SCIENCE HISTORY INSTITUTE

VISHVA M. DIXIT

Transcript of an Interview
Conducted by

David J. Caruso and Sarah Schneider

via Zoom

on

28 February and 18 April 2022

(With Subsequent Corrections and Additions)

Vishva M. Dixit

SCIENCE HISTORY INSTITUTE
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VISHVA M. DIXIT

1956 Born in Kisii, Kenya, on 24 March

Education

1980 MD, University of Nairobi

Professional Experience

Washington University School of Medicine
1981-1986 Resident, Department of Laboratory Medicine, Barnes Hospital
1982-1986 Postdoctoral Fellow, Department of Biological Chemistry

University of Michigan Medical School
1986-1991 Assistant Professor, Department of Pathology
1991-1995 Associate Professor, Department of Pathology
1995-1997 Professor, Department of Pathology

Genentech
1997-2000 Director, Molecular Oncology
2000-2003 Senior Director, Molecular Oncology
2003-2005 Vice President, Molecular Oncology
2003-present Research Review Committee Member
2005-present Vice President, Early Discovery Research
2006-present Board of Directors
2006-present Director, Postdoctoral Program

University of California, San Francisco
1999-2008 Professor, Department of Pharmaceutical Chemistry

Honors

1980 Kamala Memorial Award for Best Overall Medical Student
1983 Josiah Macy Postdoctoral Fellowship Award
1996 Warner-Lambert/Parke Davis Award in Experimental Pathology
1996 Member, American Society for Clinical Investigation
1996 Hans Bloemendel Lecture, Netherlands

1999	Menten Lectureship, University of Pittsburgh
2003	Kenneth Sell Memorial Lecture, Emory University
2007	Daljit S. and Elaine Sarkaria Lecture, University of California, Los Angeles
2008	Doherty Lecture, St. Jude Hospital
2009	Karl Landsteiner Lecture, Vienna, Austria
2011	Member, American Academy of Arts and Sciences
2012	Member, Association of American Physicians
2012	Foreign Member, European Molecular Biology Organization
2012	Member, National Academy of Medicine
2013	Member, National Academy of Science
2016	The Gutenberg Research Award, Johannes Gutenberg University of Mainz
2016	G.H.A. Clowes Memorial Award for Outstanding Basic Cancer Research, American Association for Cancer Research
2016	Dawson Prize in Genetics, Trinity College
2017	Harvey Lecturer, The Harvey Society, Rockefeller University
2017	Fellow, American Association for Cancer Research Academy
2018	Jurg Tschopp Prize
2020	Fellow, American Association for the Advancement of Science
2021	Foreign Member, The Royal Netherlands Academy of Arts and Sciences
2021	Foreign Member, The Royal Society
2022	Vilcek Prize in Biomedical Science
2022	William B. Coley Award for Distinguished Research in Basic and Tumor Immunology
2022	Dr A.H. Heineken Prize for Medicine

ABSTRACT

Vishva M. Dixit was born in Kisii, Kenya in 1956. His parents, who were originally from India, served as physicians in Kenya with the British Army, and they stayed in the country after their service. Dixit experienced segregation as a child growing up in Kericho, Kenya. After Kenya's independence in 1963, schools were desegregated, and Dixit began attending a European school. Dixit visited his parents' medical clinic as a child and saw how they treated their patients, including patients from tribal communities. While his parents worked, his family's household helper, Francis Omondi, took care of him. As a child, Dixit enjoyed reading about science and exploration and wanted to be an explorer. When he was a teenager, his family moved to Nairobi, where he attended high school. After high school, Dixit attended medical school at the University of Nairobi. He had an interest in public health and traveled to villages as part of his medical training. While working in a tropical medicine unit, he likely saw patients with HIV before there was knowledge of the virus. Encouraged by his brother, Dixit decided to continue his education and conduct research in the US.

Dixit began his residency at Washington University in St. Louis in 1981. He was amazed by the conditions at Barnes Hospital in St. Louis, which were starkly different from the conditions of and resources available at Kenyatta National Hospital in Nairobi. At WashU, Dixit conducted research on platelet adhesion under the direction of Bill Frazier. Frazier worked closely with Dixit to teach him research techniques, and Dixit attributes his time in Frazier's lab to learning how to think critically about science. In his last year at WashU, Dixit worked on his clinical subspecialty, hemostasis/thrombosis.

Dixit applied to academic positions in pathology departments, and he accepted a position at the University of Michigan in Ann Arbor, Michigan. His initial grants were funded, allowing him to focus on his laboratory research on thrombospondin. Eventually, Dixit took the risk of switching his research focus to cell death in the hopes of asking bigger questions and making more of an impact. With his student Muneesh Tewari, Dixit looked for inhibitors of cell death. They discovered a death protease that they named Yama, and which later became known as caspase-3. Then research in the Dixit lab found a signaling entity that they called FADD (Fas-associated death domain). Arul Chinnaiyan and Marta Muzio in the Dixit lab found an initiating molecular scissors that they called FLICE, which is now known as caspase-8. Dixit describes the "joy of discovery" he felt during this time and the great deal of interest that his work received. Dixit's lab continued to identify additional death receptors, cloned death receptors, discovered an adapter molecule, MYD88, and discovered a new IRAK in IL-1 receptor signaling. Dixit discusses how he balanced his home and work life while in Michigan, splitting his time between taking his children to activities and managing his lab.

After a headhunter contacted him, Dixit visited Genentech in California and was impressed by the company's leadership. He decided to accept the opportunity to direct molecular oncology, have a research lab, and play a role in drug development. Under Dixit's leadership at Genentech, new cancer therapies such as anti–vascular endothelial growth factor (anti-VEGF), anti-HER2, and anti-CD20 were approved. Partnerships with other companies also resulted in a BCL-2 small molecule inhibitor and a kinase inhibitor. Dixit's lab conducted research on the

NF-kappaB signal transduction pathway and T-cell receptor and B-cell receptors and discovered paracaspase, or MALT1. His lab has also worked on RIP kinases, necroptosis, ubiquitin modification, and the inflammasome.

Dixit discusses growth and competition in the antibody therapeutics field, recognition that he has received for his work, minorities in science, and research collaborations, including international collaborations. He also talks about COVID-19 and vaccine development, as well as the importance of educating the public about science. Dixit was an external advisor for the Department of Biotechnology in India and has presented lectures during visits to India and Kenya. He advocates for research on diseases that impact developing countries and for the support of researchers in developing countries. Dixit discusses his philanthropic work, his legacy as a mentor, and the importance of giving back to society.

INTERVIEWERS

David J. Caruso earned a BA in the history of science, medicine, and technology from Johns Hopkins University in 2001 and a PhD in science and technology studies from Cornell University in 2008. Caruso is the director of the Center for Oral History at the Science History Institute, a former president of Oral History in the Mid-Atlantic Region (2012-2019), and served as co-editor for the *Oral History Review* from 2018-2023. In addition to overseeing all oral history research at the Science History Institute, he also holds several, in-depth oral history training workshops each year, consults on various oral history projects, and is adjunct faculty at the University of Pennsylvania, teaching courses on the history of military medicine and technology and on oral history.

Sarah Schneider is a Program Associate in the Center for Oral History at the Science History Institute. Sarah graduated with a BA in American Studies from Brandeis University in 2013 and an MA in History (Public History track) from the University of Central Florida in 2018. Her MA thesis and digital project highlighted the migrations of a group of Jewish German and Austrian children who fled the Holocaust via children's homes in France. She brings an interest in studying migration to her work with oral histories of immigrant scientists at the Science History Institute.

ABOUT THIS TRANSCRIPT

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TABLE OF CONTENTS

INTERVIEWEE: **Vishva M. Dixit**

INTERVIEWERS: **David J. Caruso**
Sarah Schneider

LOCATION: **via Zoom**

DATE: **28 February 2022**

CARUSO: So today is February 28, 2022. I'm David [J.] Caruso here with Sarah Schneider. We're interviewing Dr. Vishva Dixit as part of our oral history project. We're conducting this via Zoom. Thank you again for agreeing to meet with us today. And, as I mentioned, I'd like to start with some of your earliest memories. I know that you were born in 1956 in . . . is it pronounced Kisii, [Kenya]?

DIXIT: Yeah, Kisii, Kenya.

CARUSO: Kisii, Kenya. So could you tell me a little bit about what it was like growing up there? If you could tell me about your parents, if you have siblings, that sort of information?

DIXIT: Oh, yeah, no, absolutely. I'm happy to do that. You know, I've had a very unusual trajectory in life, and maybe I'll start with my parents [Raj Kumar Dixit and Lila Dixit]. They're of Indian origin, but they came to Kenya, East Africa during the Second World War. They were both physicians that were drafted into the British Army, and they worked in the northern frontier, which is the portion of Kenya that is desert-like and abuts Ethiopia and Somalia. Very tough circumstances. But after the war, the camp disbanded, and they decided to stay on in Kenya. And they went to the highlands. And so I was born in Kisii and soon thereafter they moved to Kericho, [Kenya], which was the center of the pea-growing areas—very picturesque, emerald green, seven thousand feet above sea level, temperate weather. I don't remember a weather report because every day was perfect, right? You know, in Fahrenheit, between 70 and 80 [degrees]. No humidity, just like, just great weather. But the political times were turbulent and when I grew up, Kenya was a colony of the British Empire, so Kenya achieved independence in '63. And prior to that, there was a very strict segregation policy—an apartheid policy, essentially—so Blacks, Browns, and whites each had their own system. And you didn't intermix. You had your own schools, your own hospitals, your own communities, and you didn't cross the color line, so highly segregated. And I remember once that I . . . they had this . . . Boy Scouts had bob-a-job. Bob means a shilling for a job.

And there was a, sort of, a contest. It's how much money could the kids raise? So I thought what I would do is, the whites had the money, so I would go over to the [whites-only]

area and try to get a bob-a-job. And I remember I went over there and wasn't exactly met with a warm reception, and one of the families released their German Shepherd on me, and he came growling and snarling. And I wet my pants. And I was probably seven years old. And so it was a very unusual growing up, and so when I read about America and the days of segregation, it reminds me of that. You know, the irony is that I fell in love with German Shepherds—must be some reverse psychology over there—and I have had German Shepherds ever since, you know? But anyway, so it was a highly . . . it was an unusual time to grow up. And so that's a memory I have. I have a memory of walking with my dad and his telling me not to step onto the golf course, and I didn't understand why not step on the golf course. But that was whites-only. And then Kenya got independence, 1963. So you have to remember that Indians were a minority. The majority **<T: 05 min>** population was Black. Africans. And there were a few whites, right? And so now Kenya got independence and there was this rush to have justice, have social justice. I mean, the people of the country—the Africans—had been downtrodden. They'd been exploited. They'd suffered immensely.

My parents had [worked there] during the Mau Mau movement, which was the freedom movement, so they paid a big price for freedom. And understandably, they wanted the rewards of independence, the fruits of independence. And there was a very active program of Africanization. And so that gradually diminished the Indian population in East Africa, so maybe at its peak, it was two hundred and fifty thousand, three hundred thousand of a population at the time of independence, 1963, probably about seven million. So a small minority. But that pressure of Africanization in very short order by 1967, '68 meant a lot of people had left East Africa—a lot of Indian settlers. But a really signal moment was the arrival of Idi Amin in adjoining Uganda, and so he'd come into power and he'd thrown the Indian population out. I think he'd given them some ridiculous time frame, and they were basically all thrown out. But I think for the . . . that shook the community in Eastern Africa, the Indians who'd been there, you know, you have to remember we were relatively recent immigrants, but they'd come at the turn of the last century—most of them—to put down the railways. You've probably heard of the [lions, man-eaters] of Tsavo, [Kenya], and all of those stories that have gone on about East African railways and that saga.

And so they'd come a long time ago, and they were there for generations, but that . . . in that instant of Idi Amin, one knew that was inherent instability. And I think that propelled the younger generation to think about opportunities outside of East Africa. So that, in a sense, is a backdrop. But, you know, after independence, there was desegregation, obviously. So there was not only the Africanization, but there was desegregation. And now we could go to the European schools. So my parents were very anxious to send me to a European school, which was the local European school. And that was quite interesting, because I realized that . . . . I realized two things, that prejudice is actually taught quite early on in children—probably a reflection of their parents' feelings—and so there was initially enormous prejudice against coloreds and Blacks coming to a whites-only school. I mean, you can imagine being spat on, etc. But children are children, and I think with time, a lot of that evaporated, and playtime happens, sports happened. And I think there was a realization through that integration, we're pretty much all the same. But anyway, it was a . . . . I would say it was traumatic for . . . to go to a situation like that where you're clearly singled out because of the color of your skin or your religion.

CARUSO: You mentioned that the population of those who originated from India decreased soon after independence. Do you know the reason why your parents decided to stay?

DIXIT: Yeah, well, you know, they were professionals, so they were both doctors. They had a private practice. And they **<T: 10 min>** loved where they . . . the community. They had enormous respect in the community. They loved it, and I don't think the thought ever crossed their mind that they would leave. They wanted us to think about a future elsewhere, but for them, they were really quite entrenched in the community, and they served that community for decades. They've had a very strong bond with the community. And I'll get to this later, but I just want to mention this as—to give you an indication of the strength that the community had, and I'm talking about largely the African community—the Black African community—were very, very grateful to my parents for the service they had given over the decades. And so when my father, in his later years, was quite ill—he was dying of pancreatic cancer—he was admitted to the most expensive hospital in Nairobi, [Kenya], the capital city, and he sadly lingered on for a few months. And it's a private hospital, so bill is quite . . . builds up when you're there for a few months. There's nothing like health insurance. My brother [Rajiv Dixit] and I were in the US at that time, and we could . . . we went, when he finally passed away, to settle the hospital debts.

You know, we were prepared for quite a hit, but we thought we could take care of it. And the person at the desk said, he said, "It's been taken care of." We said, "No, no, we're here to pay for our father's hospital stay. He stayed with you five, six months. We need to clear the debt because we are going back to America." He said, "No, it's been taken care of." I said, "What do you mean it's been taken care of?" He said, "The community." Now you have to remember, this community is dirt poor. They raised the money, and they took care of it. So there was that, sort of, I would say, love between them and the community, and yeah, they never thought [about leaving]. And I think at the ground level, you have to separate political afflictions, policies like Africanization, or integration, or whatever they are, from the day-to-day lives of people. I mean, my parents were doctors, they served the community. They charged people who could afford it; they gave free service to people who couldn't afford it. So there was this very strong bond there.

CARUSO: Did your parents ever become Kenyan citizens?

DIXIT: Yes, yes. They were Kenyan citizens. Yeah, they were . . . well, it's a complicated story because soon after Britain got—I mean, Kenya got independence—the Indians had a choice of either becoming British citizens or remaining as Kenyan citizens. And a lot of the Indians—Kenyan Indians—who left had taken British citizenship. And as a result, they ended up in the UK [United Kingdom]. So if you go to London, [England], or some of the big British cities, you'll see a fair number of Asians, of Indians, not necessarily from India or Pakistan, but actually from Africa, from East Africa.

CARUSO: And so when you were [coughs] . . . excuse me. What citizenship did you have growing up? Was it just Kenyan citizenship, or was there also citizenship from India?

DIXIT: I was never an Indian citizen. There was a time I was briefly a British citizen, and then I think that was probably at the time of independence and then soon thereafter became a Kenyan citizen. So I've been a Kenyan, was a Kenyan citizen, and in fact, I tried to get back my Kenyan citizenship because now they've recently allowed dual citizenship, US/Kenyan. But that's . . . . I'm still in the throes of trying to get that work done.

CARUSO: Thank you so much for that early description. You mentioned you have a brother. Older or younger?

DIXIT: I **<T: 15 min>** have an older brother. He's, I think, seven years older than I am. He's a major influence in my life. I've tried to follow in his footsteps.

