I will work on it and I'll give it back to them.

COHEN: By working on it, you rewrite or you make suggestions to them to rewrite?

CHAN: I will actually rewrite certain sections of it by hand and give it back to them. It just depends, also, on how far along they are. If they're really stuck, as in they have nothing on paper, then we can discuss, "Well, how do you think you're actually going to order it? What are the major points that you want to write?" I mean, usually if you have the figures in front of you, writing the results is very straightforward. The introduction I could even dictate if I had to. You know, it would take me thirty minutes to dictate the introduction, but nonetheless, it's important for the student or postdoc to go through that process. So I have varying starting points.

My initial starting point is always a blank piece of paper. I just say, "Go and write, but here are the figures. This is the order." But even in terms of the introduction, you need to be able to order it in a very logical way. Most of the time you're trying to tell a story, so you've got to be able to set the story up so that the readers, or in particular the reviewers, will think this is an important problem and understand how you were led to do this line of experimentation.

So if they come back and they're stuck, then I'll try to order it by paragraphs for them as to what are the major points. The hardest one is usually the discussion, because there, actually, it requires the greatest amount of thought. I mean, usually you've already done the experiments. You know why you did them, you know how they turned out and yeah, the first paragraph of the discussion is straightforward. You usually summarize your results, but then that's where the most difficult part and yet the most intriguing part and challenging part about writing a paper is. What are the implications of your data? Why is this important? How do you relate this to the present literature? And that usually takes the most time, but nonetheless, the student or postdoc writes the paper, they give it back to me, I'll rework sections by hand and I rework the— It would be much easier for me just to write it from fresh. Okay? Just write it in the computer. But it's important, I think, for me to write it by hand, because usually I jot down the notes of why certain sections are wrong or shouldn't be where they are and then the student in particular will have an idea as to what they can compare. What did they write and what did I write? And then they'll get at least a certain understanding of why or the style in which I'm writing.

It's a learning process. It takes me a long time to write a paper unless there are certain time issues, and we go through, usually, easily, twenty drafts of each paper, especially in terms of the discussion. Then ultimately something comes up. Some product comes out.

COHEN: But you can do this by yourself in forty-eight hours if you have to.

CHAN: Well, it depends on the paper. There are certain papers— You know, you publish in *Science* and *Nature*, the papers are extremely short and in many ways, those are the most competitive timewise. So if I can only write two thousand words, there's not a lot I can write, but it has to be written in an extremely concise manner. So there, I can easily write the first draft and basically work on it over the next twenty-four to forty-eight hours to be able to come out with some reasonable product.

COHEN: Well, we're going to hit this business of competition in a little while. What about the things that your techs [technicians] are doing, because you know, the postdocs and the students have to learn how to write papers. But the projects that the techs work on, do you write those or do you encourage the techs to write?

CHAN: No, I actually— My technicians actually work on the various aspects of certain projects, so a lot of their projects are just crazy ideas that we begin with. Okay? So they're just going to see if it works. If it looks like it works, then usually the projects— many times, not always, but many times—are handed off to postdocs and graduate students to continue, because the postdocs and graduate students usually work more hours in general and they can probably get the work done faster and they're the ones that need the projects. There are a few projects where the technicians work on that are just basically bread and butter projects, and those I end up writing the papers. I mean, the other thing is that you know, I actually end up writing probably a lot of the papers in general, because a lot of the postdocs we have, English is not their first language, in which case you do the bulk of the writing anyway. So the technicians in my laboratory don't write the papers. They play an active part in each project, but in the end I end up writing those papers.

COHEN: Okay. Well, another thing that eats up time is administrative responsibilities. Well, I think this probably is a good time to talk about the physician-scientist training program. It probably fits under that, but in general, before we go there, how much of your time is eaten up by—?

CHAN: What do you define as administrative things? Like ordering stuff at the laboratory, management issues in the laboratory?

COHEN: No, I was thinking more in terms of committees, meetings, organizational things and— I don't know if this qualifies as administrative, but I know you are a contributing editor to the *Journal of Immunology* and you review papers and—

CHAN: So I'll classify through different things. Okay? There's one which is what I call service

duties to the scientific community. These will be editorial issues, ad hoc reviewers reviewing manuscripts. I try not to do that during the time I'm actually at work, so actually most of that I do at home. I just bring the manuscripts or whatever other relevant papers, and I do it at home. Probably I have usually one to two manuscripts a week, I'm also on study section, so in total I would say that may amount to about 5 percent of my time. But again, I try not to do it while I'm here, because primarily, when I'm here, I want to basically interact with other individuals that are here, whether that be in my lab or out of my laboratory.

Then there are obviously committees that I have to serve while I'm here, but I've been pretty fortunate and pretty selective in picking and choosing the committees that I want to serve on, so there are actually very few committees I actually serve on. I serve on the steering committee in the program of immunology, which is the steering committee that determines policy for the graduate program. I serve on the admissions committee for the program of immunology. I help run the physician-scientist training program. I'm also co-director of another program called the Four Schools Program for the medical students, but each one of those in and of themselves probably don't take up more than 1 or 2 percent of my time.

COHEN: Really?

CHAN: For example, the steering committee may account for a whole five hours a year.

COHEN: Well, that's not too bad.

CHAN: I have to be on the faculty committee to give preliminary examinations, oral preliminary examinations. I have to sit on thesis committees. So all and all, those I see as things I should be doing anyway as part of the educational process. I don't feel those necessarily are burdens. Those are a part of my responsibilities as a PI and so I actively participate in them, probably that may amount to another maybe forty or fifty hours a year. So when you add all the hours up, they probably don't amount to a huge amount of time commitment for my part.

COHEN: Well, tell me a little bit about this physician-scientist training program.

CHAN: The program is designed to provide infrastructure for people who are interested in academic science, coming out with M.D./Ph.D. degrees or M.D.'s with an extraordinary amount of research experience, and to guide them through the clinical training portion and ultimately back into the laboratory. What we have observed—and it has also been my experience and my observation—is that a lot of the times the major obstacle for people coming back into academic medicine occurs during that period of time.

COHEN: During the residency?

CHAN: During the residency and clinical fellowship, because what happens is that you go off, basically, into a different world, where 95 percent of your colleagues are not going to do academic science or be an academic physician. So you get distracted by a number of other issues that are not probably helpful or condone a career in academic science. So the idea of this program was to provide mentorship and an infrastructure to guide these individuals during this particular period. So when we accept an individual, they come into the program as an intern.

[END OF TAPE 5, SIDE 1]

CHAN: So the program begins at the internship year. They come in and they're basically afforded entrance, not only into the internal medicine residency program, but they are also guaranteed acceptance into any fellowship program within the Department of Medicine.

COHEN: Here?

CHAN: At Washington University, because usually, otherwise, it's a two application process. You apply for your internship, you finish your residency, and during your last year of your residency, then you apply to your subspecialty. So since we are interested in individuals continuing their academic training here, individuals accepted within this program are guaranteed acceptance through their entire internal medicine residency as well as their subspecialty fellowships. There are certain seminar series, as well as lectures, that are provided for the trainees during the six-year period. Not that they're going to do any lab work, but just so that they keep up with sort of where the general fields are going. They're assigned mentors who are themselves physician-scientists, either based on their clinical subspecialty interests or their research interests, and they're to meet with these particular individuals just to discuss anything from career planning to selection of laboratories. They're also guaranteed that once they begin their laboratory years, they're not to have any additional clinical responsibilities aside from the responsibilities that are required for board certification.

COHEN: As in the one-half-day a week.

CHAN: Whatever—

COHEN: Whatever it is, okay.

CHAN: Whatever the board certification— Certain subspecialties have slightly different requirements.

COHEN: Right, okay.

CHAN: This is just to prevent— You know, when the people are in their lab, they're sort of the low man on the totem pole, okay? And it's very hard for those individuals, when the division chief or the program director calls you up to go to the VA [Veterans Administration] hospital or to come on to service a month, to say no. But this program basically already says no.

Finally, what it also does is that it gives them certain financial advantages to minimize the need for moonlighting. It's not going to make them rich, but many of the house staff, as well as fellows, moonlight to obtain additional income, because they may be in a position whereby their spouse doesn't work, they have kids, and on just the fellow's salary, that makes it extremely tight. With the additional stipends that are given through the program, what it obviates the need for is the need to moonlight, because they're supplemented to a degree that they basically would have to moonlight two shifts every three weeks to make up the difference. Now moonlighting, I think, is just detrimental, because it's not just the day that you moonlight, but usually you're so exhausted that it takes up the next two days for you to recover.