CARUSO: Okay. Can you tell me a little bit more about what your general home life was like when you were younger? I mean, I find it interesting your parents grew up in one country, moved to another, decided to stay there. What was the . . . what were some of the discussions that were happening at home over the dinner table? Were you talking about British rule and independence? Were they talking about what life was like growing up in India? What sort of conversations were your family having?

DIXIT: You know, it was a very unusual childhood because my parents would do their private practice or the practice, and that would probably be from 9:00 in the morning till 5:00 in the afternoon. And then they would have a quick bite to eat, often at the clinic itself, and then go on home visits so they would then travel and visit sick people in their homes, and they may not come back till late evening. So I had somebody who took care of me, a helper—a household helper. His name was Francis [Omondi]. And so a lot of my early childhood was spent with Francis. He was an African, and he took care of me, took care of all my needs. He thoroughly spoiled me. I mean, he did everything for me. And so I don't think I learned how to tie my shoelaces till I was ten years old because he insisted on doing that and he would just pamper me. And so a lot of my time was spent with Francis. But when we . . . when my parents were there and we did talk, I think a lot of their worries were centered around our education. You know, what were we going to do? What was the path we were going to take? And there was a concern, as you can imagine, in the neighboring country in Uganda, Idi Amin had come in, he had taken over everyone's property, thrown them out, and there was a, sort of, a foreboding always in the background that that possibly could happen in Kenya.

And there was a sense that one should be prepared for the worst. So a lot of the conversation was thinking about, preparing for the worst, but a lot of it was very lighthearted, too. My father would often come back—my father in particular—and regale me about stories that he had about his patients, about his travels. You know, just funny encounters he'd had, how people . . . he would . . . . And now, in hindsight, I think he was a very clever country physician, but at that time, and for a long time later in life, I couldn't believe what he said. So amongst the local population, witchcraft is very important. I mean, you can't deny it's important, right? So he would have patients who would say, you know, "Doctor, I have been cursed. The witch doctor has put a curse on me. I can't eat, drink. I'm losing weight." And my dad would say, yeah. But you have to see . . . you can't look at this from a Western perspective. You have to look at it from their perspective.

They were seriously afflicted because they were convinced this was a curse, and my dad would say, "Look, I'm going to take care of it. I've got this new medicine from Switzerland. I have to tell you, it's going to be very, very painful, but to get the most out of you, you're going to have to accept that pain." And there was a vitamin B12 injection. It's very painful. So he would give them a B12 injection in each buttock. And that was exceedingly painful, **<T: 20 min>** and they wouldn't be able to sit for a few days. But that would remind them that they had gotten a very strong medicine and that had driven the curse out of their body. And I thought when I was in medical school, "Boy, that was unethical." But now I think, "Boy, that was exactly the treatment that they needed because so much of health issues are psychosomatic." And if you're convinced that you've been cursed, then he came up with a solution that you don't find in the medical textbooks, but played on the psychology of the person, the community. So there were stories like that he would always regale me about.

CARUSO: Did either of your parents ever . . . did you ever visit them at the clinic and witness what they were doing firsthand? Or did they ever take you on house calls? Maybe there was an emergency over the weekend or something like that?

DIXIT: Oh yeah. I was very . . . I would spend a fair amount of time in the clinic. I remember this is a very crowded clinic, so they would probably see maybe, I would say, sixty patients a day—very crowded. You had people come in from everywhere. So this is . . . now remember, this is the sixties. They would often walk long distances. This was the Kalenjin who are now well-known as the long-distance runners from Kenya who win all the medals—so that was the Kalenjin tribe—and the Maasai. And they would sit outside the clinic and wait for hours. The Maasai would be in the traditional dress, blanket. And they would have these gourds of curdled milk and blood so they're famous for that. That's what they would have. Tribal markings. I mean, yeah, it was . . . as a child, it was a fascinating world, right? I mean, they would . . . . I remember my . . . the Maasai were very . . . you know, it's hard to relate these stories without some degree of . . . it's just hard to believe them, but yeah, they would . . . when my mom would stitch them up because they had a machete fight or something, they didn't want a painkiller because they said men don't take a painkiller.

And I was like, dang. So, yeah, it was another world. Yeah, another world—just so very crowded—and that they . . . my parents had to see them very quickly. The diagnoses had to be done, you know, basically based on a physical exam. And so, yeah, it was . . . but I think back on it, it was tough going, but it seemed natural then, and I would go on the house visits. Yeah, I mean, I'd be very pampered on the house visits. But I remember my . . . there was a missionary hospital, and it was run by the Americans, Tenwek Mission Hospital. It's actually now quite a prominent mission hospital there, Tenwek Mission Hospital. And on occasion, the American doctor would go on vacation, and my father would have to go there. He would, sort of, do a locum there, and he would take me there, and I was enthralled by going to the mission hospital, going into the doctor's house and having a bit of Americana in that house. Yeah, so it was a very unusual time.

CARUSO: And so when you weren't visiting your parents at the clinic and you were maybe around your home more, again as a young child, what were you doing? Were you headed out playing with friends? Was <**T: 25 min**>. . . did you say that the Kenyan who was watching over you—Francis?

DIXIT: Francis, yeah.

CARUSO: Was Francis taking you around the city and showing you different things? Were you sitting in the house and just reading book after book? Were you outside playing football? What were you . . . what were some of your interests, your hobbies, your daily activities as a kid?

DIXIT: Well, yeah, you know, Francis would take me around. And again, as a kid, I was a spoiled brat, so I refused to walk, so he'd have to piggyback me everywhere to my friend's place, to the playground, piggybacked me back home. And so quite spoiled. But what started happening was that I started struggling with my eyesight. I didn't know it at that time, but things became fuzzy, and so I wasn't that attracted by sports anymore or playing with friends. I was more attracted by reading books. Later in life when I was a teenager, we found out I had keratoconus, which is coning of the cornea, the details don't matter, but it required . . . I had to have corneal graft, corneal transplant to get my vision back. But I think that I gravitated towards reading books at that time. And yeah, and the house was just filled with books. I mean, magazines, books. *Time-Life*. *Life* magazine. I don't know if you guys remember that, it was just terrific, but my parents got me this series, Time-Life series on science. *The Scientist* and things like that. I, sort of, flipped through it, and I loved it. I loved reading about it, and I loved . . . and I was always very fascinated as a child with exploration, [John Hanning] Speke discovering the origin of the Nile [River]. Howard Carter opening up Tutankhamun's tomb and peering into it. I just like, "Wow, that's a new world. I'd love to be an explorer. That's what I want to do in life is be an explorer."

But of course, it dawned on me that there weren't any new lands to explore, but science just seemed to be a replacement for that. I mean, it seemed to me, even as a child, that you could be an explorer, that you could discover new things. You could peek into the equivalent of a Tutankhamun's tomb and see treasures and also gain a measure of immortality because a lot of these people were remembered through history. And that attracted me. I was like, "Wow, this is really something that I'd like to do." But as a child—as I'm sure you know—when you say as a child, "I want to be a fireman." You really don't know what it's about. And I think there was some of that sheer naïveté that percolated in my mind that I wanted to be an explorer. I wanted to explore new worlds in science, but I didn't know what that meant. But that did impart in my imagination that there was a career available that allowed you to be an explorer, a discoverer of new worlds. So that attracted me.

CARUSO: One question for clarification. Given that this was . . . Kenya had been under colonial rule, I'm . . . . I was assuming that English was the dominant language that people shared. Did you grow up speaking English, or did you did you have multiple languages that you were speaking while growing up?

DIXIT: You know, multiple languages really. Grew up speaking English, Hindi, and Swahili. And there was a time, like especially when I was in medical school, when I had to become reasonably fluent in Swahili, where in a sentence I could comfortably interchange the three languages. You know, start up in English, say something in Hindi, and finish up in Swahili. But unfortunately, I just don't have a mind for languages, **<T: 30 min>** and English has become my dominant language. I mean, I still understand Hindi, but Swahili is, I'm afraid to say, long gone.

CARUSO: I was curious in part because since you mentioned the . . . Kenya becoming independent in '63 and this push towards Africanization, I didn't know if that extended into the languages that people were speaking or what was dominant in the country at the time. Because I'm assuming it was that English was forced on the population, but they probably retained in most instances speaking Swahili. But with the end of the rule—the colonial rule—I didn't know if there was a move to having things predominantly in Swahili instead, because I mean, you mentioned going to the—what was the white-only school at some point. I didn't know if they were teaching in English only or . . .

DIXIT: No, they retained English as the primary language. You have to remember that the key of colonial rule was divide and rule, so the tribes were divided, and prior to independence, tribal languages were given a lot of prominence because that would enforce tribal loyalty, and those languages were quite distinct. So when countries became independent like Kenya, Tanganyika, now Tanzania, Swahili had a resurgence because the expectation was that the African people, instead of being fluent just in their tribal language, would actually be fluent in Swahili, and that would be a language of unity. So Tanzania, for example, under [Julius K.] Nyerere, made Swahili the primary language. Kenya did not. It retained English, but that's where Swahili had a

resurgence. This may not be known to many people, but it was really after independence as a language to unify. Now, unfortunately, the stigma of, stigmata of tribalism has retained and continues to be a destabilizing influence in a lot of Africa. But part of that was tribalism was reinforced by the colonial powers like in Rwanda, the Tutsi and the Hutu. You know, you favor one side and not another. You develop separate languages, so you divide and rule.

CARUSO: Yeah. Now I know that your family did eventually move to Nairobi. How old were you when that happened?

DIXIT: Well, I moved to Nairobi . . . I was probably fourteen or so. I moved because my brother had joined medical school. We'd run out of options for reasonable schooling in Kericho. And so the decision was made that my mother would set up a, sort of, a satellite home in Nairobi, and she worked for some time at the Kenyatta National Hospital as a doctor, which is the big hospital there. And we lived in Nairobi, and my brother went to medical school. I went to high school there.

CARUSO: Okay. So there are two things that I want to ask about. Since you did mention the—going to the—what had been the white-only school when you were in Kenya, I am curious to know what the education consisted of in terms of the subject matters that you were studying. I don't think we need to get into the specific content, but I'm curious to know what was the focus of your education in those early years? And as an add-on question to that, were there certain subjects that you gravitated more towards or ones that you wanted to avoid more?

DIXIT: I think the schooling was along English lines, so it was a very British-oriented school. The history we learned was English history. It was . . . so, the goal of the schools was to prepare the students to go back to England—you know, that was the mother country—to go to university there. So the schooling was along those lines. The schooling was—when I think back—was outstanding. It was . . . I **<T: 35 min>** liked the sciences. I liked biology in particular. I liked the field trips. I remember that vividly. So I liked . . . and the teachers were just outstanding. Yes, I had a . . . . I think I had a primary school, which was a wonderful experience. Yeah.

CARUSO: Okay. And were you exposed to anything? I mean, obviously, there's a lot going on in Kenya. There's a lot going on in Uganda. Were you exposed to other, broader international politics or circumstances that were happening around that time? I know . . . . I mean, for the 1960s in the United States, the Civil Rights Movement is going on. As you start getting into the seventies, there's also, you know, the Space Race and Vietnam [War] and things like that. Were you aware of those other, broader international things happening while you were growing up, or was it really focused just on where you were living?

DIXIT: No, acutely aware of them. And my parents were very, very much liberally minded people. They exposed us to a lot, but you have to remember, we're talking about the late sixties, and a huge aspect on our mind, Kenya had achieved independence. There was South Africa, Mozambique, Angola, Rhodesia. These were all still oppressed people. And we were like, "Well, hold on. How can America and Britain . . . ?" I would ask my parents, "These beacons of freedom, equality. How can they be supporting these regimes?" You know, it was a naïve view, so. But that was really on our minds as what will it take to liberate the rest of Africa? It's ironical, even though we, at that time, were facing the brunt of our Africanization—the Indians—but I would say amongst the colored people—the Indians, the Africans—the concern was, colonialism has to go. Africa has to be independent, and the southern half of Africa is still not independent from the Portuguese, South Africa, and that was a big bone of contention for us. And in later years, I realized in medical school that South Africa was still not independent, and in fact, South Africa was supported by Margaret Thatcher and Ronald Reagan. I said, "Come on. We have a country—America—10, 12, maybe 13 percent of the population is African American, and they have no political power to help their brethren and we have their country supporting apartheid? How can that be?" You know, we didn't realize, being in Africa, that the African Americans were disenfranchised in a sense as a voting block and had very little political power in those days.

And so it was quite a shock where we aspired and were very respectful and admired the qualities of America, there was also a sense of why was America supporting these injustices? And why was the African American population so impotent at helping their brethren? So there was this influence, there was this sense, and it got to a point where you started exploring other options. What about socialism? What about **<T: 40 min>** communism? You know, so these were the debates I'd have. My father was fiercely anti-communist, fiercely anti-socialist. He was pro, pro, pro-capitalist. And we growing up were like, "Well, hold on. You're so pro-capitalist. But look what's happened to us in Africa. Why is that? Maybe we should look at another model." So these were the debates, these were the happenings and at university it has changed since. But at university there was a sense that we need more equality. And so we would call each other comrades. Comrade Dixit, Comrade David, Comrade Sarah, so there was that sense of there's got to be a different model. And I guess each generation goes through that, but you have to remember this time. And you have Woodstock [Woodstock Music and Art Fair] in America. The young people in America were seeking revolution. And there was a certain resonance then—maybe not with the administration, maybe not with [Richard M.] Nixon and LBJ [Lyndon B. Johnson], though in hindsight, LBJ did more for immigrants than any other president—but at that time there was a resonance with the hippies because they represented revolution. They represented freedom. They represented peace, right?

My father was very much for the Vietnam War. He felt communism had to be suppressed no matter what. And we were like, why? And the hippies and Muhammad Ali and these people were very resonant in our lives. Martin Luther King, [Jr.], very resonant. So I think that had a huge effect, and so we would wear . . . well, not hippie clothes, but we would wear bell-bottoms and colored shirts. We were influenced by that, so I think the part of America, of the West that influenced us in a positive way was that there was this groundswell of change that

was being led by the younger generation that were saying . . . it was the Civil Rights Movement that was . . . . And prior to LBJ, prior to 1965, the immigration policy was essentially whites-only in the US—essentially. And that changed. So it was a . . . when history is written, this decade—the sixties—will be inordinately important because it will be the rise of civil rights, the changing of America, the browning of America. It will be an inordinately important decade. And it was inordinately important for health care as well because there were new models of health care that we were exposed to. I remember my public health lecture when I was a medical student. I still remember it. I don't know if it's true. But the professor came in, and he said, "When the Chinese had their revolution and they needed to revamp health care, what was the single most important step that they took?" People were like, "I don't know. Build more hospitals? They did this, they did that." He said no.

The single most important step they did is they closed, shut down all the medical schools because for good health, you don't need doctors. The Chinese realized that for their population, for good health, you needed clean water and you needed vaccination. You needed public health. And that was the advent that was the rise of the grassroots doctor apprenticeship in China. So eventually medical schools were reinstituted etc., etc. But the initial, the system was jolted by saying the importance of public health. We can conquer **<T: 45 min>** a lot of disease where two very simple [interventions]—clean water, vaccination—essentially environmental sanitation. The irony of that is it's still true today. And he said, "Well, you know, the way the WHO, World Health Organization, measures the ability of a country to provide health care is to look at its infant mortality rate because that's a summation of prenatal, antenatal infant care, and that's a very vulnerable time in the life of humans." And he said to us, "The infant mortality rate in Havana, Cuba, is the same as New York City, [New York]. And do you know why that is? That's because of public health." And so these were very . . . so this revolution that was happening was happening on all fronts. Health. Social. You know, the country, it was much like in physics that there are quantum leaps, I think in societies there are quantum leaps as well, and the sixties and seventies were a quantum leap for societies worldwide. I think it was also the beginning of the end of the Soviet Union [United Socialist Soviet Republics, USSR].