So what the program does is provide infrastructure, not necessarily because we know what the formula for success is. We know the formulas for failure, and what the program does is takes out the things that we know contribute to failure and allow the trainees to at least have the least number of obstacles and the most favorable environment for their success. Ultimately, it's obviously still up to them.

COHEN: And what does one have to do to get into this program?

CHAN: Well, when they're applying for the house staff program, they have to indicate that— either because they're M.D./Ph.D.'s or M.D.'s with an extraordinary amount of research experience—they're interested in a career in academic medicine, in which case we then have a committee to evaluate and interview them subsequently, but also to evaluate whether their scientific accomplishments warrants them to be in the program, because we have to be sure that these people really are outstanding both in the research laboratory as well as the clinical arena. Because after all, we're guaranteeing them acceptance into any one of our fellowship programs also. So from that standpoint, it's extremely competitive.

COHEN: Right.

CHAN: We interviewed sixty-plus individuals this past year, and we offered eight slots.

COHEN: Oh wow. So it's very competitive.

CHAN: Yeah.

COHEN: Yeah. Now just— I mean it sounds like a wonderful idea. The only question I have about it is, most people split their training up and go somewhere else for the fellowship because they get exposure to different ideas and what not, so is it advantageous to stay in the same institution for both—?

CHAN: Well, for their clinical and their postdoctoral training, it's very, very different. Okay, I mean there are certain students that, if they're coming from our program, where I would say it's probably not advantageous for them. But for many of them, for a variety of reasons primarily family related, they want to stay in the area. And actually, we value our students, probably as a class more so, because we know what the quality of the products are. But for somebody that's coming in from another university, they're going to get their clinical training and then they're going to go back to the research side, and if they're coming from the outside, from an outside research experience, this is going to be a totally different research experience. In terms of the strengths of the basic sciences here at Washington University, there are very few fields that we don't adequately cover, so—

Oh I forgot, one of the major strengths of the program is that they actually can work in any laboratory in the entire university. They're not limited to just the laboratories within the Department of Medicine. So they can go across the street and work for a basic science laboratory, working on differentiation in flies, for example. And then, obviously, we want them to come back across the street and attract them back, to bring that kind of technology back into whatever clinical, relevant, or scientific problems that they want to address. So I think for anyone from outside the program, outside the community, and even from people within the community, because they have so many opportunities to go in different directions, that it does not end up as a disadvantage for them.

COHEN: So they don't have any trouble getting jobs afterwards?

CHAN: Well, we hope not. This program is still it's in infancy.

COHEN: Oh, I see.

CHAN: You know, we've had an informal program for about three to four years, but with the new department chairman [Kenneth S. Polonsky] coming in, we've actually had additional resources.

COHEN: I see.

CHAN: So we will see what the rate of success is. I cannot imagine that we would do anything to make it less than what it is presently. If anything, I think this program is clearly going to improve on what we presently have right now, or before the program was instituted, which is really not any significant infrastructure.

COHEN: So do you yourself in your lab have any fellows? You mentioned postdocs, but I don't know if those are graduate students who are postdocs or M.D./Ph.D. people who are fellows.

CHAN: I have a spectrum of postdoctoral fellows. So postdoctoral fellows are anybody who's actually finished a doctorate degree, so graduate students don't fall into that category.

COHEN: Right.

CHAN: So out of the four postdoctoral fellows I have, I have two people that are Ph.D.'s, I have one M.D./Ph.D. fellow, and I have an M.D. fellow. So I basically have the range of the kinds of individuals that we have.

COHEN: Okay, tell me about the Four Schools Program.

CHAN: The Four Schools Program has now been around for about a dozen years, and it was started as a program which obviously involves four schools, the four schools being Washington University, Duke University, Johns Hopkins University, and the University of Pennsylvania. The purpose of the program was to encourage people to take an interest in academic internal medicine. So this is sort of an unusual program in that students that have completed the third year of medical school—in other words, having completed all of their clinical clerkships, like internal medicine, surgery, etc.—before they go into their fourth year electives, will actually take a year out to do either basic science investigation or clinical research, and they have the opportunity to do research at any one of the four universities.

COHEN: I see.

CHAN: So each university typically picks two individuals, the program then has eight individuals per year, and they pick laboratories or clinical mentors to study with for that one year. Now, I mean realistically, I tell the students, you know, it's impossible for us to really train you in a year's time. What it does is primarily to expose these individuals—it allows them to address a couple of questions. One, what is the life of an academic physician? Two, might this be an area of research interest, whether it be clinical or basic science investigation, that you may want to come back and pursue after you finish your clinical training? So those are the primary goals of the program.

COHEN: And do you have any of those students that you mentor?

CHAN: No. I mean, I basically administer the program. We only have, like I said, two students per year from each institution and it's been more difficult to recruit individuals into this program from Washington University, because for this particular institution, there are already an enormous number of research opportunities for students between the first and second year, between the second and third year, so there's— You know, the pool of individuals who are actually interested in research after the third year becomes extremely small. You know a quarter of the class are M.D./Ph.D.'s in our program.

COHEN: A quarter? Really?

CHAN: So somewhere between twenty-five and thirty students are M.D./Ph.D.'s.

COHEN: So the class is 100, 125.

CHAN: About a 125. We usually have anywhere from two to six students that get master's degrees in conjunction with the M.D. degree. We usually have a handful of students that take a year out to do a Howard Hughes Medical Institute [HHMI] fellowship or go to the NIH [National Institutes of Health] for a Cloister Program [also known as the HHMI-NIH Research Scholars Program]. So by the time that the third year comes around, probably fifty students have already done research, so anybody that really is interested in clinical or basic science investigation has probably already taken off on one of those routes. So on average, we probably don't get two students per year. We may average one student per year. For those students, it's been a highly valuable experience, but the pool is not that large.

COHEN: All right. Well, we're working our way through all of the things you have to do as a PI. What about traveling? Some people travel a lot.

CHAN: My wife tells me I travel a lot. [laughs]

COHEN: Okay, what's a lot?

CHAN: That's a good question. I usually go to—my guess is probably, maybe—half-a-dozen meetings a year and probably I'm visiting professor probably somewhere between six to eight institutions per year. So I probably take about twelve to fourteen trips a year. It seems more than that. Probably somewhere around there.

COHEN: So a little more than once a month on average.

CHAN: I think it averages out probably one-and-a-half times a month. Yeah, that seems about right.

COHEN: Now, how does that impact— I mean, it seems to me of all the things one would do, that might be one of the more disruptive things, because it literally takes you away.

CHAN: Right. That's clearly very disruptive. The meetings are probably the most disruptive, because there you're gone for multiple days. So for example, the Keystone [Symposia] meetings are four to five days, and that's a long meeting. The FASEB [Federation of American Societies for Experimental Biology] meetings are four to five days. Those are long meetings. Usually most people don't make it through the entire meeting. And then the other days, where I am actually visiting professor, we're somewhat fortunate in St. Louis because we at least have a hub, we have TWA [Trans World Airlines]. So I don't, you know—primarily for family reasons and other reasons— I don't usually get into town until midnight the night before, and then I leave that following evening. So at most, I am at the institution probably for a whole twenty-four hours. So that makes it a little bit harder sometimes for me, but it also minimizes my time away.

I remember one trip where I had to go to San Diego to the Salk [Institute of Biological Studies] for a meeting. I took the eight a.m. flight out of St. Louis. I was there by 10 a.m. I gave my talk at three o'clock, had dinner and visited various people all afternoon, and I took the midnight flight back. So I was back into St. Louis by 6 a.m. the following morning. So I actually

had only been gone for twenty-two hours. I don't know how long I can keep that up for, [laughs] but still that's pretty much how I try to minimize the time away. It's important to be able to go to the various places to interact with other investigators, as well as a recruitment tool for your own laboratory in terms of graduate students, but it's also, as you pointed out, extremely disruptive. So I minimize the time away by having these crazy flight plans.

COHEN: Now, one of the things that you have to do that non-M.D.'s don't have to do is you probably have to do some attending.

CHAN: Right.

COHEN: What are your attending responsibilities?

CHAN: I have to attend on medicine, internal medicine, on the ward internal medicine service for four weeks, and I attend on the rheumatology consult service, the hospital consult service for four weeks.

COHEN: Are they the same four weeks or are they two different—?

CHAN: I try to make it the same four weeks. It actually works out pretty well, because usually for the internal medicine attending responsibilities, I usually start at seven-thirty [in the morning] and by and large I'm done by noon. And the first day, I tell my rheumatology fellow, I tell him there are only five rheumatologic emergencies and I don't want to be called unless it's one of those five before three o'clock in the afternoon. So then I begin my rheumatology rounds starting at three o'clock in the afternoon and go until whenever it takes us. Sometimes we're done by six, sometimes we're done by eleven p.m. Whatever it takes. But then I'm able to maintain three hours of sanity in my laboratory, in which case I have to deal with all the administrative stuff. I have my meetings organized so that I can meet with everybody in a timely fashion. I can pretty much still run the lab pretty orderly during those four weeks.

COHEN: They sound like they're four tough weeks though.

CHAN: They are four tough weeks, but you know, I arrange it so that it's in the summertime—so there aren't as many seminars going on. There's no teaching going on. So basically it's the same amount of time— Well, not the same amount of time; it's not that much of a tradeoff as compared to the full-time academic months where there are seminars, there are teaching responsibilities. So it all evens out. As long as you keep it pretty orderly, it by and large goes

fine.

COHEN: Now, is that something that you enjoy doing?

CHAN: I actually enjoy doing it. I do it primarily for teaching purposes. You know, I bring a certain dimension of science into the medical arena that many other individuals that are not basic scientists cannot bring into their training, and hence, I think actually— I think it makes this particular university or academic centers such as this extremely unique, because in a center like Washington University at Barnes [Jewish] Hospital [also called Mallinckrodt Institute of Radiology], house staff are exposed to full-time clinicians, they're exposed to individuals like myself or basic scientists, as well as private practitioners. So each one of us actually brings a totally different dimension of the science of medicine, the art of medicine, and medicine itself into their training and they learn—

You know, if it was just me or just the basic scientists, that's not a good experience. If it was solely the clinicians, that's probably not a complete experience. If it was just private practitioners, it would not be a complete experience. So I think it's important for me to be able to be on the wards for that purpose. And discussing many of the diseases, actually, is still extremely interesting and it's sort of a mystery, trying to figure out what the patient actually has. In many ways, it's a scientific problem, and you think about it in that way.

COHEN: Well, I guess the flip side of that is, you said that you liked taking care of patients. Is a month a year enough?

CHAN: No, it's a different way. I like taking care of patients. I had great experiences when I was a fellow. It's part of the reason why I went into rheumatology, because these are chronic illnesses and it's not like you have an infectious disease. You have a pneumonia, you cure them, you never see the patient ever again. So it's a very unique subspecialty in that you develop certain bonds with the patients over long periods of time. You've seen them through three or four really, really bad flares of the [systematic] lupus [erythematosis] or rheumatoid arthritis and hence you build a special bond with them. So I miss that part now, because I think the only way to be able to do that is to do outpatient medicine. But with the emphasis that I have on my laboratory, I've had to give that up, because when you have a sick patient, you have to take care of that problem. I think it's extremely difficult to be basically on call twenty-four hours a day, seven days a week in anticipation of that one sick patient and still be able to run a laboratory full time. That, I think, becomes extremely difficult.

COHEN: Now what about— You know, people who practice medicine daily have a hard time keeping up with the newest and the latest and everything. They have to work at keeping current. So if you're only doing it one month out of the year, how do you keep current?

CHAN: Well, the— Okay, so let me answer that in terms of rheumatology first. In terms of rheumatology, actually, I have the advantage, being at an academic center, because the drugs that are being developed I've known about already for years, because they come out of basic science developments. So for example, one of the more recent developments that came out two years ago for the treatment of rheumatoid arthritis is a drug that basically binds up cytokines. We have known from that observation since 1990 that in the first model that was built, which was studying something totally unrelated—they were studying stability of messenger RNAs—and what they found out was that there's a particular cytokine called TNF, tumor necrosis factor, which had this very unusual regulation. They were studying the regulation of this gene when they deleted a part of the gene and, lo and behold, they got this regulation of TNF and the mouse got arthritis. So that observation we've known about and obviously, the obvious thing to say is, "Well, what's going to happen with soluble TNF receptor or an antibody that's directed against TNF?" And we've kept up with those kinds of literature seven years before the drug came out.

So from that standpoint, we already are well aware, based on other basic science findings, what the next entire generation of drugs that are going to be coming out are. So knowing that kind of information, you know, the problem is that clinical studies take a long time, so I don't necessarily have to read every piece of information between now and then, because I'm just waiting for the major trial to be completed and I'll know what the result is. So from that standpoint, doing rheumatology isn't so difficult. It's actually easier.

From the standpoint of general internal medicine, I think that's much harder, but again that's the advantage of being in an academic center. Grand rounds, for example, here, you cover all the major topics, so within an hour, you—without having to go to the primary literature—will have the most up to date seminar on that particular field with a discussion of what the shortcomings and the strengths of every study.

COHEN: So you go to grand rounds regularly?

CHAN: We go to grand rounds not regularly, but there are enough colleagues around that you know this kind of stuff is going on. There are general internal medicine journal clubs and then when you're on the— Actually, you learn a lot when you're actually attending on medicine. So when you're on general internal medicine, if there is an issue, you can always ask for a consultation. So then the subspecialist will come in, whether it be the cardiologist or nephrologist, and say, "Well, these are the studies. These are the data." So you learn also sort of on the job as to what the latest stuff is.

So with that collection, actually, it's not that hard. I mean the house staff here are really clinically very, very outstanding. I think where our decisions come into play really is a judgment issue, is being able to recognize the forest from the trees. Okay, and sometimes I remember, as a house staff you're inundated with so much information, this consultant says this, but this is an

apparent contradiction to this. It's attending, when you don't have to deal with those issues on a minute to minute basis, so you go, "Wait a minute, this is so simple, this is ridiculous. Don't worry about this. We have to be able to decide upon this issue. This is clearly the most important issue, and then these become secondary issues. This is the definitive issue that needs to be addressed." So it's sort of just more guiding the house staff in being able to recognize and prioritize what the major issues are.

In many ways, the science is very helpful to that, because you always have a zillion possible experiments to do, and yet by prioritizing and recognizing what experiments are going to make or break your hypothesis, you develop a certain degree of clarity in terms of thinking. If you can apply it to clinical medicine, the same thing holds. I mean, I remember many clinical situations where you're always sort of in a bind with a patient that has bad coronary artery disease, that also has kidney disease, and the problem is that you need to subject that patient to a cardiac catheterization. But then by giving the patient dye, they're going to end up with end stage dialysis or they're going to have to dialyze them. Then, you know, the attending comes in and goes, "Well, this is all superfluous. What you need to ask is, 'Is the surgeon going to operate at all?' Because if the surgeon's not going to operate, I don't need to know what the anatomy is. There's no reason whatsoever to subject that patient to the dye load anyway." Or if the surgeons are waffling, you say, "This is the situation. Would you even, with the worst disease, operate?" And if the answer is no, then there's no reason to know. That's just come sort of experience and being able to recognize sort of the bigger picture as to what to do.

So from that standpoint, I actually feel very comfortable attending on medicine. But then again, you know, if I was out on the front lines and not academic-centered, I think the story would be very, very different.

COHEN: All right. Well, the last thing that I can think of that takes up time or takes up some people's time—let's see if it takes up your time— But there are a couple of things that some people spend time on and others don't. One is the internet, which can consume a great deal of time, and the other, actually, is television. Do you spend any time on either one of those things?

CHAN: So internet-wise, I mean the only thing I usually access the internet for is primarily for data searches, the library. I don't use the library anymore. Everything is electronic.

COHEN: The library is in your office.

CHAN: The library is in my office. Basically, I can access almost any article. And now, actually, what I do is that every article I download is in my computer. I don't even actually keep a hard copy of the paper, so if I need to print it up, I'll basically pull it directly from my computer. But other than that, I don't use the computer that much, I mean in terms of the internet, which is probably antiquated for present-day stuff. We're just sort of at the— So I

don't use it that much otherwise.

Television, I actually find it, depending how hard I worked that day, to be sort of totally mindless for me. It's basically noise, but I turn it on and then I read the newspaper. But it's background noise. Maybe it's part of growing up that, you know, I had three other kid brothers and sisters and a very loud family that you just need some sort of noise. I just don't like it when I sit, when I'm trying to relax, in a dead silent room. It doesn't work out well. I always feel like there's something wrong. So I turn it on and basically, I go into a vegetative state while I'm doing something else or that. That's about it.