CARUSO: So thank you for providing that broader international perspective that you were getting while growing up. Unless there are other things that you'd like to discuss about your time in Kericho, I was thinking that we could shift to the move to Nairobi.

DIXIT: Yeah.

CARUSO: So when you went to Nairobi, this was . . . you were entering high school. What . . . ?

DIXIT: High school, yes.

CARUSO: High school at the time. How is that transition for you? And did Francis come along for . . . ?

DIXIT: Francis did come along.

CARUSO: Okay. And so how was it transitioning into high school?

DIXIT: I was so spoiled. I am embarrassed to say these things. Yeah, so Francis came along, and I'm going to high school and medical school, and he was always with me. And I would come home, and he'd say, "Beta, son, what do you want to eat?" And I'd say, whatever, you know, and he'd make it with a lot of love. I was so overweight. [laughter] Yeah, but I was very spoiled. Yeah, no, he came with me. But you have to realize that . . . and this is the, sort of, destabilization that happens in societies here. You have a group of people which is quite wealthy—that would be my family—that could afford houses, cars, servants. And then you have the rest of the population that is rather poor. And I think that's a recipe in the end for instability. I think the cement of a stable society is a middle class. And what a lot of countries lack is a middle class. And I think part of that instability is this. So yes, I had a very privileged life, very privileged life. Gosh, I can't even begin to tell you half of it because you wouldn't believe it. And yeah, but he came with me and I went to high school. In high school, I was, sort of, I would say, a reasonable student. I wasn't really . . . didn't set the world on fire, but I did enough to be able to get into medical school, which is . . . so this is a British system. Remember in the British system, you go to medical school after high school, but the first two or three years of medical school would be like the equivalent of a college in the US because medical school is a six-year program, so it's two or three years of introductory courses and then the rest.

CARUSO: I think Sarah has a question.

SCHNEIDER: Yeah, and so going back to—you mentioned Francis and making food in the home for you, what kind of food would he make and how did that . . . . I'm curious about, sort of, the cultural traditions in the home if you had any Indian cultural traditions or food or if you were more influenced by, you know, what Francis chose to make or other influences. So I'm curious if you could share a little bit about that.

DIXIT: Yeah. I mean, it's a great question, Sarah, because **<T: 50 min>** it again underscores how unusual my childhood was. My parents and my mother in particular was a very observant Brahmin Hindu, so she was a strict vegetarian, and so the food at the house was vegetarian. And so Francis—bless his heart—learned how to become a vegetarian cook. He was an excellent cook, but he really became an Indian cook. So the food, the fare was traditionally North Indian

but vegetarian. And so in that sense, the family was quite traditional. I mean, you know, just very [conservative]. My mother wasn't religious, which is . . . . I mean, in the sense she never imposed her religiosity on us. There was nothing like you should be religious. She never said to us . . . or you should believe in God. She kept her religion to herself, but she was very observant.

SCHNEIDER: And was your father observant in any way?

DIXIT: He was a good boy at home, and he was a strict vegetarian. But when he went out, he would indulge in meat, much to my mother's chagrin. [laughter] Yeah.

SCHNEIDER: Yeah. And are there any other Indian cultural traditions or practices that you'd observe in the home?

DIXIT: Yeah. You know, I would say that even though we weren't religious, we would observe the holidays like Diwali, but really observed them more from having a good time—the celebration, the fireworks, the mithai, or sweet meats, as you know, desserts really from that [tradition]. And the sense I got—at least the interpretation my mother projected to me—was that Hinduism is quite liberal. There are no expectations—strict expectations—and that's more a philosophy of life and it's more about doing good. I don't know if that was her interpretation, but yeah, I think other than being vegetarian at home that she insisted on, it was . . . yeah, there wasn't any. . . yeah, we'd celebrate Diwali because the entire Indian community would celebrate Diwali. That was an important occasion for all of us—important in the sense that it was parties, good food, entertainment, and there was nothing not to like. I think the weddings in the community were often Indian weddings, so they would be very traditional Indian weddings. You may have been to some in the US, and they were very much along those lines.

So those were also a lot of fun because you got a lot to eat, but, you know, had a good time. Yeah. So still, I would say even after independence, and this is unfortunate because I think integration is a generational thing, the communities were still rather insular—rather insulated—from each other. So the Indians would have Indian weddings, Indian festivities, and a lot of the life revolved around Indian, Hindu events. So that was . . . yeah. So it's a bit schizophrenic, right? We're living in an African country. And we're living small immigrant community that's very insular, observant of traditions that are thousands of years old—Diwali and things like that. But then in a sense, a bit disconnected, like I didn't learn how to write Hindi. So the umbilical cord was being cut, the cords of societal contact were being frayed, right? I was much more comfortable with English. I would pick up a novel in Hindi and read it, for example, so that you could see that change happening at that time.

SCHNEIDER: Yeah. And there's one more thing I'm curious about in . . . on a similar line is when you made that transition from Kericho **<T: 55 min>** to Nairobi, was there . . . what were the Indian communities like in each of those places? And was it . . . did it feel like a different scale of community in Nairobi? I'm just curious what that was like.

DIXIT: Yeah. You know, I would say that the Indian community in Kericho was a very small community. When I was growing up, maybe fifty families, so really small, whereas Nairobi was much bigger. We're talking about hundreds of families. But they came from all parts of India, and I think one difference one noticed was that there was . . . we all got on rather well with each other—the communities—because in . . . there are often, unfortunately, sectarian divisions like Hindus versus Muslims, for example, that have existed in the Indian subcontinent for a long time and led to a lot of violence and tragedies. Whereas, we forgot all of that. We were friends across those lines, though I think it would be unusual for marriages to happen across those lines. But there was a great deal of friendship, and there was a great deal of intra-integration at a social level, not necessarily at a personal level of weddings and things like that within the Indian community. So the foods, yeah.

SCHNEIDER: Yeah, thank you. Very interesting.

CARUSO: So just to follow up with the move to Nairobi and your education there, I'm curious to know was . . . . I'm only familiar with American educational systems, and when I was going through school, you know, you had set classes each year: you're going to be taking English, you had a foreign language, you had history, you had science. The sciences were not just generalized science classes, but specific to an area: biology—I think we had biology—then chemistry then physics. And then in your senior year, you could take an advanced course. There were laboratory components to those science classes. Was high school education similar for you?

DIXIT: Yes. For the last two years, which you would call in the English system the A-levels, you're expected to do three subjects—specialize in them. And in fact, it can get quite specialist. You could do pure math, applied math, physics, so that's all you would do for two years of high school. Last two years of high school. You could do . . . . I did physics, chemistry, biology, which is probably as disparate as it gets because often people would do chemistry, pure math, applied math—something like that. So yeah, the last two years were very specialized, so you really, before you went to university, you had specialized considerably. Very different from the American system, which gives you a much broader education. In the English system, you very quickly get channeled into a discipline there, and then it's unfortunately very difficult to move out of. So I prefer the American system that gives you a broader perspective and that ability to move.

CARUSO: So you use the word "channeled" into a system. Do you have choice, a choice about what system you were getting channeled into?

DIXIT: Yeah, you had a choice. But in my situation, I would say there was a lot of parental pressure to do the subjects that would allow me to go into high school—sorry—allow me to go to medical school. [barking] That's my German Shepherd. I'm sorry. He meant to be quiet. I told him about the interview, but . . . and so there was a lot of parental pressure. I think part of that pressure came from the fear that we would one day have to flee. And if we had to flee, then being a doctor was better than being a lot of other things. So it was that sort of pressure.

CARUSO: And do you think your older brother felt the same pressure?

DIXIT: Oh, yes, <**T: 60 min**> they all did medicine. My older sister [Manjul Dixit], my older brother, they all did medicine.

CARUSO: You also, early in the interview, I think you mentioned that your older brother served an important role in your life. But did I . . . am I misremembering?

DIXIT: Yes. No, no, he was really, really critical in my life because my father was such a busy man. He didn't have really, really have much energy to devote to home life. He was a very loving father and would do what it took, but he wasn't a constant presence at home. I'd go weeks without seeing him. And so my brother, sort of, took his place and helped me formulate my career plans. I mean, he took me when I was young, when I was . . . . I didn't want to go to medical school. I really didn't. And I wanted to do something like physics maybe. And he took me to the hospital once—he was a medical student—and we went onto the pediatric, the children's ward, and he had me look at a kid, just talk to him in Swahili—lovely, lovely child, very lovely. Really beautiful kid, big brown eyes, lovely kid. And we played a bit. I remember that. And I thought that was nice. Then he said to me when we were alone, he said, "You know, he's not going to be around in another six months. He's got leukemia. He's done for."

And that just struck me. Wow. I should say, leukemia in the West is a curable disease these days—childhood leukemia—but at that time . . . . It was like, wow, serious. And that, sort of, I would say, sparked my interest in biology and like why couldn't we save him? He seemed so healthy. He was smiling and laughing and jovial. Why couldn't we do anything? So that . . . so I think it was events like that that he introduced me to. He took me to grand rounds when I was a high school student. So grand rounds is when a case is presented and the physicians discuss. It's like a detective story to say, you know, patient presented with this very unusual presentation. It could be this, it could be that, it could be so. But we did the following tests. We narrowed it down to this and then we did this test and we narrowed it down to that. And you're

like, “Wow, this is like a detective story. This is quite interesting.” So I think that really, really helped me, propelled my interest in medicine.

CARUSO: You mentioned that your brother was about seven years older. How much older was your sister?

DIXIT: She was another five years older. So, you know, I didn’t know my sister well at all because of the age disparity.

CARUSO: Okay. Yeah, I just wasn’t sure when you moved to Nairobi if there was another sibling. Well, I knew that your brother wasn’t there, but I wasn’t sure about your sister. And in terms of that move, I mean, you grew up in one place for a long period of time. You had friends there. Was it difficult for you socially moving to a new location, starting with . . . starting at a new school with people you hadn’t known before?

DIXIT: Oh, it was very difficult. You know, it was because I think young teenagers can be especially cruel, and they can be quite cliquey. And initially there was . . . it was difficult, but you form your own friends and your own group. And it was fine. But I think that’s true no matter where when you change schools in your early teenage years, there’s a sense of tribalism, cliqueyness, and you have to find your own group.

CARUSO: Is this the period of time that you had the corneal graft or the transplant <**T: 65 min**> to correct your vision?

DIXIT: Yes, this was the time when I went to the UK to have a corneal graft. Moorfields Eye Hospital. I would say it was probably my first year in medical school when I went. I, sort of, lingered through . . . with poor eyesight through high school and probably first year of medical school. My father took me to the UK, to London, Moorfields Eye Hospital, and I had a corneal graft.

CARUSO: So that was more in 1975-ish?

DIXIT: Yes.

CARUSO: Okay. Okay. So when you were going through high school, you had the idea that you wanted to go on to become a physician. Were there going to be multiple choices for where

you could go to receive that education, or was the system funneled to the degree where if you were going to be pursuing a medical degree, you had to go to one institution specifically?

DIXIT: Yeah, there was only one medical school in Kenya, so that was University of Nairobi. And so that was the only choice. One had to go to medical school there.

CARUSO: And was there any consideration of possibly going to a school outside of where you were living, going international for an undergraduate education or a medical education?

DIXIT: There was. There was, but it transpired that it would be easier to go to medical school being a Kenya citizen to go to medical school in Kenya, and my brother was already in that medical school. And so it just logistically seemed simpler.

CARUSO: And was there any sort of formal application process, or was it simply that you passed your exams and therefore you were admitted to the school?

DIXIT: No, I was very, very fortunate to get into medical school. I mean, very, very fortunate because they had a strict quota system. So they had . . . I think the class was about a hundred students—a hundred medical students—and they decided they were only going to admit, I think, four Indians. And I didn't make the cut. And then my father appealed the process and convinced them to make an exception and admit one more Indian. And that was me. Now how he did that, I don't know. But it happened. So that's what I mean with my father, he was there when I needed him, but he wasn't a constant presence. So I was very fortunate that I got into medical school.

CARUSO: Okay. And did you—were you still living at home when you were attending medical school? Or did you then move into some sort of dormitory or apartment or . . . ?

DIXIT: I still lived at home, and Francis still took care of me.

CARUSO: And what about your classmates? Were they also living at home, or were they living on campus or some sort of . . . ?

DIXIT: Most of them lived on campus. The vast majority lived on campus that come from different parts of Kenya. They lived in the halls of residence there. And, you know, that's . . . yeah, but I lived at home.

CARUSO: And just to . . . since I'm unfamiliar with this type of system, when you enter . . . so you were entering medical school proper? It wasn't a combination of an undergraduate—what we would consider an undergraduate—and then medical school in college?

DIXIT: It was medical school proper. But in reality, what happens is you, remember those A-levels? I said, you have two years of specialty. You continue to extend that. You still do more basic science courses because now the curriculum is six years in medical school versus four years in the US. So you're going to do five years of medical school and one year of internship in the British system. And the first two years, the first two years—may have changed now—but the first two years you don't see a patient. You're still taking courses, taking anatomy, physiology, biochemistry. **<T: 70 min>** So you're still taking courses.

CARUSO: Okay. And so how did you enjoy entering medical school?

DIXIT: Oh, I loved it. I loved it. I just really . . . it was, sort of, a revelation. One was that university teaching was a revelation. You know, there was the expectation that you would teach yourself. There was a certain degree of that, a certain degree of independence. I really liked the teachers. This was . . . so when the medical school was begun, they had staff—teaching staff—from McGill [University] in Canada, Glasgow University in Scotland, and [University of] Padua in Italy, so a lot of the faculty came from those institutions. And there was also some African faculty, there was some . . . it was a mix of faculty. But a lot of the faculty, especially the Canadians from McGill, were retired physicians or close to retirement, and they were just outstanding teachers, I mean, just really good teachers. But I think the teacher that influenced me most was somebody I had written about, was a professor of physiology, [Edward] Hettiaratchi. He was a Sri Lankan professor. He'd gotten his degree in Edinburgh, [Scotland], his PhD. But he was just an outstanding teacher of physiology, and he, for the first time, made complex things simple and really emphasized the principles of biology, you know, homeostasis, the constancy of the internal environment, Claude Bernard's work, which was so important, of feedback loops of systems, once they're perturbed, have a tendency to go back to their original state. Theories of [Charles] Darwin. And so that if you looked at biology through the lens of Claude Bernard and Darwin, then it all makes sense. And so that really influenced me, and I liked that because you could study, you could think of a lot of medicine from those sorts of first principles of physiology. Yeah, that really influenced me.

CARUSO: So I have two questions. Since you had spoken a little bit about international perspectives and a general awareness of what was going on in other countries and, you know, what people growing up normally do thinking about different political cultures and ways of living, were you aware of the, what was dubbed The Rumble in the Jungle, the Ali-[George] Foreman fight in Zaire? Because I think that was 1974.

DIXIT: Very much so. Very much so. And it was televised. You know, it was televised live, which was unusual in those days. And Ali was a larger than life presence for many reasons. One is he had spoken up, had the guts to speak up against the administration, against the Vietnam War. He'd actually sacrificed, he'd sacrificed . . . he was at the height of his career when he was disbarred from boxing, and he'd given up on principle. And for the . . . . I would say in Africa that had a real resonance, for colored people that had a real resonance that here was a person who gave up enormous wealth for a principle, right? What was his saying that the Vietnamese didn't do anything wrong to him, he didn't see why he had to go kill them. And yes, so that was enormous, and I think Foreman, who was this hugely muscular giant **<T: 75 min>** of a man, it was almost a foregone conclusion that he would pound Ali into the ground. I'm not . . . at least many of us couldn't conceive how Ali would win such a fight and therefore, The Rumble in the Jungle with Ali winning, of course, was a very special moment for everybody. I think it is because of the Ali standing that he was a, he is a man of color who was willing to make sacrifices for his people, for his stand, for . . . .