COHEN: So when you consider all the things that you do, you know, the grant writing, the paper writing, the administrative, the committees, all the things that we talked about, is there any time left to be at the bench?

CHAN: There is actually. That's why I'm going in and out right now; I'm doing the experiment. It depends. When I'm going out of town, it's very hard for me to do anything, but there are still certain things that I can do, because usually the people in the lab are pretty already maxed out in terms of things they can do. Sometimes I come up with a particular idea of a particular experiment I want to do that may require me to make a certain construct, certain cDNAs, and that is pretty mindless. That's basically—you can start, you can stop, you can start, you can stop, you can throw it in the freezer. So that I still do. I make certain constructs and then I hand it off to somebody else, just because of manpower issues. But I also find that many times, it is extremely time-demanding for that issue, because I feel like I'm always running around trying to do two different things, three different things at the same time. It's important to be able to do the labwork, because otherwise, you can never troubleshoot for people and a lot of it is just basically troubleshooting.

COHEN: Do you like it?

CHAN: Oh, I like the lab work. A lot of the scientific work takes a long time before you get an answer, whereas when you do molecular biology, at least you have the satisfaction to know that you got it right. You completed that particular ligation or you sequenced a cDNA and it was correct. So from those standpoints, those are sort of the very small benefits of life. The little short-term gratifications.

COHEN: So from talking to you, it sounds like you're somebody who's really good at organization and sort of making things fit together, but how do you juggle all this stuff? I mean, it seems like there's million things—

CHAN: Well, I think everybody organizes to some degree. It just depends how hap-hazard one wants to be. Other people live extremely well-organized lives, and I can tell you that mine is not like that, you know? I'm sometimes a procrastinator in certain things and things sit on my desk for long periods of time. I had tried a while to have this policy whereby I only touch every piece of paper once. Okay? So there is this— You know, I knew somebody, basically I asked him, "How do you get organized?" And he goes, "Well, I touch every piece of paper only once, so that I touch it, I make a decision, it's done. I don't put it on my desk and let it sit and have to keep coming back to it." That can be done for certain things. Okay? So I try to do that when it's very, very straightforward and simple, but there's obviously lots of things in science that that just can't be done with and that goes to a different pile.

So the organization, I think, nonetheless is extremely important, so that you have some idea what it is that you're going to accomplish that day, what it is you're going to accomplish three days from now, and what it is that you have to do today to get ready for three days from now. But it is always a juggling act. You always feel like you have five different things going on, but I think that's life. My philosophy is that, "Well, if I have nothing left to do, then probably I'm dead." [mutual laughter] But there's always something to do. There's always something to do. I think in science, that's always true. There's always something else that you can think about. There's always something else you can look at. I know of no scientists who feel that they have nothing to do or they have a huge amount of spare time.

COHEN: Right. Well, you know, Tuesday you had talked a little about how having children has sort of changed the number of hours that you spend here, mostly on the weekends I think.

CHAN: Right. I mean, as well as during the week. I mean, you know, if I was single, I could easily see putting in probably three or four more hours per day.

COHEN: Oh really?

CHAN: As graduate students, that's what we did. You know we would be here in the morning, be here in the afternoon, you go home, you eat dinner or you eat dinner around here, you go back to the lab and work until ten or eleven o'clock. Then you go home. You come back the next day at eight o'clock in the morning. That's what most graduate students did when I was a graduate student, and still that's what a lot of graduate students—I shouldn't say most, but a lot of graduate students—do now. They are working twelve, fifteen hours a day, six to seven days a week sometimes.

COHEN: Has doing that, cutting back your time, had any real impact on your productivity or did you just get more efficient?

CHAN: No, I think it's twofold. Okay? I think when you are a postdoctoral fellow, you are it. It's your hands. When you go home, your career stops at that point.

COHEN: Work stops, yeah.

CHAN: Whereas as a PI, it's different because you have built a laboratory of ten to twelve people and, yeah, they're not working at night, a lot of them are not working at night, but it's not just your work. I mean, you're not the only sole set of hands there. You have ten to twelve additional sets of hands. Yeah, of course, there are ten other projects I'd like to be able to embark upon today, but the number of hands don't allow us to do that, so I think that's just one of those realities that we get to accept. You basically have to prioritize what are the best experiments. What are the experiments that potentially have the greatest payoff and go from there.

COHEN: What is a typical day in your life? [tape recorder off] A typical day in the life of Andy Chan.

CHAN: So, typically, I get in probably some time between eight and nine o'clock, depending on what's going on in the morning.

COHEN: Do you do anything at home first?

CHAN: No.

COHEN: I mean do you take your kids [Michael A. Chan and Jennifer C. Chan] to school or—?

CHAN: No. So our nanny comes in at seven thirty. My wife usually has morning meetings, so usually she comes in early and I come in later after she arrives. So I only have to take care of myself in the morning, usually. There are rare instances when she's out of town or something like that, that I have to get the kids up and get them breakfast, etc. But usually, I just have to take care of myself, so I get in sometime between eight and nine. Usually I have some time to take care of just administrative issues, you know, E-mails, phone calls, that sort of thing by about nine o'clock. And most days, especially during the earlier part of the week, I then pretty much have meetings from nine until about four or five with various people in the laboratory, because you know, as I said before, I meet with my graduate students every week. I have an hour-and-a-half slotted for each one of those people. Each one of my technicians has an hour-

and-a-half slotted for him. Then I meet with my postdocs once every two to three weeks for an hour-and-a-half. Then there are various seminars and meetings during the day. So by about Thursday, usually, my schedule's a little bit less hectic, because I tend to centralize my meetings with the people in the lab during the first three days of the week and depending, again, on whether I'm out of town or whether I'm doing lab work that they may be interspersed by various experiments. Then somehow, usually when I look up, you know, it's five thirty and I say, "Well, I should be getting ready to go home," and the next thing I know, it's seven thirty and eight o'clock. So I usually get home probably sometime between seven and eight, usually, on the weekdays. So that's hour-wise my typical day.

COHEN: Now, do you eat with your kids or they've already eaten—?

CHAN: No, they eat very early. They get grouchy if they don't eat by about five o'clock in the afternoon.

COHEN: Okay. So when you get home, I know you said you play with them for a while and then they go to bed.

CHAN: Yeah, depending on their mood. [laughs]

COHEN: Their mood. Okay.

CHAN: That's not up to me. It just depends what activities they're doing that particular evening.

COHEN: And then if they're not interested in you or after they go to bed, what do you do?

CHAN: More recently, it's been harder. On the weekdays, by about nine o'clock and ten o'clock, I'm just not in a highly— I'm not in a capacity that I can concentrate, so there I just take care of bills, read the newspaper, deal with house issues, things like that. It's pretty boring. Nothing exciting.

COHEN: How about the weekends then, because I know you said you don't spend more than a few hours here.

CHAN: Yeah. So usually in the weekends, you know, again it sort of depends what my wife's

schedule is, because half the time she has to come in to rounds in the mornings. If she has to come in to rounds in the mornings, I usually can't come in in the mornings, although there are sometimes when I have appointments scheduled for Saturday morning, in which case we can usually get our nanny to come in on Saturday mornings. But otherwise, usually I— For whatever reason, my kids like Dunkin' Donuts, so we end up going to Dunkin' Donuts on Saturday morning. We usually run errands throughout the morning. It's, again, a pretty boring weekend. Sometimes, I intersperse it. If I have some things to do, my kids actually are at the age where I can bring them into the lab and they can stay in my office, you know, doodle on the board and things like that for at least a couple of hours. Sometimes, I can get a little bit of work done between that kind of scheduling.

COHEN: What do you do for fun?

CHAN: The only thing I really do for fun, outside of work, is play tennis. You know, I used to play a lot of different sports, but it's hard to come up with nine other people that want to play basketball or a lot of people to play football, so one of the fewsports that I can still play— You know, you only have to get one or three other additional individuals to play tennis. So actually, I play a lot of tennis. I try to play— I usually, at least, play twice a week and then sometimes I can get in three times a week, but that's about it.

COHEN: Does Mary play or—?

CHAN: Mary does play. She just started taking up tennis about a year ago, so I haven't played consistently with her yet. [mutual laughter] That's the plan.

COHEN: Okay. Now, you know, this is just a little aside, an interesting one I think, but you were raised with this sort of understanding that you were expected to achieve educationally. How do you handle your own kids in that respect?

CHAN: That's hard. I mean both of us, both Mary and I, feel pretty comfortable with our kids' educations. We don't do anything, I think, out of the ordinary to push them, as far as I can tell. I mean they go to public schools. They happen to be in a very, very good school district. Each of the kids excel in their different ways, and we just try to increase their exposure to a variety of different things that are available around town. You know, there are some opportunities: for example, the art museum that I had my daughter go to. This summer they're going to go to a variety of activities at the botanical gardens, but it's really more of trying to increase their breadth than it is necessarily pushing them in terms of depth right now, because I think that will come. That's just a matter of time. They're only in first grade.

The things that Mary and I have tried to emphasize is just to increase the diversity of exposures. That's about it. I mean, even the classes themselves, they don't have anything that really pushes the students until third grade. I don't have any preconceived notions, at least right now, as to what they will do. I think fields are very, very different you know, whether one wants to be a social scientist, a scientist, humanities, etc. I think both of us expect them to go to college, but not necessarily anything subspecialized at this particular point.

COHEN: Okay. Well, I want to shift gears a little bit now and talk about your work. So maybe you can tell me a little bit about, you know, what you're doing—

CHAN: The work that we're doing now?

COHEN: —now, keeping in mind that the people that look at this in the future will probably more likely be historians, historians of science, so they're not going to be completely clueless, but—

CHAN: So the major interests or the major questions that we like to address, really are centered on what are the biochemical mechanisms that permit immune cells to function. In our laboratory, we began with studies in the T lymphocyte or the T cell, primarily because that's what I was predominantly trained in. Over the last few years, we have now expanded our interests to other cells in the immune system, most notably the B lymphocyte.

So again, during my postdoctoral training, what I had been trained in was trying to— I had identified one new level of regulation in the signaling mechanism of the T cell antigen receptor. And we've continued our studies studying this particular enzyme that we coined, called *ZAP-70,* and we've been interested in how this particular enzyme is regulated during signaling events, how this enzyme regulates the development of cells, and more recently by utilizing this particular molecule as a switch—

[END OF TAPE 5, SIDE 2]

CHAN: So by altering the level of signaling, we want to see what the effect on the outcome of the developing T cell is, to evaluate the effects, basically, of the immune system to see whether that compromises the immune system or compromises it a different way that allows cells that should die to escape and cause potential autoimmunity. So that's been sort of the entire paradigm we've been interested in. We've taken it, over the more recent years, an understanding of what the signals are in the B cell antigen receptor system by defining, again, a novel molecule that we had discovered, that we coined *BLNK,* for B-L-N-K, for B cell linker protein. It relays the messages that are activated by the B cell antigen receptor with a generation of second

messengers. Again, similar kinds of questions arise. You know, "How does this molecule regulate the multiple signaling pathways that are activated following B cell receptor cross-linking? How does the B cell utilize the expression of this molecule or differential modifications of this molecule to be able to achieve different outcomes during different stages of B cell development?" So those, in general, are the types of questions that we're trying to pursue.

COHEN: Okay. And how is this going to increase our understanding of autoimmunity, for instance, because that's really your field, right?

CHAN: Well, there are a couple of possibilities. First of all, it's important for us to define what the normal signaling pathways are and that, obviously, is important just in terms of basic science, but the elucidation of these mechanisms are also important in potentially identifying targets by which one can interrupt the signaling pathway. So as one example, *ZAP- 70,* which is the kinase that interacts directly with the T cell receptor that we discovered when I was a postdoc in 1990 or '91, is selectively expressed in T cells and in natural killer cells. In the generation of mice that are missing this particular kinase, the only selective defect that we found was in T cell development and T cell function. So what this permits then, is that it identifies a target— If one were able to develop drugs that target this enzyme specifically, then one is able to develop potentially an immunosuppressive drug that only affects T cells. And to this day, we don't have that kind of selective armamentarium in terms of immunosuppressives.

Most of the immunosuppressives that we have, such as steroids, corticosteroids, or cytotoxic agents such as cyclophosphamide, azathioprine, basically target multiple cells. Even drugs such as cyclosporine, which was initially developed as an immunosuppressive, actually it suppresses its target, which happens to be expressed in all cells—many, many different cells—and that actually accounts for a lot of the toxicity that you see with tremors, seizures, liver or hepatotoxicity and things like that. So the identification of novel molecules that are cell specific may provide, actually, phenomenal targets for the drug industry to be able to target that.

The second thing, obviously, is if we can define genetic or molecular mechanisms for diseases, the most obvious one, obviously, is immunodeficiencies. First of all, one defines a new molecular basis for disease, and second of all, potentially opens the door for gene replacement therapy, because now we know what gene is actually missing in these particular individuals. So that's a second order of significance in terms of how our work would apply.

The third really is a more general issue which now relates to autoimmunity for which we know very little about and undoubtedly is not a single disease. But here what we want to begin to establish is our mechanisms by which autoimmunity may arise. So rather than— There are two ways by which one can approach this. One is to take patients with diseases and be able to work backwards to figure out what the defects are. The second is to basically understand how signaling mechanisms work and then utilize those systems and manipulate them to see if you can actually disturb the system enough to cause autoimmunity, and then given whatever disease one produces, go back then to the human diseases to find their parallel. We've sort of chosen

the second strategy because, number one, we're more interested in what basic science mechanisms are. And two, I think it's a much more manipulatable system.

Now, the first approach may actually have a place over the next ten to twenty years. It's been very difficult in the past unless you have a clearly genetically inherited disease with simple Mendelian genetics to really figure out what the ideologies are, because most autoimmune diseases, such as rheumatoid arthritis or [systemic] lupus [erythematosis], clearly—number one— is not a single disease but, two, it's a polygenic disease with variable penetrance with effects in the environment. Okay? Which makes simple genetics just very, very difficult to be able to figure out what's going on. So the increased knowledge that we've had over the last few years or even over the past decade will probably allow us to better address some of those problems.

Secondly, I think the opening of a new field that's been termed proteomics may also allow us now to look at the cells, or what the disturbances are within cells, to a much more sensitive degree. I mean, there may be a role for, again, looking at the cells directly and then making certain predictions and trying to figure out what the defects are. So the last part, the autoimmunity, is much less clear cut, but I think that's just because we don't know as much about this particular field as the first two ventures that I discussed, more of drug discovery and molecular defects of immunodeficiencies.

COHEN: Well, a couple of questions about the— First of all, I haven't heard the term proteomics before, so what is that?

CHAN: Proteomics is a field— You've heard of genomics. So genomics is basically identifying all the genes that are in the human genome and being able to determine the expression of these genes in various cells, whether it be disease states, etc. So for example, there have been several examples whereby you can take cells from patients with various types of lymphomas and determine, based on the types of genes that are expressed, what kind of diseases or what general type of phenotype they may have, as well as prognostic value. So the genes, obviously, are important and the genes, nonetheless, have to be transcribed and translated into proteins. After all, that is the business end of the cell, is the proteins. It's very difficult, for example, to detect subtle mutations within genes, because you're not going to be able to detect it by hybridization.

But proteins are different. So the idea with proteomics is that since we will eventually have, or may soon have, all the genes, we should be able to predict what all the proteins are, and then we should be able to take cells out from any source and be able to identify every protein that's within the cell by first running on these very large gels, which separate proteins by two dimensional gel electrophoresis based on isoelectric point as well as apparent migration by molecular masses. Then you should be able to sample each one of these spots and subject them to various enzymatic digests and then tap into the database, because that enzymatic digest can now be analyzed by mass spectrometry. And you should be able to tell and identify what each one of the proteins are based on their fragmentation pattern. So taken to an extreme, and

hopefully the technology will follow soon, we should be able to take, for example, a lupus patient, a T cell out of that lupus patient, and, ideally, be able to say these are the spectrum of proteins that are being expressed in this particular cell. Then we should be able to say, "Well, this is different from a normal individual," or even the same individual when the patient is in remission, in that these seven or seven hundred proteins are different.

So that's the essence of proteomics, is to be able to identify every protein that is present within the cell. The idea is that we can take these cells out from patients and be able to say at a protein level or following receptor activation which proteins that should have been modified are no longer modified. I mean, we're still quite a ways off from this kind of ability, but given the advances in technology and how fast they occur, I don't think that this is too much more into the future than probably no more than five years.

COHEN: Really? Wow.

CHAN: So that's the essence of proteomics.

COHEN: Okay. Thank you. And then going back to— You talked about gene replacement. Actually, that's been pretty dismal so far.

CHAN: That's correct.

COHEN: What do you see in the future? I mean, do you think we're really going to be able to do that anytime soon?