CARUSO: So during course of medical school, you're taking the traditional courses, first two years is pure coursework and then after that you're moving into clinical experience?

DIXIT: Yeah, clinical experience. Yeah.

CARUSO: So did you start to think about what area of medicine you wanted to specialize in?

DIXIT: I did. I was very attracted by public health, you know, in the public health term, we had to go out and live in the community. This was a small community outside a town, Machakos, in Kenya, and that really influenced me. And we traveled all around Kenya besides Machakos. I mean, they wanted us to talk to people and get to know them in the villages. So go to the bar and talk to the prostitutes. "Why are you a prostitute?" "Well, I need the money. I've got a baby." And then you realize that things like prostitution—at least in those countries—are economic activities. You went to what was a leprosarium. People with leprosy. And you talk to them, and they say, "My village is convinced that the evil spirits reside in me, even though I'm totally ostracized. I have no life." It gave me a human element to do things like that. For me, I had a rather protected life. I'd never spoken to a prostitute before and never been able to ask, "Why are you doing what you're doing?" I'd never been to a bar with a village, sort of, that small town bar. So it was awakening and then I started reading about public health and the China experience and I was thinking about what it took to improve the lot of a community.

And the public health resonated with me because I remember I read an article while I was in this field hospital, which said that if you look at the incidents of gonorrhea—the sexually transmitted disease—it's—this was the times of Communist China—it's going down in China.

And it's going [gesture straight up] like that in the US, and I thought, that's curable. Obviously, you've got penicillin. But why is that? And that's because you can't control behaviors. There's no . . . there isn't an emphasis on public health. And I really thought that's what I wanted to do was to be a public health doctor. Very influenced by a wonderful South African professor—a white man—Professor [Francis John] Bennett, who . . . . I remember we were out in the arid area. And I said, "Professor Bennett, that guy had a gash in his calf. And do you know what he did, professor? He peed on it." And he said, "Listen, son. What is the only source of sterile water in this arid environment? If he wants to flush his wound, what's he going to use? He's going to pee on it."

So lessons like that, all the time, emphasized **<T: 80 min>** to me that if you really wanted to improve the lot of a people and you know, now we are not talking about . . . we're talking most of humanity that you have to devote yourself to public health. So that's what I wanted to do. But then I realized that boy, when you start talking about public health, you start talking about politics, and you start talking about changing the political system. And those two are very intertwined. You only have to look at our country here now to see how true that is. We have the most expensive health care system in the world by far, by far. And yet, when we look at first-world countries, you look at our statistics—choose whatever statistic you want—we are towards the bottom if you compare us to Germany, Switzerland, Australia, France, UK. But we are happy with it because that's the political system. That's what . . . it's very difficult to change. So I realize that, while I was attracted by public health and I really wanted to do good, you'd have to be a politician, and that just wasn't for me.

CARUSO: I meant to return to this. So I'm sorry that we, kind of, moved past this temporally. It's also . . . it's those first couple of years when you're in medical school that you wind up getting the eye surgery, right?

DIXIT: Yes.

CARUSO: Was that your first time to the United Kingdom?

DIXIT: I'd been to the United Kingdom before. My father loved to travel, so he had taken us to a number of countries. We'd been to India, we'd been to the UK a few times because remember in the sixties a lot of the Indians left Kenya, settled in the UK, so he had a . . . he knew a lot of people, so he would go there. I remember I think I was in seventh grade when he first took me to the UK. Went to Brighton, [England], London, and saw the sights. And coming from a village in Africa, it was both exhilarating and terrifying at the same time. It seemed like I'd landed on another planet, you know. Just like, wow.

CARUSO: And so it wasn't your first time there. How was . . . how long did it take you to have the surgery and recuperate from it?

DIXIT: You know, it took an inordinately long time. Remember, these were the early days of corneal transplant surgery. Nowadays, it's an outpatient procedure. It was almost, I would say, experimental at that time. And so I . . . it took me four weeks. They feared I was rejecting my cornea, which is very rare because the cornea is avascular—it has no blood vessels. But they felt that I was suddenly vascularizing it and that would lead to rejection and they put me on high dose steroids. And that was my first real exposure to how medicines can be damaging because you get put on high dose steroids, you all of a sudden gain a lot of weight, you become puffy, you become exhausted, you get backaches, you know. Fortunately, it was temporary. But yeah, so it . . . that passed. I didn't reject my cornea. So I was . . . so I had to stay in the UK. I think I stayed in the hospital maybe just one night, maybe two nights, maybe one night. But then I stayed with a family friend for about a month so that I could go for checkups and then finally back to Kenya.

CARUSO: And so did this interrupt your medical education? Or was this during some vacation time?

DIXIT: It was during vacation time, yeah, which was very fortunate. But by the time I got back, my fellow students jokingly said they could barely recognize me because of all the weight I'd put on. [laughter]

SCHNEIDER: And, you know, you mentioned the family friend and some people your family knew abroad. Were . . . did you have grandparents living when you were growing up? And if so, where did they live?

DIXIT: No, my grandparents passed in India. My grandmother from my mother's side did come and live with us in her **<T: 85 min>** last maybe year or so of life. She came to Kenya and she lived with us in Nairobi. But the grandparents had passed away. My grandfather on my father's side, he was a physician in Patiala, [India], in Punjab, [India]. So the grandfather, my grandfather on my mother's side, he was a landowner in UP [Uttar Pradesh]. And I don't know too much about them, but that's what I do know.

CARUSO: So there are a couple of questions I have about your time in medical school, and I don't know the best order to ask them in. I know that you received several awards as a medical student, one in obstetrics and gynecology, pathology, overall best medical student. So I'm curious to know a bit more about those. But I also wanted to ask a bit about, you know, when I think of early 1980s and medicine, the major thing that comes to mind, which is, of course, what

. . . something that Ronald Reagan tried to ignore for a long period of time, is the beginning of what became the AIDS epidemic. And so I was curious to know if you had any experiences in those early times with individuals that would become known later as AIDS patients.

DIXIT: Yeah, no, actually, it was . . . so I came to the US in [1981], and in 1979 I worked in a tropical medicine unit that was headed by Dr. Philip [Howell] Rees. He's since passed. He was a British physician, and he looked after complex patients, the patients that we really could not understand the etiology of their disease. And, you know, when I think back at the time of . . . hepatitis was prominent, a number of what you'd call "tropical diseases" like schistosomiasis, leishmaniasis, which is a terrible disease, trypanosomiasis. I mean, very few people have seen trypanosomiasis but Trypanosoma cruzi. Sorry. I think people have seen Trypanosoma cruzi, which is South America. But this is rhodesiense, which is the African trypanosomiasis, which is fierce when it hits the CNS [central nervous system]. So really very, very unusual cases that the vast, vast majority of physicians have never seen. So it was a wonderful experience, but during this time . . . and so he ran this unit and he would have visiting professors from the Dutch Tropical Institute in Amsterdam, [Netherlands], and the London Tropical Institute, University of London. So it was a really highfalutin, high-powered group of physicians who were investigating these patients. They would come for a short time to this unit because it was well-known that you would get—in a very short period—you would get to see patients that you wouldn't see in five lifetimes, right? Because you had all these unusual cases.

Tropical ulcer. Oh my god. Burkitt's lymphoma. And the list goes. Kaposi's sarcoma, which was a very unusual cancer but very prominent in Africa. But then I started taking care of these patients who came in and started wasting away. And one thing was that they were—I noted to myself, discussed it with Philip Rees—that a lot of them were drivers—long-haul drivers—who were driving from Mombasa, the coastal town, to Rwanda. So this is a distance of, you know, 1,500 miles or so. So that was one thing they had in common, so they were traversing a lot of geographic areas that they could have been exposed to infectious agents, and we thought of all sorts of things, did all sorts of investigations. I don't even know if they do this, but we did a splenic wedge biopsy, which is very unusual because essentially what these **<T: 90 min>** patients had was fever of unknown origin means that they were febrile. And in this case, they were also wasting away. But we didn't know why. And then I came to the US. Mystery. They died. Boom.

And then I came to the US, and HIV and AIDS happened. And then I realized this was probably HIV. These were the long-haul drivers who were getting exposed to sex workers on their way, and they were dying of HIV, and we had no idea whatsoever. We wouldn't have known. We couldn't have known. It would have been impossible for us to know. And what also happened was that, you have to remember, the conditions when you're practicing medicine are very difficult in the sense that I would often come home from what we would call the operating theater where you would do the surgeries soaked in blood. I mean, you were just around blood all the time. And then a few years later, a number of my medical school classmates unfortunately died of HIV as well. And I think it was that. We didn't know at that time, but it was that, sort of, carelessness of handling blood. Many times you couldn't avoid it. I remember

that we were once anesthetizing a woman. She had hepatitis. And the anesthetic assistant, the needle slipped and pricked me. And I was terrified. There was no cure for hepatitis in those days. Well, I just prayed I wouldn't get hepatitis. You know, now in hindsight, it made sense that this was HIV. And then when I went back to Kenya a few years later, they said to me, they said, "The wards, they're just filled with HIV patients. The morgue is just filled with HIV patients. All we see is HIV." It was devastating. I'd long gone, but this is what I heard from my colleagues.

CARUSO: You mentioned going to the United States or continuing your medical training in the United States. When did you make the decision to go to the US, and why did you choose to go to the US?

DIXIT: Well, there were a number of reasons. One was my brother was already in the US. My sister was in the US. They had . . . and my brother, who I was very close to, he knew I was interested in research. And he said, "You really want to come to the US because rather unusually, in the United States, there is a track. There is an expectation. In fact, you can make—physicians, doctors can do research. They just don't have to see patients all day. They can actually do research." I'm like, "Really? A doctor can do research?" He said yeah. That was very unusual. And when you ask me why I got those prizes in medical school, well, early on I thought, "I'd like to go to America." But, you know, I wanted to be a student who excelled and, sort of, stood out. But also, there was this whole battery of American exams one had to pass to get one's degree accepted. So there was reason to be studious. And then it just seemed that here was a great opportunity that I could do research, I could be an explorer, I could really live my childhood, and I could do that. It just seemed unusual. I was half believing, so he said, yeah. And he says, "I am at Barnes Hospital."

This is Washington University, St. Louis, [Missouri]. He was an **<T: 95 min>** internal medicine resident. And he said, "I talked to the chief of lab medicine." It was a branch of pathology. And he said, "Yeah, you can come here, you do a one-year residency and then you can do up to three, four years of research in a lab." I said, "Really? That sounds impossible." He said yeah. So that was very attractive to me. And so that's what attracted me to the US was that opportunity. And I would say that having the Canadian physicians—though of course they're not Americans, and Canadians would be very angry and upset if you thought of them as Americans—but I enjoyed their—at least the ones I was exposed to—there were some American residents who came through. I liked their, sort of, go-getter attitude, you know. I enjoyed their persona. There was a certain attraction about American life, and obviously there was . . . America was a major part in one's imagination if you were an explorer. I mean, they'd been to the Moon. Wow, that was amazing, right? The science and technology. You heard about places like MIT [Massachusetts Institute of Technology], like Caltech [California Institute of Technology]. Just amazing places. So yeah, it seemed like the place to go.

CARUSO: And do you know what attracted your brother and your sister to the United States? Were they also interested in doing research, or were there other reasons?

DIXIT: No, they really were interested in doing clinical medicine and doing . . . . You know, at the end of the day, they were interested in a better life. And when you see what's happening in Ukraine now and you see in other conflicts, and this is one thing that public health helped me realize is that people are the same everywhere.[1] They just want a good, safe life, and enough for their kids, an education. And because of the uncertainty in East Africa, was another Idi Amin going to come about? Because of the turbulence, they came to America because this was, for immigrants like myself, the land of milk and honey. I mean, it was a land where you were told—and I believe I've experienced that—if you work, you were given a reasonable deal. I think that really attracted them as physicians. They wanted to come here, work, specialize—they both specialized—and do medicine. And yeah, my . . . all of that happened to me. I would say that my ambition was really to come to America and fulfill my dream of being an explorer. And that was the opportunity.

CARUSO: And did you have . . . . I want to hear what it was like arriving in the United States, but I also want to know what it was like leaving not just your home but also leaving Francis.

DIXIT: It was very difficult. You know, I think about Francis often. I think of . . . the last night is, sort of, seared in my memory. Here is this older African gentleman just inconsolable, crying like a baby. And there is me crying as well. And it was very difficult because that was just such another world and then coming to America, which was another world . . . you have to remember, I worked at Kenyatta National Hospital. Four thousand patients, but very difficult conditions. It may have improved now but I'm talking about when I was there. We had often two patients per bed. A patient between beds on the floor. We never explained a procedure. I mean, we didn't have time. Like if I wanted to do a lumbar puncture on you, I'd just say, "Get into the fetal position and bend your back, and I'll reach in and put a needle in your back." I didn't have time to tell you, "Oh, I'm going to do a lumbar puncture. Do you accept?" Nobody had time for that, right? So it was a very . . . **<T: 100 min>** pressurized situation where you were looking after desperately ill people, often with few resources, often doing things flying by the seat of your pants—crowded, crowded conditions.

And then I came to Barnes Hospital, Washington University, St. Louis, and if you haven't seen what the inside of the hospital looks like, you should Google it. Red carpets. Clean. Quiet. Sterile. Big portraits of famous physicians hanging from the walls. Carpeted. I was just wonderstruck. I was like, "Where am I?" You know, it was completely a shock to see such a wealthy palace of medicine, so it was a huge change to come from that environment of Kenyatta National Hospital where . . . . And I think about that often because I think about, you know, now

[1] See Encyclopedia Britannica, "Ukraine Summary," February 24, 2022, accessed May 4, 2022, https://www.britannica.com/summary/Ukraine.

they have this thing in California that the doctor has to get your permission before they weigh you, it's because they could be fat shaming you, so they can't just tell you, "Get on the weighing scale." And I would think, moms would come with their babies, and we'd often—because we were in such a hurry—we'd have to take blood from the external jugular. So we'd hang the baby upside down, put a needle in the external jugular, draw the blood. And the mother would say nothing. There was no explanation. There was no time for explanation, right? Just a completely different world.

CARUSO: And so how was it adjusting to doing medicine differently in the United States where you couldn't just stick something in a patient when you thought it was necessary to do so? But, you know, people would . . . they would get angry at you if you were poking them or prodding them or flipping their baby upside down and sticking needles in their necks. So how was that adjustment for you? And did you have anyone who, kind of, advised you or helped you understand the transition?

DIXIT: Well, I think I was savvy enough to understand it was a completely different system, but I certainly had my brother advising me. But I would also say that in lab medicine, other than the transfusion service, you didn't really have patient contact because it was more blood banking, microbiology, clinical chemistry, so you didn't have that, sort of, contact, primary contact with the patients. But certainly, the ones—if there were transfusion reactions, I'd have to go to the floor. If there was plasmapheresis, I had to work with the patients. It gave me a totally different perspective, too, because patients have rights. They have opinions. They have . . . it put perspective because the way we practiced medicine, there was no other choice. There was no other choice. I'm not saying it was right or wrong. There was just no other choice. You had hundreds of patients. And I'll tell you one thing, talking about revolutions in medicine. The one depressing thing about doing pediatrics in Kenya and Africa and the developing world at that time was dehydration. We would lose an enormous number of kids from diarrheal diseases—they would become dehydrated—to the hospital. Very difficult because all their veins collapse. You try to put [butterfly needles] in scalp veins [to rehydrate]. You may have to do a cut down [to access] a vein in the leg. Very, very difficult. Huge mortality. And then there came oral rehydration, the Dhaka regimen. So now the villages, they would have a Coke bottle or equivalent—a **<T: 105 min>** certain amount of sugar and salt—and they were told to rehydrate.