CHAN: I think eventually it will be done. The problems right now, from my understanding and not being an expert in the field, is really the delivery system and the vectors that are being used. And what the problem has been, for example, with adenovirus is just their immunogenicity. So I don't know whether adenovirus will turn out to be the best system, but with time the vectors will be changed one— You know, they keep going back and they basically delete another gene within the adenovirus vectors that turn to be immunogenic and then they use those new viruses.

And if there's another minor reaction, they go and figure out what that is and they go and delete it. So probably in a matter of time, they may be able to churn out a delivery system, for example, using adenoviruses or retroviruses that do not have the immunogenecity issues. That probably will come, but it's just taking— It's going very slowly. But with time, I think, it will potentially occur. It's just, obviously, not happening right now.

COHEN: Okay. Well, you mentioned the technology, you know, that you need to do the—Well, really everything you do. And for the most part, science is pretty technology dependent right now. Is there any downside to the technology that we have?

CHAN: Downside in terms of problems that it causes society or—?

COHEN: Or to you as a scientist.

CHAN: Well, for me personally, as a scientist, what it does do is basically you have to maintain a certain degree of technical competence over all the years of your career, because again, you cannot be using the same technologies five years from now in terms of approaching science as what we're doing right now. Good questions will still remain. Questions may well be very similar, but you may well be able to address some of the questions that you couldn't address five years ago due to technical limitations. So from that standpoint, it does— Technology clearly moves quickly and you have to keep up with it. So from a scientific standpoint, it's not a disadvantage, but it does put additional pressure on one to be able to maintain that edge.

COHEN: I've heard some of the scholars say that they actually lose their edge a little bit, that the postdocs often know more about how something works than they do. Has that happened to you?

CHAN: Well, that's true in that, you know, when you're developing a new technique, you rely on your postdocs and your students and your technical people to be up on every little nuance of that particular technique. That's what you have to do. There's no way that you, yourself, are going to be able to maintain that kind of competence for every technique. What you have to be able to understand, though, really are, what are the possibilities? What are the limitations? How can using this technique fool you in terms of interpretation of data? Because there is no perfect technique. I mean, every system has its limitations; every system has its caveats. Some systems have their strengths and weaknesses. You, obviously—for a biologically driven hypothesis, in terms of what we're interested in studying—have to utilize different systems to try to be able to come up with the hopefully correct answer. But you're right in that you can't keep up with every little tiny aspect of that particular technique. But if you're going to use that technique to any great degree, you have to really at least fully understand it.

COHEN: Well, that brings up another interesting thing that some of the people that I've talked to have mentioned, and that is that as a certain technology becomes mainstream, it comes out in a kit form, for example, and that nowadays many of the students don't really understand how something works because they just run it with the kit.

CHAN: That's true. That is clearly true.

COHEN: Do you see that as a problem?

CHAN: It is a problem and I think then it's the PI [principal investigator]'s responsibility to make sure that the student understands what they're doing, to understand the principles that underlie solution A plus solution B equals solution C, but I think that's the PI's— That's part of teaching. That is really understanding what the technique actually is. It's not just adding three different solutions together, but what happens when you add solution A to your bacteria. What is it actually that you're trying to accomplish? So I think you're right in that a lot of the students lose a lot of the technical understanding as well as theoretical principles which many of their experiments are designed around. But the good students will come around and understand what they're trying to do, and a good environment will guarantee that the students understand that.

COHEN: Well, you've mentioned a few times these crazy ideas that you experiment with sometimes, and it brings up the whole subject of "where do ideas come from," you know? Do you know where your ideas come from?

CHAN: The ideas come from everywhere. They come from talking to your colleagues, reading papers, and [finding that] your interpretation of the data is completely different than what the author's conclusions are. Or having just, out of the blue, read a certain series of observations or making notations of certain series of observations and then a certain spark is ignited when you read another paper and you go, "Oh, I can explain so and so's results twenty years ago by this other observation," even though they haven't quite utilized it this way or that's not their spin. Then you can generate hypotheses, which is unique, and these are the crazy ideas that you can then go out to test. So those come up with just increasing one's exposure to other people's science aside from just what you're used to. Most of the time they don't work. [mutual laughter]

COHEN: Do you think of yourself as creative?

CHAN: I don't think of myself as creative. What I try to impress upon my students and my postdocs is that you want to ask the best question, and if the question is worthwhile doing and if the technical support is there, then it's probably worthwhile doing the experiment. Most science is not very creative. Most science— The difference many times is whether somebody's really willing to commit eighteen months of their lives for a particular project. With the exception of a very, very few phenomenal ideas, most experiments take that long, if you really are willing to go the whole nine yards instead of just making a brief observation here or a brief observation

there, to really make the observation, understand the observation, be able to explain the biological significance of that observation. To be able to do that, in total, takes a lot of time and really takes the commitment of the individual. That's what I want to impress upon my laboratory, that that's the style of science we want to do. Some sciences may be more creative than other science, but that's a relative term. What's creative to one person can be very mundane to the next. But I think good science is really being able to push an observation all the way through, not just making a stab at one aspect of an observation.

COHEN: Now, what about this business of serendipity, because we've danced around this a few times already and, you know, we all know it happens. What do you think the role of fate or serendipity or whatever is in the sciences?

CHAN: I mean, science, I think, is basically a series of opportunities. As a scientist, you either take the opportunities and run with them or nothing happens. So you're basically dealt a hand, the way I look at it, and you can decide what you want to do with that hand. You're either going to fold or you're going to play it. So you're always given certain observations. You may do an experiment; you have certain observations. The question is first, do you recognize what the potential importance of those observations are? Second, are you willing to commit the efforts in understanding that particular observation. I think that, in part, is probably 90 percent of it; that's the sweat. And yeah, you're dealt a hand and you already have two aces and you're sitting in a pretty good boat. That's fate. Still, you have a pair of aces: You can either work with it or you can sit on it. The person that's only dealt a pair of twos can work on it and make it four twos and beat the pair of aces.

So a lot of it is being able to recognize opportunity, and that is not so easy. I mean, I think there the better read you are, the greater breadth you have, the better appreciation for science increases your ability to expand on those particular opportunities. You know, that comes with experience too. I hope, and I think this is true, that circa 2000 versus circa 1994, I have a much better appreciation of where the science should go. I have a better feel as to what things are going to work and what things aren't going to work, but still, that requires 90 percent effort.

COHEN: Have you ever had a situation where you something's gone wrong and something has come out of that error?

CHAN: Oh yeah, this happens a lot. In my brief career here— I mean, let's see. When we initially came into the laboratory, I began a yeast two-hybrid screen with one of the tyrosine kinases known as *syk.* What a yeast two-hybrid screen does is that it utilizes yeast to be able to determine proteins that interact, but the problem with the screen is also that there are a lot of false positives and people have been known to chase false positives for many, many years. We happened to pull out a molecule that's called *nck,* an adapter protein, and the poor postdoc that

worked on it worked on it for about eight months. And basically, we couldn't convince ourselves that in a normal cell that that interaction exists. So it doesn't mean that that's not true, but we just couldn't convince ourselves. And yet one of the other graduate students in the laboratory was working with this molecule, this linker protein called *SLP-76.* It was tyrosine phosphorylated following T cell receptor cross-linking. We were trying to identify molecules that would bind *nck.*

So here they are— They're these two totally different projects. This *nck* project just wasn't going anywhere, and I forget exactly what the circumstance was. Somehow, it was decided that what we should do was to see what would interact with *nck* in a cell, and we got this band at 76 kilodaltons. Okay. So basically the *syk* part was gone, and immediately the two projects converged, even though this first project was just absolutely going nowhere and we had all the reagents already for *nck,* because we had been hammering at this for eight months trying to figure out what the story was in terms of what are its interacting proteins. So that's one example. You know, we could have just said "Ah, *nck* project's dead. Let's start something else." But again, we're lucky to have done that one additional experiment and gone off our way that way.

Another one that actually led to the discovery of *BLNK* and our entire entry into the B cell field was that when *SLP- 76* was cloned, it was reported to be expressed in B cells. We had shown, at least in some artificial systems, that the *syk* kinase that is expressed in B cells could phosphorylate *SLP-76.* So I told the graduate student, Chong [Fu], at the time, "Well why don't you go and just investigate what the interaction is between *syk* and *SLP-76* in B cells." He came back three weeks later sort of sheepishly telling me, "Well, there is no *SLP-76* in B cells." So contrary to the initial report—and he had actually done an extensive amount of work analyzing many, many different B cell sources as well as many different types of antibodies—there was no *SLP-76* in B cells. Hence, that led us to going back to the drawing board by saying' "Okay, it's likely there's going to be a family of linker proteins just like in T cells." That began our search for these linker proteins that turned out to be *BLNK.*

So again, it was a bad hand. There is no *SLP-76* in B cells. So you can say, "Okay, let's give up the B cell business and let's continue working on our T cells." But usually, it's telling you something, and if you're willing to commit, because then Chong went off and basically spent a year of just purifying protein, you know, many times of which he probably thought, I know of which he thought, "Maybe it's time to give up," but he stuck through that entire project and then ended up making this major discovery. But that's the commitment part. That's the part that he wasn't even dealt a pair of deuces. He had one. [laughs]

COHEN: Well, you know— Was he a postdoc?

CHAN: He was a graduate student.

COHEN: He was a graduate student, yeah. Because one of the things that is of some concern is that if a graduate student ends up in a blind alley somewhere, then they don't have anything to write their thesis with.

CHAN: Yes and no. I think actually my philosophy is that graduate students, if they're technically capable, should actually take the higher-risk projects, because they'll get their thesis one way or the other. There are always backup projects to work on, whereas a postdoc has a very limited time frame. They have three to five years for which they have to justify their existence. They have to have publications so that they can get a job. Okay? So here, taking the highest-risk projects may not be the best thing for them. I mean, this is a question that doesn't have a right answer, but if the graduate student has the initiative, has the technical expertise, and has the attitude to attack that kind of problem, that's actually one of the best training environments you can give them. They're going to go out and try to get something to work and the great thing is that they don't know failure at that point. They have not experienced failure. So actually, it's more blinded, but then you have to depend to make sure you have a good PI to know when to stop and that's always a hard call.

COHEN: Okay. Well, the other thing we've sort of touched on a couple of times is this business of competition, which we all know exists in science, but the question is, is that good or bad?

CHAN: I think competition is good for a variety of reasons. One is you require a certain push to get certain things done. Okay, so the competition obviously does that. Everybody wants to be first. For most things, not for all, usually competition also results in a conclusion being substantiated by two different kinds of approaches. With the exception of cloning genes and making knockouts and reporting sequences—most other types of biological questions—the papers are just not the same. Your knockout papers pretty much are the same. You know, you knocked it out, this is the phenotype and the story, but in terms of addressing biological questions, usually the approaches and the experiments that you outline in the paper are very different. So you have two different ways of approaching a problem, and you come up with the same answer. That actually increases one's confidence of that particular result, and I think that is good. So I think on the whole that competition, despite causing many of us sleepless nights and ulcers, by and large is a good thing.

COHEN: Is there any downside to it?

CHAN: Well the downside obviously are the—

COHEN: Sleepless nights and ulcers.

CHAN:—sleepless nights and the ulcers. One can argue, for societal reasons, "Do we really need a thousand laboratories in the world working on the *ZAP-70?"* Maybe even not a thousand, but odds are people are going to come up with different kinds of aspects of looking at the same question and by taking different angles at it, not only will you get confirmatory data faster, but you probably will get different insights and different kinds of questions and different kinds of systems, some of which may take one to different systems. So aside from the personal grief, for society, actually, I think it's a worthwhile thing.

COHEN: Have you ever been scooped on anything?

CHAN: We've been partially scooped on some things. We have so far—knock on wood—lived actually a very blessed life. [laughs] I mean, for example, there are two clear-cut examples or three examples that I can think of. Okay? So I didn't know this, but when I was a graduate student, one of our competitors apparently had another student in his laboratory almost mirroring the studies that I did. He told me this, because subsequently he was department chairman of pediatrics here. We were fortunate that at each major manuscript that we had, we were in front by about four months for like three different stories, unbeknownst to me. So that was just blessed ignorance, I think.

In the case of the cloning of *ZAP-70,* retrospectively, many people told me subsequently they had the clone. They had the cDNA in the freezer. As it turned out, it was *ZAP-70;* they just didn't know what it was.

In the case of *BLNK*, the most recent stories, that's probably been the most competitive thing that we've been involved in, in that two other groups also cloned out *BLNK* within six months after we had done it. So we reported it and then within the next four months, two other groups reported it. In describing the knockout, there was another group that, actually, its paper came out about a week before ours. Then subsequently, over the next eight months, two other reports came out. So even though those were six or seven months later, the generation of the mice were not that much later than the generation of our mice.

I think what stands out though, in the long run—you know, you're obviously going to get scooped at some point—is probably the quality of the science that one does, so that if you put out a comprehensive, well-analyzed paper, people will recognize that.

COHEN: Even if you're not first.

CHAN: Even if you're not first. I mean, just so for example, this is— Well, it depends how you look at it. For the *BLNK* knockout, there was another group, in Germany, which actually reported it one week prior to us. But in our report, we had back to back reports not only of the

mouse, but also of the human. So that story, entire story, is a more full and potentially more far-reaching story than just describing the mouse. In terms of the cloning of *BLNK*, you know, we had not only cloned it, but we had actually defined four different major molecules that it interacts with and provided mechanisms of how those interactions may regulate B cell receptor activation. In contrast, one of our competitors basically just reported the cloning and one interacting partner, which was previously known, of the molecule.

So over time you have to establish a certain standard of science that you want your reputation to rest on, to the point where I have actually forbidden students to write papers, just because I don't think it's going to be a good paper. They think that they have a publishable product and I agree, we could probably get this published, but it's not the kind of work I want them to do. Not the kind of work— Not that I don't want them to do it, but not the kind of work that I want them to think that this is a completed product. That's important. I mean, the quality of science has to stand for something, and that's the commitment to really fleshing out the story, rather than just taking three observations and putting them together in a paper.

COHEN: Well, the flip side of competition is collaboration. Do you have any collaborators?

CHAN: We have a number of collaborators. You know, I'm a fairly open collaborator. I mean, first of all, if people want reagents, I just send them out. You know, many people are concerned about what it is that they will do. I say, "I don't care. It's published, you can have it." I don't even ask them what they're going to do with it. Because if I asked everybody as to what they're going to do with it, I would spend half my time on the telephone. Again, 90 percent of the experiments don't work, so you want something, you can have it. If you want to develop a collaboration to pursue a problem, I'll be happy to do it as long as, obviously, it doesn't conflict with already present collaborations that have been set up or projects that are already ongoing in the laboratory.

COHEN: Do you have any current ones going on?

CHAN: We do. We have two cocrystallographic collaborations with a group in England and a group here. We have an ongoing collaboration with one of the other independent investigators here, as well as a group in Toronto. We have collaborations with people in Seattle on *BLNK*, you know. I've sent my mice and reagents elsewhere, to Dallas, to everywhere else, to Northwestern [University], etc.

COHEN: All right. Well, when you look at your life as a scientist so far, how do you think you're doing in terms of meeting your own professional goals for yourself?

CHAN: The way I see it is that we are doing okay. All right? I think we can do a lot better. If I could turn back time, of course there are certain projects I probably would have pushed on more and certain projects I would have abandoned earlier, but I think, as always, we have to more creative. We have to obtain greater breadth, because everybody's doing the same thing, very similar things, and it's the creativity, in the end, that's going to make one stand out or be able to accomplish a higher quality of work than other laboratories. So I don't think that we— I still think there's a lot that we need to strive for, but I've been criticized by people saying that, "You're never happy with what you have." [mutual laughter]

COHEN: Well, that's probably part of being a scientist, is—

CHAN: Well, I appreciate what I have. Okay? I absolutely appreciate what I have. You know, you think about— I have lots of discussions with a number of friends of mine, you know, and in many, many ways we are extremely fortunate. Whereas other individuals around the world are concerned about exactly where they're going to get their next meal or trying to deal with just the bare sustenance issues, we have the luxury here to actually think creatively, to do what we really like to do. And they even pay us. So you know, from that standpoint, I truly appreciate what it is that I have, but again you have to, I think, always strive for more. I don't think one can be complacent about what one has, because this is a competitive field and the science moves.

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COHEN: Well, let's ask the same question, only now instead of how are you doing professionally, how are you doing personally with your life?