That was a revolution. And *The Lancet*, they looked at the advances in the last century in medicine, and they said oral rehydration in their perspective was the top. So oral rehydration has saved countless lives, but that was one example of how medicine changes. You know, in America, you may not be aware of oral rehydration, but for the rest of the world, that was huge because by the time they got to hospital, we could barely resuscitate. But now, in the villages, they can be treated with this Dhaka regimen. I'm sorry, I was . . . . Yeah, so anyway, so we were . . . I was talking about how difficult things were, you know, we were trying to rehydrate kids and all of these things. You didn't have time to get into explanations. But I think the other thing was that there was a certain belief that the population had in the doctor. I mean, it was almost like you were, in some senses, a god. You were . . . they didn't question. And obviously in a

first world society where more luxuries are available—luxuries of time—that's not appropriate. And it has to be a two-way street. And I feel bad because you have to realize there just weren't enough doctors for the thousands of people that needed treatment. So there was no explaining, there was no . . . . They were desperate, you know, people come to hospitals there when they're seriously, seriously ill. I mean, you see stuff that it's hard to imagine.

CARUSO: When you showed up at Barnes and you were moving into a medical research field, were you . . . did you go into . . . ? So I know physician researchers in the United States and they received their medical degree, but they also had a general affiliation or had done some medical research, biomedical research beforehand. And often, you know, they were in joint MD/PhD programs at that time and so there was the medical education, but also the research going on at the same time. You had a more traditional medical education, and you were now coming to a place to do medical research. Were you going into someone's research laboratory, or were you coming in with an idea for a research project and you were going to use the resources at the hospital to conduct like maybe a clinical research project? What was it that you were doing in terms of medical research when you arrived at the hospital?

DIXIT: You know, I was very fortunate because I had no business being in that program, and again, it was my brother's . . . just like my father had helped me get into medical school, my brother helped me get into this program. And this, sort of, reminds me of a saying from [William] Shakespeare that there's a tide in the affairs of men, which taken at the flood leads onto fortune omitted all the voyage of their life is bound in shallows and in miseries.[2] And so this for me, getting into medical school and getting into the residency that allowed research, were the two tides in my affairs. And I say I had no business [being in the program] because I had no research. I was honestly an ignoramus. It's like somebody saying, "I want to play in the NBA. You know, what does it really take? What is it?" I was just ignorant, right? I wanted to be an explorer. But what was medical research? I'd never done research. And we can come to this later, but I remember interviewing with Bill [William A.] Frazier, the person I eventually worked with in biochemistry. And he said, "Okay. Have you used a pipetman?" I said no. He said, "What about a pH meter? Have you used a pH meter?" I said no. **<T: 110 min>** Now, seriously, if somebody came to me today and said that, I'd be telling my secretary to hail an Uber for that person, show him out the door, there'd be an investigation how I ever got to interview such an ignoramus. Like how the hell did that happen, right? I knew nothing.

I mean, just a complete dolt. I just wanted to do research. I wanted to be like Howard Carter and explore Tutankhamun's tomb. So really, I had no business being in that program because my other, fellow residents were MD/PhDs. MD/PhD from University of Pennsylvania. There was an MD/PhD from UCLA [University of California, Los Angeles]. I mean, there were just really serious researchers. And I didn't know how to use a pH meter. You guys know what a pH meter is, right? And I was just like, whoa. So, wow. But what . . . this was a very

[2] William Shakespeare, *Julius Caesar*, ed. Albert Harris Tolman (Yonkers-on-Hudson, New York: World Book Company, 1913).

enlightened department, so they said, “Listen, it’s unlikely somebody is going to be jumping up and down at the opportunity of taking you, but we’re going to pay for your salary. So you’re a free pair of hands. So maybe, you know, they’ll see you as somebody who will come in maybe make the coffee in the mornings. What do they care? You’re free.” So this is where I was really lucky, and maybe that was the third tide in my affairs of men is that I landed up with Bill Frazier, who was a professor of biochemistry at WashU for my research.

And remember, professors generally don’t work at the bench for reasons we can go into, but he did. He actually worked at the bench. And he said to me, he says, “Look, I’m going to be working at the bench this entire summer. Just join me, and we’ll do it together.” He said, “When I teach you a technique, just go back and read about it, you know, the basics, the foundational stuff, and you’ll be fine.” So it was an amazing apprenticeship, so in that very sense of the word that is such a rare happening these days. I was an apprentice. I was stuck to him, to his hip and worked with him all day and actually learned the trade. When I say I learned the trade, I also learned to think and probably the most important part of it was not simply the trade, but the ability to think because prior to coming to WashU, I thought what was written was the gospel truth. But in our Department of Lab Medicine, we would have weekly meetings that were dubbed the “Shark Tank,” and we would go over work. We would either go over published work by others, or we would go over somebody’s own research work that has been done internally. And it was all questioned. Nothing was taken for granted. It was brutal. Everything had to be proven.

Where’s the data? Aaah, that doesn’t look convincing. Ah, it’s only a 1.2 fold change? I was like wow. It was almost pugilistic. It was almost like you were in a boxing match. There was give-and-take, exchange of ideas, thoughts. That knowledge at the cutting edge is amorphous. It’s not solid. It has to be molded. The truth has to come out through debate. I mean, I was just awestruck. I was like, “Wow, this is how it happens.” So for . . . that was the most . . . so Bill was amazing in teaching me the trade. But what really was like a tornado in my intellectual life was this question, the ability to question. To think, then to think creatively, which came later in life. I was just so dazzled then to ask questions like, “Are you really asking an important question, or are you just dotting the i’s and crossing the t’s in your work?” But **<T: 115 min>** a lot . . . all those formative happenings were at WashU, either in the journal clubs or research in progress, either in the Department of Biochemistry at WashU, which was a very famous department, or the Department of Pathology. So that just that was like somebody put electrodes on my scalp and put it on max power. It was electrifying, just changed me. Just boom. Because before that . . . yeah.

CARUSO: I was just going to ask: what was the focus of Bill Frazier’s work? What was he interested in specifically?

DIXIT: So he worked on Dictyostelium discoideum, which was slime mold. But he . . . . I was interested in human medicine. And he thought that a project that I could do . . . so slime mold, they get together, they adhere, and so adherence, adhesion is a key aspect of their life. But

adherence is a key aspect of biology, and one area where adherence is very important in human biology is in the formation of a blood clot where platelets aggregate to form the plug that stops the bleed. So platelet aggregation is very important. And, of course, when platelet aggregation goes awry like it does when you get a heart attack, you get a thrombus, you get a blood clot that prevents the further flow of blood, and that's a very serious issue. So I was interested . . . my last year, my interest in lab medicine was in what you call hemostasis/thrombosis. So I was interested in the science of blood clotting, in platelet biology, coagulation factors. And, at that time, because I was interested in coagulation, liver transplants were just coming of age, so I had to . . . . I was on the liver transplant service. I had to—whenever they transplanted a liver—I had to be in the operating room to monitor the indices. It's become a lot more routine now—liver transplants. But in those days, it was still, sort of, semi-experimental cells, so I was always thinking about coagulation and experimentally how to monitor it. And so I had a natural interest in coagulation and Bill said to me—now in hindsight, it's quite funny—he said, "Hey, you know, platelets adhere. In a sense, they're like slime mold. Why don't we study platelets? In fact, I know somebody in pathology, Sam [Samuel A.] Santoro, who works on platelets. We could do a project together. We could study platelet adhesion. I study slime mold adhesion. We could do platelet adhesion."

But here was the other lesson is that you could go into a field. This was a new field, right? This was very important for me later in life when I changed fields because here is somebody who said, "Let's just work on something interesting, which is platelet adhesion. Yeah, there's a lot of literature on there. I can barely spell the word platelets, but I'm a biochemist. I can think. I'm a scientist. I can think along those lines, and there is some help we can consult with this person—Sam Santoro who's in pathology, who knows about platelets, and we'll just start." I'm like, "So, Bill, how do we start?" He says, "I don't know, why don't you purify platelets." And then I go to Sam, we get a protocol and, you know, so it starts that way. And that was research. It was very different from studying for an exam. There was no curriculum. It was just like, you're in the wild blue yonder. Some days you feel you're without a compass in the dead of night. And you are running at full speed not exactly sure where you're going. But that was research, and I liked it.

CARUSO: And so you mentioned that you had, kind of, an apprenticeship with Frazier when you first got there. What was the overall size of his lab at the university? Were there just a handful of people, ten, twenty, thirty? Were they post-doctorates? Were they graduate students? What . . . who was in the lab?

DIXIT: He ran a relatively small lab from what I can remember. They may have been two **<T: 120 min>** graduate students, a couple of postdocs, and a technician or two. So it was relatively small. I certainly interacted with everybody in the lab. I learned tons from the students, from the technicians. I just . . . people were very generous with their time and just very generous. And the other thing about America you learn is there isn't a stupid question. You could ask anything, and people were genuinely helpful. So that really allowed me to learn exponentially. I mean, I was just drinking from this fountain of knowledge—nonstop—that was in front of me. And it

was a very . . . in my mind, a professor—coming from the British system—you had a . . . they had a certain station in life. There was a certain way to address them. There was a certain way to behave. And that all got thrown out of the window when I came to America and at least in the research world—maybe different from the clinical world where there still are hierarchies—but in the research world, people didn't care that you were a big professor. A graduate student could question you.

Anyone could ask you something. And I really found that liberating that hey, Bill was just like another guy in the lab. He'd joke. He was casual, easy. He'd share his fears with me. He'd share his successes with me. He'd have me over to his place. It's like, "Wow, this is really unusual." So I really, really liked that, sort of, informality of the research world and the lack of hierarchy—there is hierarchy—you have to get grants and there's always hierarchy in any societal structure, but the day-to-day, the inquisitiveness. Yeah, that was wonderful. It was a small lab, quite interactive, but because they worked on Dictyostelium discoideum and I worked on platelets, we are talking about two different worlds, and that was such a blessing because in the lab meetings, I could hear, listen to their problems from Dictyostelium, from slime mold. When I talked, I'd have to explain my world of platelets. You can't imagine two more disparate worlds, right? The underlying principles are, of course, often the same, but disparate worlds, which was great training for me.

CARUSO: And so once you started working in Frazier's lab, what was your schedule like? Were you . . . was it nine to five? Was it like ten in the morning to ten at night? Were you there five days a week, six days a week, seven days a week? What was just your daily research activity like there?

DIXIT: You know, it was a bit of a blur. I would say I worked very hard. I mean, I worked as hard as I could. I put in a lot of hours. Somewhere along the line, I realized that putting in a lot of hours wasn't the same as working productively, so I did change midstream because I almost spent night and day in the lab, and that the productivity per unit time was dropping. I became more organized. But, you know, I was . . . it was like a thirsty man finds an oasis, and the first instinct is to down as much water as you can, even at the risk of choking yourself. And that was me in the first year or so. And then you realized you've got to pace yourself, and there's a lot to be learned. It's a long journey.

CARUSO: In that first year or so, did you find yourself missing clinical interactions at all? Did you miss seeing patients, diagnosing **<T: 125 min>** them, or anything like that?

DIXIT: You know, I desperately missed it, to be honest. I desperately missed it because it was a world that I'd grown up in, and it was a world that—if I may say so myself—I was quite good at. You know, when I had to do the American exams, for example, I mean, they were trivial for me. I was just so well-trained in clinical medicine. And then you walk away from that, and you

go into an area where you're a complete buffoon—you're the bottom of the bottom in terms of the knowledge, right? I mean, that's a big change. Yeah, when I think back, that's a big change because I was really well-trained as a clinician, very capable of taking, of doing clinical medicine, like I said with the exams. And now you're going to an area where you're the bottom, and you're just learning everything. You're making just elementary mistakes. I mean, just laughable mistakes. Yeah, so I missed it, but . . . . I don't know, I think I enjoyed the lab overall. I think I liked that atmosphere of discovery. I also thought that the environment in which I was in—academic medicine—there was a certain reverence around doing academic medicine, doing research at WashU in St. Louis. It was thought of as special. And I guess that . . . and I was quite busy, so, yeah. I mean, I think of patient care—I've always thought of patient care—even at times now when I think about should I go . . . if I go back to Kenya, could I really run a clinic again? Of course I couldn't. But you think that.

CARUSO: Yeah. And what was it like transitioning to American life? I mean, when you . . . when we first started speaking and you were talking about growing up in Kenya, it was like, you know, it was 70 to 80 degrees most days and beautiful. And now you're living in St. Louis, and it's cold there for much . . . for part of the year. And, you know, just experiencing life from that perspective. But also, I mean, this is the US in the 1980s. The . . . . I guess this is . . . the HIV epidemic is going on. There are discussions about rights for individuals who identify as homosexual. There's a different culture here generally. What was that transition for you like?

DIXIT: It was a massive transition, and it's a transition that is continuing to this day, really. I would say that, for me, very personally, I found America to be the land of milk and honey, to be the land of opportunity to be . . . just an amazing place. And I'm often saddened that many Americans who haven't lived in other countries don't know how good they have it here. So that was the first thing that astounded me was the richness of the country. But the generosity of the people, the friendliness of the people. Now it may have been casual, it may have been superficial—I don't know—but the people were genuinely friendly to me, genuinely helpful, genuinely accepting. And I was really, really taken by that, it really surprised me because, you know, I had this sense of maybe Americans were aggressive, gruff, you know, you get that movie, Hollywood portrayal. The weather, of course, stunk. I mean, St. Louis in the summers, I thought, was the hottest place on Earth. In the winters, it was **<T: 130 min>** freezing. But what struck me is also and that is just the spectrum in this country is huge. The gaps are massive between rich and poor, educated and uneducated, and it's almost like it's two countries in one. There's the country of NASA [National Aeronautics and Space Administration] and Caltech and MIT and Google and Apple, that. And there's the country of Alabama where there isn't, in many parts, sanitation. So it's just a huge spectrum, amplified by something like the anti-vaxxer movement, right? Difficult to understand how that could happen. So, for me, the . . . it's something that I'm still coming to grips with, this . . . that there are aspects that I still don't get like this love for guns, where does that come from? Why should people have assault rifles? But overall, as an immigrant, it's been a hugely positive experience. And that started off in St. Louis with everybody just being so incredibly welcoming. And I say that because you can go to many other countries and get a very different welcome. So this is very unusual.

SCHNEIDER: Do you remember any of those—the first days you arrived in the United States and . . . or the journey to the United States? Do you remember those first moments?

DIXIT: Oh, I remember them very well. I think we came via Cyprus. I think it was a long flight to Cyprus and then to London. And then London, I remember, there were a lot of, I think, Persian, Iranian students were boarding the flight to the US. And I remember I arrived in New York. And I think it said I could change airports, and I think it said the taxi was . . . it had twenty dollars—I don't know what it was—let's say it was twenty dollars, and a taxi pulled up, and I didn't realize this that there was something like illegal taxis. And he hurriedly loaded it and furtively we left. And then we came to the airport and he said, "Okay, you owe me twenty-five bucks." I said, "No, no, it's twenty dollars." "Hey, pay up." [laughter] This was my first exposure . . . unbeknownst to me, I'd gotten on an illegal taxi and had to pay an extra few dollars. Yes, I remember that. I can remember coming to St. Louis. I remember a couple of funny things that happens with the English language. I remember talking to the departmental secretary, Marcia [Tenenbaum], who was always suspicious of me that how did this person from the middle of Africa get a position here? And she was, sort of, prim and proper, and I went up to her and wanted an eraser, and I made that old error.

I said, "Marcia, can I have a rubber?" She said, "I'm sorry. What do you mean, a rubber?" And I quickly realized. And then that same week, I said, "Marcia, I need to take time off. I'm joining the AA." She said, "You really have that problem? You never told us about it." I said, "It's okay. I just have to go this afternoon." And little did I realize that AA, for me, meant Automobile Association. And for her, it meant Alcoholics Anonymous. So, you know, there was those, the usual language gaps, which were amusing in hindsight. But the food, food was another . . . gosh, the richness of the food here was really startling. What really startled me was ice cream. I mean, I had ice cream everywhere. But American ice cream, at least at that time, was so sweet. So incredibly sweet. It's, sort of, almost like woke you up with the sweetness. Yeah, yeah.

CARUSO: You'd mentioned that you were pretty devoted to lab life for **<T: 135 min>** a little while. When you started to find a new balance in terms of the amount of time that you were spending in lab, were you doing other things? So no, not were you doing other things. What were you doing with your newfound free time? Were you going out to cultural events? Were you just hiking? Were you taking trips places? What was your personal life like?

DIXIT: Well, I went out with some friends. I developed some friendships. I dated some, and it was . . . . But I would say I spent most of my free time reading—reading about science, reading about the work. I was very . . . still very enthralled. So I never really . . . yeah, I didn't go on any hiking trips or nothing like that. I went to a scientific meeting during my first year. It was in LA [Los Angeles, California], and I remember going to LA. I think it was in the winter—maybe

February or March—and one of the residents who was from UCLA said, "Let me take you around." And the place was sunny. It was warm. And he said, "Let's drive through UCLA, my campus." And we drove through UCLA. Palm trees. Girls in shorts. Bicycles. I'm like, "This is another world." Coming from St. Louis to UCLA campus, it's like, whoa. And attending that scientific meeting was, I think in hindsight, it was a meeting where a lot of the giants of American molecular biology, Phil [Philip] Leder and others spoke. It was quite . . . he made quite an impression. It, sort of, also said there was a huge distance to go. It gave me an idea that the journey would be long to reach that level of accomplishment.

CARUSO: You said that you went to the meeting. Were you presenting at it or just attending it to see what it was like?

DIXIT: No, this is again . . . this enlightened department, this department at WashU in St. Louis, they said, "You know, if you're going to be a scientist, you really should go to a meeting. And we'll pay for it because, you know, you're not going to present anything. We'll pay for the entire trip—hotel and everything. Just to expose you."

CARUSO: And what . . . did you get a sense of how the scientists there were seeing you as a non-PhD trained medical researcher? Were they open and welcoming? Were they pushing you aside because you weren't . . . didn't fit the traditional mold?

DIXIT: Well, I think people were always very welcoming and always very polite, but I think in that it was also evident that I was a rank amateur. I was unlikely going to make it. I probably, you know, for a lot of people do research and then go back to clinical medicine. It's, sort of, a rite of passage in many fellowships. And so, yeah, people were polite. I suspect many of them thought that I was just there as part of my training and soon would be back in a hospital setting. But yeah, and I realized that, which was fine. I had . . . . I wasn't even at the base of the mountain. The mountain was at a distance at that time in my training.

CARUSO: During your time at Washington University, did you accomplish enough research to warrant publication of a paper?

DIXIT: Yeah, no, I was . . . and Bill was very good in that way. I mean, he would say, "Okay. Have you written a grant? Have you written a paper?" And I'd say, "No, I haven't." He said, "Okay. All right, I'm going to be your secretary." So he'd **<T: 140 min>** get onto the word processor, and he'd say, "Okay, let's start. Abstract. What do you want to say?" And then I'd say something and he'd type it out, and then we'd wordsmith it. And then we'd go to the next section. And he'd say, "Okay, what do you want to say?" And now when I think back, really, David and Sarah, this is why it was a tide in the affairs of men. Who's going to do that now? If

somebody came to me, my postdoc, and said, "Can you help me write my paper? Can you sit down with me?" I'd be like, "Are you nuts? Get out of here." But yeah, he sat with me, he showed me how to write a paper, how to submit it, how to deal with referee's comments, how to get it published. But I was very productive with him. I wrote a number of papers. We had a whole slew of papers come out, which was great because that was my passport. I mean, that's the currency of our trade, really, is publications, credible publications in front-line journals is really the currency of our trade. And so that really paved the way to a faculty job. But it was Bill, he sat me down, showed me how to write a paper. I don't know why he did it.

CARUSO: I know you were there for roughly four or five years. Is that correct?

DIXIT: **[**Eighty-one] to '86. I was there for [five] years, yeah.

CARUSO: Okay. [Eighty-one] to '86. So can you tell me a little bit about . . . so I mean, you're doing research, you're publishing papers, you're learning how to publish, you're learning about grants. What were you thinking about your overall career trajectory during that period of time? Was it that well, I'm going to do research and then I'm going to go get a faculty position somewhere? Or were you thinking, "I'll need to . . . . I'm going to go back to Kenya and open a clinic?" What were you thinking about your overall career?

DIXIT: It was clear there was no going back to Kenya. I mean, there was just not that opportunity. The expectation in the department—and this is why one is so influenced by one's environment and one's peers—the expectation was that you would go and get a faculty job. Everybody before you who had trained had gotten a faculty job. Everybody with you who's training is aspiring to get a faculty job. So if you didn't do that, you'd really be the odd person out. And it'd also be a sense of betrayal. I thought they'd given me . . . really gone out on a limb and given me a position, and I wanted to do good. I wanted to do right. I wanted to say that I was worth the risk that you took. So yeah. And since I had the papers, a faculty position was possible. I didn't know if I could get one, but it was certainly possible. And they were very encouraging—the chairman of Jay [M.] McDonald, who was the head of lab medicine, and all the faculty—were very encouraging for me to apply, and they expected me to get a faculty job, and they were going to help in whichever way they could to help me get a faculty position.

CARUSO: Were you thinking faculty position at a medical school or faculty position at a more traditional research institution?

DIXIT: No, I was thinking of a faculty position at a medical school . . . well, for a number of reasons. One is my work, which was on platelets at that time, and was more suitable for a medical school environment, was more suitable for a medical school department. Also, to be

quite honest, the salaries were better at a medical school. And I'm not sure at that stage whether I would have been competitive for a top-notch basic science department. I mean, I had very good publications, probably, you know, good enough to get into a good clinical department like a department of pathology, but maybe a bridge too far to get into a department of biochemistry.

CARUSO: Yeah. I mean, that's partly what I was wondering was whether or not . . . **<T: 145 min>** even though you had been doing the research, if you thought that you would have needed those three letters—the PhD—in order to really move into just a traditional research university.

DIXIT: Yeah. No, that occurred to me. But my colleagues, my mentors at WashU said, "What you do is what matters." And this is the great thing about America. You know, we care less about pedigrees—for that matter degrees—we care about what you've done. And they said, "You've got a publication record that should make you competitive for not only jobs, but also for funding because the area you work in, there are not that many people." So I was encouraged to do that. And really, at that time—'86—I really did want to work on platelet biology. And so, yeah, going to a clinical department, pathology department, at least I would have colleagues who were all, who would be speaking my language of human pathology, human pathophysiology.

CARUSO: But Washington University also did have a graduate program, right? So there were individuals there who were receiving their PhDs.

DIXIT: Oh, definitely. And I honestly, coming from the British system, which is very degree conscious, very degree conscious, if you see British investigators, they'll have a whole line of alphabet after their names because . . . so I definitely wanted to do a PhD. But again, Bill Frazier said, "Yeah, you could do it, but to what end? Just do your research." So Bill, who was a mentor in the program, a PhD mentor who had students, wasn't that encouraging for me to undertake a PhD. He just . . . he was, I think . . . and this was part of his apprenticeship approach. He was like, "Learn as you go." I'd be like, "Bill, should I go to classes, graduate school classes?" He says, "Yeah, if you want to." And I did. I went to a lot of graduate school classes. He says, "Yeah, go to them if you think they'll help you. Go to some medical school classes; you've probably forgotten a lot of your early . . . . " And I did. So I would intersperse the day by going to a few classes. But he wasn't for getting the degree.

CARUSO: I guess the reason why I'm asking this line of questioning is simply because based on what you've described, it sounds like you were doing the work for the PhD.

DIXIT: Yes.

CARUSO: But because you weren't officially enrolled in a PhD program, it didn't count.

DIXIT: Right.

CARUSO: Which seems a little tragic from my perspective that you did all the work, but no one's willing to put that little stamp on a piece of paper saying, "Yeah, you're a PhD now."

DIXIT: No, in hindsight, I'm just surprised it went that way, or why Bill wasn't more encouraging. And if he had been, I'd have definitely done it.

CARUSO: Okay. And so when did you know that your time at . . . in St. Louis was going to need to come to an end? Was that a decision you made, or did the department say, "We like having you here, but you might want to start looking elsewhere for a new position?"

DIXIT: Well, the last year was, you had to go back to your clinical subspecialty, which for me was hemostasis/thrombosis. So I spent my last year doing hemostasis/thrombosis. So this is working on . . . with the plasmapheresis and doing the blood bank and those activities. And then the residency ends. So you have to leave, right, that's the end of the program. It's like, see ya. And obviously in that last year, the expectation is you're applying for faculty positions, and the people are helping you with letters, calls, whatever it takes. You're going out for interviews. And I'd interviewed at a number of places and ended up in Ann Arbor, [Michigan]. I'd gotten offers from a few places in the Midwest, but Ann Arbor seemed the most attractive.

CARUSO: So a couple of questions about that. How did you decide what places to apply to? Like what was . . . what made you think I'm going to apply here instead of applying to some other . . . ?

DIXIT: I didn't. You know, it was the old adage, "Beggars can't be choosers." I pretty much shotgunned every department that—pathology department—that did **<T: 150 min>** any research in the United States. I may have sent out seventy letters. And just see who responded. You know, who was serious? And then I probably went for, I would say, half a dozen interviews: [University of] Iowa, [University of] Wisconsin, [University of] Michigan, Temple [University], University of Pennsylvania.

CARUSO: So mostly the Midwest and, kind of, the Northeast?

DIXIT: Mostly the Midwest, Northeast, yeah. I applied to Stanford [University], I remember. It just didn't work out.

CARUSO: Hmm. Yeah. Well, you'd been mentioning life in LA so I was wondering if you wanted to get a little west and a little south.

DIXIT: No, it's interesting because by . . . in '84 my brother had left St. Louis and moved to the Bay Area, to San Francisco, [California]. Eighty-three, maybe. So I visited him in '84. I was newly married. My wife [Manjul Sharma Dixit] and I came. Again, as fate would have it, it was one of those dreary winters in St. Louis. We came to California and came to the Bay Area. They lived in the East Bay, which was warm, nice, sunny, blue skies, and then they said, "Well, you should go to the Stanford mall." I wanted to visit the universities. I wanted to go to [University of California] Berkeley. I wanted to go to the cyclotron. I wanted to go to all these amazing places. I wanted to go to the Stanford linear accelerator. You know, I wanted to go to Stanford. Very odd things but my wife was nice enough to go along. And then we went to Stanford Mall. It's in Palo Alto, [California]. It's an outdoor mall. Incredible stores, warm, sunny, people in shorts, T-shirts. I'm like, "Oh, if I could ever, ever have a wish come true, it would be to live here." This was '84. I mean, the funny thing is that I live now just a couple of miles from that mall. [laughter]

CARUSO: So your wish did come true.

DIXIT: It did come true.

CARUSO: So you mentioned that you got married in 1984. Can you tell me a little bit about how you met the woman who became your wife?

DIXIT: Yeah, no, I got married in '83 and a year. I met her by the equivalent of—you would say—the equivalent of Stone Age Tinder. She was a friend . . . the families were friends from a long time [ago]. She's of Indian descent as well. Her parents had come to the US in the 1950s, and she had grown up in Chapel Hill, [North Carolina]—sorry, grown up in Greensboro, North Carolina—gone to school in Chapel Hill. And she was doing a pediatric residency at Georgetown [University], and I was in St. Louis. And so the parents said . . . they knew each other, that maybe we could introduce them. And so we were introduced, and we had a long series of phone calls, visits back and forth. And then finally, I proposed. But there was the small problem of she being at Georgetown and I being in St. Louis. But fortunately, she was able to get a transfer for the last year of her pediatric residency to the Children's Hospital in '83. And yeah, and so she joined me there and finished her residency, and then she worked in the

children's emergency room while I finished my training so that in '86, we moved together to Ann Arbor.

CARUSO: So was that another factor for consideration for Ann Arbor? Because I know that when you have two professionals, you have the two-body problem, right? Like . . . .

DIXIT: Oh, that's what **<T: 155 min>** sealed the deal, you know? There it was very clear, she had a position, and I had a position, and that was it . . . and for a . . . in a two-body problem when that happens, you don't look a gift horse in the mouth. You just . . . boom, we took it.

CARUSO: And so was she going to be working at the university hospital in Ann Arbor?

DIXIT: She decided to do a fellowship in allergy immunology, so she decided to subspecialize in that while I was an assistant professor. So we were both at University of Michigan in Ann Arbor.

CARUSO: Okay. And so that position started in 1986, that's correct?

DIXIT: Yeah, yeah.

CARUSO: So when you started at the University of Michigan Medical School, I'm assuming you were given some funds to set up a lab?

DIXIT: Yes, I was. I mean, I was given money. I would say that the other really important factor for my . . . in the early days was that when I was at WashU in St. Louis with Bill Frazier, he'd given me a technician to help me with my work because I was often called to the hospital. You know, there was this liver transplant service I had to go to and sometimes the emergency plasmapheresis. And her name was Karen O'Rourke. And so I convinced her—she's, I don't know, sixth-, seventh-generation St. Louisan, very traditional German-Irish family—I convinced her. I said, "You know, I really need the help. Can you come with me to Ann Arbor for six months and just help me set up the lab?" She had to talk to her parents, to convince them. They thought she was going to another country. I'm like, it's Michigan. And, you know, the irony is she still works for me. She's my lab manager now, thirty-nine years later. So short . . . a long story short. So she came to . . . she came, went ahead of me to Ann Arbor to set up the lab. So let us say I started July of '86, and she went, I think, March of '86 to open up the cartons and get the equipment going. Obviously starts are really slow, but without her help, I would have been in dire straits.

So she was a . . . it was a real blessing. The startup money was good, but it was very evident . . . and Peter [A.] Ward, who was a wonderful chairman, he was as honest as the day is long. And he said to me, he said, "Look, you get money from grants, and you can pay your salary largely from grants, then you don't have to do clinical work. You don't have to essentially be a pathologist. You can spend your time in the lab." I was like, "Oh, okay, well, that's a great opportunity." And so I went around and asked people if they could share their R01s with me because I'd never really written a grant. You know, people are so generous. They did. So I had an idea on what to write. So I wrote my first grants, and they got funded. And then I didn't have to do any hospital work. I could just devote my energies to the research lab. So it was a . . . very fortunate again that I ended up in a situation with a chairman who was very supportive. I mean, tough, but supportive. He said if you could get your money, yeah, do your research.

CARUSO: And so you came in with grants to work on thrombospondin?

DIXIT: Yeah, I came and did work on thrombospondin. And this was, you know, I had to set up the platelets again and you had to resource them. And now HIV had happened. All of these blood-borne pathogens, it was a pain in the neck to work with platelets, but we were able to do that. And started off on thrombospondin. I had a couple of technicians: Karen, myself. I worked at the bench. And then I got my first graduate student. And, yeah, when I think back, when you're young, you're . . . you don't realize all of the risks you're taking. I think there's a great deal of . . . . I **<T: 160 min>** mean, there were some enormous risks I took in those early days, but they worked out. I think the technicians were . . . they were transient. They were only with me for a year or two, but they worked hard. My first graduate student was fantastic, Carol Laherty. And then we got our first paper or two out. We got the grants renewed. So yeah, things . . . the work on thrombospondin was really going well. It meant that I got the NIH [National Institutes of Health] grants, publications. I got promoted to associate professor, got tenure. [inaudible]

CARUSO: You mentioned . . . sorry, you mentioned risks, right? When you're young, you take these risks. What were the risks that you were taking?