CHAN: Personally with my life. I mean, again, I feel very blessed from that standpoint also in that I have a great family. I have a supportive family. I have healthy kids [Michael A. Chan and Jennifer C. Chan]. I have a healthy wife [Mary F. Chan]. And I only need to go on the attending service to realize what I have. Sometimes not even that. All I need to do is go downstairs to the cafeteria and eat lunch and see what I have. So from that standpoint, I likewise appreciate what I have. You know, having a wonderful family, obviously, still takes a lot of work. Raising kids takes a lot of work, but there I don't think— There, just like the science, we always strive for more. There's no obvious deficiencies necessarily that I can point to. Yes, I would like to spend more time there; yes, I would like to spend more time here, but again, one has to be somewhat compromising to be able to hit some balance that one is happy with. So from that standpoint, I'm pretty happy on that level also.

I mean, the challenge in life, I think, is that you never know what you're going to do. Five years from now, I don't— I would say yes, I would like to continue doing what I'm doing now, but at the same time it's possible there are opportunities that may arise for me to take other

career avenues or other areas of investigation. So that's what I find exciting about it. Challenging, as well as somewhat sometimes unpredictable and unsettling. But that, I think, is the excitement of life.

COHEN: Well actually, you preempted my next question which is, what do you see yourself doing in five years?

CHAN: I foresee myself doing similar things, but the thing is you just—

COHEN: Right. You never know.

CHAN: —never know because the scientific world changes.

COHEN: Sure

CHAN: The medical world changes. Science is going to be in a different position probably five or ten years down the road than it is now. The possibilities, in terms of drug discovery, in terms of research being done by consortiums, may well change the entire outlook of what research is going to be like. I mean, you're already seeing, if you go and take a look at journals, that many of the major discoveries are no longer made in academic laboratories. They're made in the private sector. That's in part because the private sector has realized that they need to have very, extremely active research programs to be able to obtain certain advantages in the marketing phase. Maybe—it's hard to predict—twenty years down the road, that's where most of the research will be.

COHEN: So you might be with a biotech[nology] firm.

CHAN: It's possible. There's clearly certain things that the biotechs do not do that I enjoy. One of the major ones is teaching, but then that, likewise, may change. A lot of the universities are working with biotech firms and pharmaceutical companies to increase exposure. So maybe those opportunities may not be so limited in the future in terms of research. One of the things that the Pew [Scholars Program in the Biomedical Sciences] has opened—you know, my discussions of and my thoughts also—is public policy.

At some point I've been told by others that I will want to build something and, yes, I've thought about it. So does that mean that at some point I will want to take a directorship of an institute or division chief or department chairman? Those are all possibilities. Those are not

necessarily things that sound extremely attractive to me, at least as of today, given all the other headaches that one has to deal with, but the world may change. I think one of the things I realize is that, for me, I also have to change with it. So it's hard to predict. I enjoy what I'm doing right now.

COHEN: Okay. Could you ever see yourself practicing medicine?

CHAN: That's possible. I don't think it's very likely, because again, I really enjoy— I do enjoy taking care of patients, but one gets extremely spoiled at academic centers, such that one has the latest and greatest whatever. One has a phenomenal circle of colleagues. One is able to think in certain areas or in certain directions and be able to instigate discussions or even potentially instigate certain studies. And those are all possible. I mean, in the present day environment for practice, I think it's not what I initially trained myself as a physician to do, even outside of the research issues. There are a lot of administrative and payer-related issues. The primary responsibility isn't necessarily just to take care of the patient, and those aspects of medicine I actually don't like. So going into that kind of environment, I wouldn't want to do it.

COHEN: So what do you like most about being a scientist?

CHAN: The thing I like most being, at least in the present job that I have, is that I really can think very freely as to what kind of science needs to be done. I have control of that, especially at an academic institution as compared to the private sector. I have the opportunity to teach. My schedule is totally flexible in that I can decide when I want to meet people, when I want to do this experiment, but within certain boundaries. And I like doing and thinking about the kind of science that we do.

So from that standpoint, this is almost like hobby. I mean, this is basically what one does as a hobby. You do something because you like it and this is sort of how this started. When I began research, it wasn't the thing that I had to do. This was something, an elective. This was something that I became interested in, and hobbies are things that you're interested in, versus a job which may not be necessarily something that you're interested in, but happens to be what you're trained in. So from that standpoint, this is a job, but yet it's sort of a hobby. And like I said, they pay you for it. There aren't too many hobbies that I know that they pay you for. So those are the various facets of science that I like. I like interacting with people. You know, I have great colleagues here, and you develop a certain circle of colleagues. Part of the reason— I've entertained briefly, at times, potentially moving to another institution. You know, a number of institutions would ask you, and I said I'll come out and look, and basically, "Sure, I'll do it, but you're going to have to move these eighteen people from Wash U. [Washington University] also." [Cohen laughs] You know, it's the environment. The environment makes up a lot of what you like to do. If those people weren't here, Wash U. would still be here, but it wouldn't be the same.

COHEN: What do you like the least?

CHAN: What do I like the least? I like the least the experiments that don't work. [mutual laughter] The thing I like the least, I would say, but it is just the reality, is the time that it takes to know that an experiment or hypothesis is wrong. Okay? I think of a hypothesis. I know that there are eight experiments that need to be done. The thing that I don't like about it, it's going to take me six months to finish those eight experiments. So that's clearly one aspect I don't like.

The other aspect that— It's not that I don't like, it's not one of my favorite aspects, is dealing with personnel problems. I like to deal with people that, obviously, are very much into what they're doing, who have good hands, and can get over the technical aspects fairly quickly. So instead of six months, it should take six weeks. So those are the aspects I don't like. I don't like having to call somebody in and say, "It's obvious that you're not happy in this laboratory" or "What is the source of irritation of why you're fighting with so and so now?" Those are not aspects that I aspire to be. If I was, I could either be a psychiatrist or a psychoanalyst or a personnel manager. So those are the two major things that are not the most attractive to me.

COHEN: If you couldn't be a scientist—You know, tomorrow morning you woke up and God said, "Andy, it's over. You can't be a scientist anymore," what might you do?

CHAN: Assuming that I would excel in whatever else that I could choose?

COHEN: Sure.

CHAN: I mean, actually, I could see myself doing lots of different things. If I could excel— I mean, part of the fun part of what one does is, obviously, excelling in it. If I knew I could be Michael Jordan, I would be Michael Jordan. But I think that's the major part for me. I don't want to be in a field in which I don't excel. Okay, that to me is the downside. I don't want to be a mediocre scientist. I don't want to be a mediocre basketball player, even though they may pay me two million dollars a year. But, you know, there are a number of things in life for which I would, if I excelled in, love to do. Sports, law, public policy, business. I could easily do any one of those things as long as I excelled in them. I think, with the exception of sports, which requires certain physical attributes, the amount of time that I have spent or most scientists have spent in developing their careers in science, they could be equally successful in almost any one of those other fields.

COHEN: Sure, sure. Well, I've actually come to the end of the questions that I have and so I'd

like to offer you the opportunity at this point to add anything or clarify anything or expand on anything that you might like to have on the record.

CHAN: Well, I just want to make the statement that science, actually, is a phenomenal field. Okay? One can take many different avenues, and it's really just the curiosity as to why or what, and how. And within science, as a career, you know, whether one is a physician-scientist or a scientist, that in itself is a microcosm with thousands of different opportunities of either teaching, of mentorship, of research, of clinical applicability, of public policy, of trying to develop the next generation or increase public awareness or public interest in science, all of which have to be done. So the possibilities really are limitless.

For people that are beginning their careers, whether it be their training, what there's, you know, very little mechanism of, really, is to provide these individuals with the breadth of opportunities. Okay? And I think that's an issue of exposure, of who you happen to run into during your life, who you train with, who you're exposed to in terms of role models. And hence, I've been fortunate enough to have outstanding role models that clearly have led me to where I am now. Obviously, what I hope to do is be able to return back some of that, now as well as in the future, serving as a role model for other individuals.

Now, in fact, while I serve as a mentor to my students, my students and trainees actually also serve as mentors to me, because what they have enriched my life with, for example, is that my life experiences are few in terms of, you know, this is the path that I have taken. Yet, what I appreciate from my trainees is that, well, there's actually a thousand other paths to get to where I am and a thousand other paths by which our paths may cross and their ultimate destination occurs. So I think that's one of the fascinating things about being a scientist, is that just by the brief interactions with the graduate students, even though they spend anywhere from three to five years in your laboratory, or other trainees, you gain their life experiences. From that standpoint, it's also a wonderful career.

COHEN: Anything else?

CHAN: I think that's about it.

COHEN: That's it. Okay. Thank you.

CHAN: Well, thank you.

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[END OF INTERVIEW]

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