DIXIT: Well, in the universities, you have a five-year period to get tenure generally and you have to be productive in that period. And so the . . . you have to be sure you embark upon projects that are both exciting but doable. I don't think those were as . . . the risks I really took to be honest, David, is the risk that I took once I was . . . during the tail end of my assistant professorship. I had been . . . I was well-funded. I had published on thrombospondin. It was clear I had enough to likely get tenure. And then I decided to take all of that and throw it out the window and start on something totally new. That was the risk. That was the beginning of the work on cell death because I could have led a happy, contented life working on what I had. But I

took that and threw it out the window because I realized that I was going to be a bit player in this field. I was dotting the i's and crossing the t's. It was a well-established field. I would have a reasonably productive career. But I wasn't going to be hitting any home runs. I wasn't going to be a prominent . . . a person who had made prominent discoveries. I wasn't going to be the childhood explorer. I was more of a journeyman. And I thought, "Well, I come all this way. And I don't want to be a journeyman. And if it doesn't work out, I guess I'll go back to medicine. But I need to really, really take a stab at something larger."

And so I used all the grant money I had from thrombospondin and embarked on cell death. But before that, there was this huge period of internal discussion with myself, of turmoil, of what do you work on? So okay, you're not going to work on what you've been successful. So now what are you going to do? What field are you going to make your mark in? And that was a very difficult question. And I really struggled with that one because it's easy to think of big questions, but those big questions have to be addressable. They have to be solvable in a reasonable period of time. And when you put those constraints, then it becomes very difficult to identify such a question. [. . .] I started thinking like that, and I thought, you know, there were many areas that were very exciting at that time. The cell cycle was exploding. But then you realize that the, sort of, the train has left the station in many of the fields that are exploding today. I mean, that early work, the pioneering **<T: 165 min>** work was already done. And so I really wanted to find more virgin territory, find a fallow field. And so I started thinking about it, and in that sense, I was influenced by my environment and I was surrounded by people who worked on inflammation, Peter Ward's lab.

And he had an Australian visitor, Rory [M.] Marks, visiting scientist who was very interested in endothelial cells. And we got talking. I was very interested in endothelial cells because they play an important role in coagulation. You know, the endothelial cell surface is the most anticoagulant surface because that allows for blood to flow. But once it gets activated, it becomes the most procoagulant because now it supports coagulation, so it supports the formation of a blood clot. So this is what . . . there was a lot of common ground with Rory Marks. And I said to him, I said, "You know, when you activate the endothelium, now suddenly the most anticoagulant surface known to man is becoming the most procoagulant surface known to man. And we understand some of why that is. There's the expression of procoagulant factors like tissue factor, etc. But if we look at it at a [mechanistic level], let us say we activate the endothelium with tumor necrosis factor (TNF), which is a very important cytokine, pro-inflammatory cytokine. What exactly are the molecular events that lead to the exposure of the surface that is now procoagulant, right?" So that was the question. He was a visiting scientist from Australia. He'd worked with endothelium. He'd worked with human umbilical vein endothelial cells, and that's what he was doing in Peter Ward's lab. And that was the question.

So when you take endothelium in culture, put in TNF, anticoagulant becomes pro-coagulant, what are the molecular events? Well, we can address that because molecular biology was in its heyday. You could ask which genes are expressed. There was a whole technique of differential hybridization. We could say we've added TNF, what new genes are transcribed, what new genes are activated? What is the program that TNF is activating that allows anticoagulant to become procoagulant? So these were the conversations we were having. And

then I said, “Maybe this is something to study that . . . let’s do this experiment. Let’s . . . you grow the endothelial cells. We know the molecular biology. We’ll do the differential hybridization, and we’ll find the genes that are responsible for this switch.” Now during this time, as I was reading about it, it became evident that TNF, which is pro-inflammatory, has another reported function that certain cells in culture that when you expose them to TNF, they died. I’m like, “What in blazes? How does that happen? They die?” I became . . . I thought what’s the pathway to death? I mean, you just don’t die. TNF is a [molecule], is extracellular molecule. It binds to its receptor. And then the receptor signals death? Well, that’s not possible, but it’s happening in these cells. What is the machinery for death? So now I became distracted with this question. I did work with some . . . Rory on this gene program that TNF activates, but now my imagination was calling up this question: why do certain cells die? **<T: 170 min>**

And so I wrote to Genentech to send me TNF. And they sent me a large amount of TNF. And at that time, I had an MD/PhD student who had joined the lab, Muneesh Tewari. And he was very ambitious. I said to Muneesh, “Let’s work on this, so here, let’s set . . .” We set up the system where you could take cells, treat them with TNF, and they would die. And I said to Muneesh, “Let’s look for inhibitors of this path. Maybe kinase inhibitors, phosphatase inhibitors, calcium chelators. There’s a whole catalog of inhibitors. Let’s see what inhibits this, because that would be a toe in the door into the pathway.” So it’s a positive selection screen; cells are destined to die. If they don’t die, bingo. You’ve hit on something. During this time, a couple of developments happened. One was Shige [Shigekazu] Nagata and Peter [H.] Krammer had defined another receptor like the TNF receptor that they called the Fas, or CD95 receptor. This receptor was more potent at engaging the death pathway, so we thought we should work on this receptor because you always want to work on a larger phenomenon. So I wrote to [Shin] Yonehara in Japan, who had an agonist antibody to this Fas receptor, and he sent it to us. And so now we have the system with Muneesh, we could take cells in culture and especially with the agonist Fas antibody. We’d put them, we’d add the antibody, and there was a spectacular dance of death that would unfold within a few hours.

The cells would bleb, they would vacuolate, they would form these apoptotic bodies, the cytoplasm would become what looked like a boil. They would essentially implode. It seemed like a very organized dance of death. Now Nagata, Krammer, [David V.] Goeddel, they’d also identified their . . . they also cloned their receptors, so now the death receptors were available for manipulation. So now we realized we had a system—a cell culture system—where we had the way we could engage the receptor, the Fas receptor. We knew exactly what that receptor was because it had been cloned and characterized. And magically, that receptor induced this dance of death. So now that set up the perfect system. It was very simple. We were going to look at inhibitors of this pathway. And in the first year that Muneesh was there, it was a massive exercise in frustration. I think we threw the entire Sigma Catalog at it. I mean, we tested hundreds of compounds. Many would inhibit. Many which were claimed to be inhibitors in the literature would inhibit, but it was always partial. And that wasn’t what we wanted. And so we never came to a point where we found a full inhibitor. And that was very disappointing. So why don’t I then take the next chapter, which is then how we made the breakthrough in our . . . is that . . . is this a good point to stop, or do you want me to complete?

CARUSO: No, no. You know, we're out of time for today. I think that's a good stopping point. I **<T: 175 min>** had one quick question.

DIXIT: Yes, please.

CARUSO: I'm just wondering if there was someone who at all you overlapped with. There's an individual who I know who was at Michigan in the early 2000s—I don't know if he started there beforehand—who worked on apoptosis, Arul [M.] Chinnaiyan?[3]

DIXIT: So he was my student, right? He came after Muneesh. Yeah, he came after Muneesh, so I had some spectacular students, yeah.

CARUSO: Yeah. I conducted an interview with him, as part . . . because he was a Pew Scholar in the biomedical sciences [Pew Scholars Program in the Biomedical Sciences]. And so I interviewed him because he was a Pew Scholar. And so when you were talking about apoptosis and cell death, I was like, "What are the chances?" I mean, then I remembered he was at Michigan, and I was like, I just needed to ask you that.

DIXIT: Yeah. And he will feature in the next segment because it was Muneesh, Arul, and a postdoc, Marta Muzio, who made the next . . . the breakthrough.

CARUSO: Yeah. And Rory Marks was also a Pew Scholar if it's the same Rory Marks that I'm thinking of. He was also a Pew Scholar of biomedical sciences, and so we have his interview as well.

DIXIT: Very interesting.

CARUSO: Thank you very much for today. I'm looking forward to picking things up when next we meet. And as I mentioned to you, if you do have any questions between now and then, please reach out and let me know.

DIXIT: Great. And is this what you wanted? Am I talking too much, too little? Is this okay?

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[3] Arul M. Chinnaiyan, interview by David J. Caruso at the University of Michigan, Ann Arbor, Michigan, 21-22 October 2008 (Philadelphia: Chemical Heritage Foundation, Oral History Transcript # 0650).

CARUSO: If you want to talk more, I'm always happy to hear more. But yeah, this is perfect.

DIXIT: Okay, great. Thanks.

CARUSO: All right. Thank you so much. Have a good day.

[END OF AUDIO, FILE 1.1]

[END OF INTERVIEW]

INTERVIEWEE: **Vishva M. Dixit**

INTERVIEWERS: **Sarah Schneider**
David J. Caruso

LOCATION: **via Zoom**

DATE: **18 April 2022**

SCHNEIDER: So today is Monday, April 18, 2022. My name is Sarah Schneider, and I am joined by David J. Caruso. We are conducting the second session of an oral history interview with Dr. Vishva Dixit online via Zoom. So thank you, Dr. Dixit, for joining us again today. And we'll jump back into the conversation following up on where we left off in the first session. So we were talking about your work on the topic of cell death, and you had started to mention that you had some frustrations, but then reached a point where you had a breakthrough. So I was wondering if you could share a bit more about that process of doing the research and when you had that breakthrough moment?

DIXIT: Yeah, you know, this was work that was initially conducted by an MSTP [Medical Scientist Training Program] student in my lab, Muneesh Tewari. And this was the time of frustration because we were looking for inhibitors of cell death. And, as I'd indicated, that everything we tried either didn't inhibit or partially inhibited. And then we were struck by this paper from Bob [H. Robert] Horvitz's lab at MIT, who'd been working on the . . . on defining the cell death pathway in the worm *C. elegans*. And they had discovered that the centrally important gene for death in the worm was a protease. And this protease had sequence similarity to a mammalian protease, interleukin-1 converting enzyme. And this was a real revelation because it suggested that a death component was a protease, was essentially a molecular scissors and that this may well be conserved in evolution. And so very quickly, we began to ask whether maybe when we were looking at death receptor-induced apoptosis, whether there was involvement of a protease like the one that Bob Horvitz had described, an interleukin-1 converting enzyme-like protease. And in order to address that question, we were very fortunate to strike up a collaboration with Guy Salvesen and David [James] Pickup, who were then at Duke University. And they provided us with an inhibitor to this protease dubbed CrmA. It's encoded by a pox virus. It's a serpin. It's a protease inhibitor. And so the experiment was blindingly simple and obvious, which was to express CrmA in cells and see if we could now inhibit death receptor. In our case, Fas-induced apoptosis.

And that was an amazing day in my research career . . . evening, I would say. I think I was writing a grant in the evening, and Muneesh Tewari, who was the student working on the experiment, burst into my office, and he said, "You have to come to the microscope." And lo and behold, cells that previously had sickened and died on engagement of the death receptor, in the presence of this CrmA, this inhibitor of ICE [Interleukin-1β-converting enzyme]-like

proteases were now in full bloom.[4] They were healthy, vibrant, divided as if nothing had happened. So we realized we'd completely and totally negated the death signal with this experiment. And what that also said was that in death receptor-induced apoptosis that the effector must be ICE or an ICE-like protease. So now the ICE protease—interleukin-1 converting enzyme—had been previously described by Nancy Thornberry when she was at Merck, and Roy Black, who was at Immunex [Immunex Corporation]. And they had defined **<T: 05 min>** this as a molecular scissors that is responsible for the proteolytic maturation of pro-IL-1β and pro-IL-18 to the mature cytokines IL-1β [Interleukin 1 beta] and IL-18 [Interleukin-18]. But our work suggested that it was likely that ICE itself or a related protease had another role, which was a role in apoptosis. So during this time, it became evident that in . . . while the worm had a single ced-3 gene, mammals had many ced-3-like or ICE-like proteases, and these were renamed with the terminology caspase.

The "c" in the caspase denotes that these are cysteine proteases. And the "aspase" denotes an unusual substrate specificity in that they cleave after an aspartic acid residue. And so the race was on to find the death protease. Caspase-1 appeared to be a protease involved primarily in inflammation because it was responsible for the proteolytic maturation of cytokines. So it dawned on us that there may be another protease that is the real death protease. And so we began a search in collaboration again with Guy Salvesen to look for this protease. And we discovered that the protease was another member of the family. We called it Yama after the Hindu god of death. But it's now known as caspase-3, sort of, a less interesting term. But it was clear that caspase-3 was the death protease in the pathway we were studying. But now we were faced with a problem, we were faced with a dilemma because you're engaging the receptor and you're activating a caspase, so you're engaging a receptor and you're activating a molecular scissors. And the question was, well, how does the receptor activate this protease? So that was a major question in the field, right. And receptors at that time were thought to function either as ion channels or by altering phosphorylation, de-phosphorylation events. So that's the way receptors signaled. This is in the early nineties. And so a lot of people started working on the favored mechanism was that it probably influenced phosphorylation, de-phosphorylation events. Now you recall that the system of death receptors that initially had been defined by the work of Peter Krammer, Dave Goeddel, and Shige Nagata had also defined that there was this . . . in the cytoplasmic segment of these receptors, there was a short stretch of about eighty residues that they dubbed the death domain.

And they dubbed this the death domain because mutations within this domain disable the ability of these receptors to engage the death pathway. So, in other words, when we looked at the receptor and asked, "How is it signaling?" We were very disappointed in seeing that the cytoplasmic face of the receptor—the entity that would do the signaling—didn't encode an enzymatic activity. It didn't encode a phosphatase, kinase. It . . . there weren't any discernible identities that would give us a clue to signaling. There weren't any known docking sites. All we knew was there was this death domain. And so the picture then was that the death receptor, using its death domain, mysteriously activated **<T: 10 min>** caspase-3, Yama, the death

[4] Muneesh Tewari et al., "CrmA, a Poxvirus-encoded Serpin, Inhibits Cytotoxic-T-lymphocyte-mediated Apoptosis," *The Journal of Biological Chemistry* 270, no. 39 (September 1995): 22705-22708, https://doi.org/10.1074/jbc.270.39.22705.

protease. So now this was quite perplexing, which was how did the death domain of the receptor activate the protease, activate the molecular scissors. And so we undertook a search to look for a partner that may engage the death domain. We postulated that maybe the death domain is a protein-protein interaction motif, and then it binds a partner, it recruits a signaling entity. And indeed, we found such a signaling entity that we called FADD, for Fas-associated death domain. Now FADD had a death domain, and so we were able to show for the first time that the death domains were nothing other than homotypic interaction motifs.

So like-like motifs. And that was very satisfying. But we noticed that FADD had another fold that resembled a death domain. And, for want of a better word, we called this the death effector domain. So now the picture was getting more interesting. We were looking at the problem at high resolution. We had the death domain of Fas that was recruiting an adapter molecule that we termed FADD through a death domain-death domain interaction, and FADD had a second death fold, this death effector domain. But again, how does it signal? We were unable to address that question till Arul Chinnaiyan and Marta Muzio, who were in the lab, did an experiment to ask, "What does the death effector domain bind to?" And lo and behold, they solved the problem in one fell swoop because the death effector domain bound and recruited a death protease, an initiating death protease, an initiating molecular scissors, that we called FLICE, but now known as caspase-8, that also contains a death effector domain. So now you can see how through the sequential binding of death domain and death effector domains we recruited an initiating molecular scissors to the receptor complex. Now what we had recruited was a zymogen form, and we showed with Guy Salvesen that induced proximity that is mere recruitment to the receptor complex is sufficient to activate it. And once you activate the zymogen, you generate the active protease. And this was very important because it said death receptors signal, not by acting as ion channels, not by altering phosphorylation, de-phosphorylation events, but rather by an entirely new mechanism.

The second messenger they generated was a protease, was a molecular scissors. And once caspase-8 was activated—this molecular scissors—it in turn went and activated the zymogen form of caspase-3 or Yama. So you had a cascade of proteases. So you can see that this leads to amplification of the signal, and cascades of proteases are well-known in physiology. That's how the coagulation system works. That's how the complement cascade works. You get tremendous signal amplification. So then we realized that once you triggered this event, you get this cataclysmic activation of proteases in a very short time, and with this abundance of molecular scissors and cleavage of substrates that leads to this dance of death or the apoptotic demise of the cell. So that was really the work that we had done at Michigan in '96, '97. And it, sort of, culminated in the solving <**T: 15 min**> of a major problem, which was how do death receptors signal. And I think subsequent work by others who made knockout mice or who did structural work completely validated the model. You know, this is something . . . you put forward a model with biochemistry and then there's much gratification when you see other people enter the field and do genetics, knock out those genes, do structural work, get an . . . get a real biophysical handle on the death domain interactions. But it all fell into place as our original biochemistry had predicted.

CARUSO: I was just going to ask. I saw . . . . I see that you published on this work starting in 1995. That was when your FADD article came out, Yama also in '95, and then the FLICE piece came out in '96.[5] You're publishing only in . . . or those publications came out in *Cell*. I'm curious to know, I mean, *Cell* is one of those top-tier journals. How did it feel to have your articles accepted to that journal? And also what was the reception of your work in the broader community once those papers were published?

DIXIT: Yeah, I would say that, you know, I had not submitted to these journals before. Most of my work was in *Journal of Biological Chemistry*, *JBC*. And so it was with some trepidation we submitted this work to *Cell*, but it seemed that it was important enough. And Ben [Benjamin] Lewin, who was the editor of *Cell*, was quite gracious, but he was also . . . he recognized its importance right away, and he helped midwife the manuscript through its phases into publication. The fact that we delineated this pathway, it was like we solved a jigsaw puzzle. All the pieces fell into place, and there was no controversy. I mean, it just seemed . . . . I had people like Nagata come up to me, and he said to me that, "When I looked at your paper in *Cell* on caspase-8 . . ."[6] And he may well have been a referee. He said, "I knew it had been solved." So getting that sort of accolade from a distinguished scientist in the field when I was relatively young was really very positive. So I think it just . . . and what it also did was it brushed aside a lot of publications that had implied other mechanisms by which death receptors operated. So that's the, sort of, nice thing, once you, if you solve a jigsaw puzzle and it's done, then the . . . all the others who were struggling with the puzzle and had fit it in a manner of a round peg in a square hole, sort of, manner, it gets brushed aside because it's solved.

CARUSO: During the review process for the pieces . . . . I've heard different tales from different scientists about how that review process goes. Sometimes articles go out to competitors, and those competitors trash pieces, say that this article is completely unsound. Some get reviewers who just, sort of, gloss over things. You mentioned that your piece was, kind of, ushered through the process, but do you have any sense of how the reviewers were responding to your piece or responding to the fact that you were publishing in a major journal having come from a nontraditional route into this research field?

DIXIT: Yeah, no, it's a very good question, because throughout my career, I've had major chips on my shoulder. And so, like I said, it was with trepidation I submitted them in the first place, I mean the first chip on my shoulder was, of course, coming from a background in which

[5] Arul M. Chinnaiyan et al., "FADD, A Novel Death Domain-Containing Protein, Interacts with the Death Domain of Fas and Initiates Apoptosis," *Cell* 81, no. 4 (May 19, 1995): 505-512, https://doi.org/10.1016/0092-8674(95)90071-3.; Muneesh Tewari et al., "Yama/CPP32β, a Mammalian Homolog of CED-3, is a CrmA-Inhibitable Protease That Cleaves the Death Substrate Poly(ADP-ribose) Polymerase," *Cell* 81, no. 5 (June 2, 1995): 801-809, https://doi.org/10.1016/0092-8674(95)90541-3.; Marta Muzio et al., "FLICE, A Novel FADD-Homologous ICE/CED-3–like Protease, Is Recruited to the CD95 (Fas/APO-1) Death-Inducing Signaling Complex," *Cell* 85, no. 6 (June 14, 1996): 817-827, https://doi.org/10.1016/S0092-8674(00)81266-0.

[6] Marta Muzio et al., "FLICE, A Novel FADD-Homologous ICE/CED-3–like Protease, Is Recruited to the CD95 (Fas/APO-1) Death-Inducing Signaling Complex."

one's race mattered a lot—a background of segregation. The second chip on my shoulder was coming from **<T: 20 min>** a medical school that nobody had heard of from the . . . in the middle of Africa. But I think what was the wonderful thing about America and the wonderful thing about society here is that if you work hard, they give you a break. And I slowly gained confidence. And when I submitted those papers, I wasn't really expecting a warm reception. But I have to say that the referees were tough but fair. And I have to really credit the editors, because obviously when you propose a new mechanism, there . . . it raises more questions than can be addressed reasonably. And Ben Lewin, who was then the editor-in-chief of *Cell*, he, sort of, stepped in and said, which is very rare today. I mean, he's a legendary editor. But he stepped in, and he said, "I've read the reviews, and I think we would be willing to publish your paper, provided you address point number three of referee one and point number two of referee three." You know, something like that.

So he'd gone through it, and he said . . . and once those were addressed, it was accepted. Now it's unfortunately, what happens is there is such an enormous surge of papers hitting the shores of the journals. It's very difficult for the editors to give the attention it's due, and it's easier when you're an editor—and I have certainly been guilty of this—is to just say, "You need to address the referee's comments." And sometimes those are not fair comments and . . . but I have to credit Ben Lewin for setting an example of what I think an editor should be. He looked at the reviews. He first determined whether the work was important, and then if he felt it was important, he looked at the reviews and decided what needed to be addressed in the reviews. And then it got published. There wasn't, sort of, back and forth that went on forever. Now that hasn't been my experience since, but I think Ben Lewin was very special in that sense.

SCHNEIDER: And did you feel like at that time there were other groups working on similar topics? Did you feel any sense of competition or urgency in getting those articles out, or was it more that you felt like you were working on this unique area?

DIXIT: There was a great sense of urgency. You know, the cat was out of the bag. And I remember—you know, it sounds archaic—we didn't have Federal Express those days. So I had on both instances for both manuscripts in *Cell*, I had the graduate student fly them out to Boston, [Massachusetts], and hand them in the office when it opened in the morning. So yeah, that was the state of affairs. It was highly competitive. We didn't want to lose. And when I look back on it, it seems bizarre one would do that, right? But you have to remember, there was no Federal Express. I mean, no, this is . . . hold on. There was Federal Express, but flying it was faster. I take that back. Federal Express had come into being, but we felt just . . . on one of the manus . . . so it sounds a bit crazy now when I think back. Sarah, you're really jogging my memory. So with this last paper—the paper on FLICE—which really solved the conundrum, this was a paper that was in collaboration with Peter Krammer and Matthias Mann, who were in Germany and our group in Ann Arbor. So we worked on it through the night, and we were in communication with the groups in Germany, and we finished editing the manuscript like at four, four thirty in the morning. We were all in the lab writing it up. We did a very quick check through. We photocopied—I don't know—they wanted six photocopies, and my technician,

Karen [O'Rourke], she drove Arul to Detroit airport so he could catch, I think, the seven-thirty flight to Boston and take the manuscript. So those **<T: 25 min>** were the heydays. So we wrote the manuscript literally overnight and flew it out in the morning. I just felt we had solved a major problem. It was just like really exciting at that time for us. It was like . . . it was another way receptors signaled, and I was just really excited.

SCHNEIDER: And you mentioned naming Yama. And I'm curious, how did the process of naming the different things that you discovered, how did that go? Did . . . you know, it's named after the Hindu god of death, is that what you said? Was that from your background, or how did those names come about?

DIXIT: No, it was interesting. It was really mostly the names were driven by the first authors, and Muneesh, who came up with the Yama name, he had a . . . he was quite a student of Indian mythology. I really didn't know of it. And he suggested the name, and it had a ring to it, so we went with it.

SCHNEIDER: And did you . . . how did, once those articles came out, you said the scientific community, it sounded like, responded very positively or saw the importance of those findings. And were you presenting at conferences and sharing your work at that time as well?

DIXIT: Oh yeah, I mean, all of a sudden—and I was not used to this—one got, sort of, jettisoned into the limelight. You were being invited to conferences. People were going out of their way to be nice to you. And the funniest thing was that editors were coming up to me and saying, "You know, we'd be interested in your work as well." And that was like, wow. [laughter] Instead of me going on bended knee, this was a role reversal. And so, yeah, it was flattering, but it was, I think, the memory I have of it is just the sheer excitement and just the joy of discovery that it had. And the funny thing is when things are going that well, you just think they'll continue. I mean, because they did continue for some time. We identified a number of other death receptors because we now had a collaboration with Human Genome Sciences and we could look at their—they called it a EST [Expressed sequence tag] library—short segments of cDNA. And we suddenly discovered that there was a death receptor three, death receptor four, death receptor five, death receptor six. All of those were published. And then we made, I think, a very important contribution—if I may say so—in realizing that this death fold had an implication that was untrue. It implied that these protein-protein interaction motifs—these death folds—were exclusively used in the death pathway. And that turned out not to be the case, that they were simply protein-protein interaction motifs that allowed proteins to come together, to assemble together to form signaling complexes. And I think there's . . . our work on MYD88. So we discovered this adapter molecule, MYD88, which is just a household term now in innate immunity because all the toll-like receptors, the IL-1 receptors, all signal through MYD88 . . . it was . . . .

But when we made the discovery, we didn't realize how major a finding it was going to be because toll-like receptor signaling hadn't really been studied. We were looking at IL-1 receptor signaling. And we realized that the IL-1 receptor engages its transducing kinases, the IRAK [interleukin-1 receptor associated kinase] kinases through this adapter molecule, MYD88, that has a death fold. So that death fold allows it to engage the IRAK kinases that also have a death fold. So this was very . . . this suddenly said that you have to look at this protein-protein interaction motif widely in other signaling pathways and across through evolutionary time. And that was indeed work **<T: 30 min>** by others showed that to be the case. But the finding of MYD88, which became I think a Pillars in Immunology article because of its importance as a conduit for signaling for a whole slew of innate immune receptors—I've mentioned the toll-like receptors, IL-1 receptor, etc.—I think underscored that point. And so that was . . . . So things were going well. We had cloned death receptors. We published that in *Science*, I think, and MYD88 was in *Science*, and we'd also defined IRAKs, a new IRAK in IL-1 receptor signaling.[7] And so, you know, in this, sort of, period of euphoria, you feel that that's the way it's going to be, right? You don't believe . . . you think . . . but, of course, all good things come to an end and eventually the field cooled off, and that was a bit of a letdown. Editors were no longer returning my calls. Other fields had blossomed, like I think it was at that time, the craze was RNAi [RNA interference] and things like that. Other things came to the fore.

SCHNEIDER: And during the period of time when there was a lot of excitement and a lot of new discoveries happening, was . . . what was the atmosphere in your lab like? And if you could just talk about, sort of, the day-to-day experiences in the lab or your work day-to-day and what that was like.

DIXIT: I would say it was very electric. I would . . . we were making discoveries just all the time. Big discoveries. I mean, discoveries that are today in the textbooks, introductory textbooks. So it was really . . . these were major findings that we were fortunate enough to make, and I think it didn't dawn on us 1) its importance and 2) the ramifications of the work. It was like solving a puzzle. We knew it was an important puzzle. It was almost like being a kid in a candy shop. You didn't know . . . and everything you, sort of, touched turned to gold. So it was this wonderful thing. You pulled things out of a candy jar and everything you pulled out was a winner. And it seemed like this was an amazing time. So there was a lot of excitement in the lab. I remember telling Arul . . . people worked extraordinarily hard, and I remember telling him that it would be worth it because this was really important work. And you also make . . . there's a saying that the worst of decisions is made in the best of times. The economists say that. But I think there's something true that when you're riding high in your own work, you sometimes probably don't take paths you could have taken. And when I say that, I mean, I was . . . this was, at the time, I was coming to Genentech and there was a postdoc in the lab who had done all the work on death receptor cloning. So we were looking through the databases, and he had found the death receptors. And then we'd become interested in the LPS receptor. And I said

[7] Marta Muzio et al., "IRAK (Pelle) Family Member IRAK-2 and MyD88 as Proximal Mediators of IL-1 Signaling," *Science* 278, no. 5343 (November 28, 1997):1612-1615, https://doi.org/10.1126/science.278.5343.1612.

to him, I said—he had some candidates for the LPS receptor—I said, "Nah, I don't know if it's that important. It's like the IL-1 receptor, probably similar pathway."

Because I was so focused on signaling. I said, "It'll probably use MYD88." Which, in fact, it does. But it was a major question in innate immunities. What is the LPS receptor? But **<T: 35 min>** we decided not to work on it, even though we had candidates. We decided, nah, we won't work on it. So sometimes I think there's very important work in front of you, but you don't realize it. And this is . . . becomes especially true in the business world. I think I mentioned when you think of Palo Alto Research Center that was owned by Xerox, where essentially the entire technology for personal computing was developed, you know, the people at Xerox said, "Which household needs a computer, right? Who wants a computer?" I mean, it didn't relate to them that they were looking at the dawn of a revolution. So I think that that happens. And when I look back, we had this opportunity. We had candidates for toll-like receptor signaling. But I was also distracted by my move to Genentech and really didn't pursue it, which, in hindsight, was a mistake. But yeah, so it was an exciting time. And I wish everybody that time in science. I think that's why you go into science. There's that joy of discovery, and you just have to realize that it's a special time and it's not going to be all of the time and that is for sure. And if you are fortunate enough to experience it, then you're truly blessed.

SCHNEIDER: And so as you were having these discoveries, you were also progressing in your career. So I'm wondering if you could share a little bit about the tenure process at Michigan, and did your . . . as you moved along, did you have a change in any of your responsibilities or how involved you were, say, in the lab or any kinds of changes in your day-to-day work as you moved through the tenure process?

DIXIT: Yeah, no, the tenure process went fine, I thought. I mean, Michigan was a very supportive school. Like I said, they were very generous in terms of letting me devote my energies to my lab work. The understanding was that as long as I [email ding] brought in my salary or most of my salary from grants that they would support me. Let me just switch off my email, otherwise I will get continual distraction. Sorry about that. Yeah, so the tenure process went fine. But what I devoted a lot of my time to was writing grants. And I think when I left Michigan, I had seven R-01 grants on which I was the principal investigator. And I had a Department of Defense grant on which I was also PI. So that took a lot of energy to have that number of grants. I mean, the science was great, so I was taking that data and the success and transforming it into grants because we needed the money. And so that was a major role that I played. And, you know, when I think back on it, it's hard to fathom the energy I must have had to write all these things. I remember that when I took flights, I would often be reprimanded by the air hostess or the staff, because I would—as soon as I boarded the plane—I would put down the [service], the desk and start working. I mean, I worked from the moment that I could till it landed, and that just seemed natural to me. But it seems very unnatural now. Yes, so it was . . . so that was . . . my role was—had changed in that to fuel this work, we needed a lot of money.

SCHNEIDER: Yeah. And how many people were in your lab? What was the makeup of different kinds of students in your lab and people?

DIXIT: Yeah. You know, I don't recall everyone, but I think we were probably a dozen people. We had an excess of money. So I never wanted a situation where somebody said, "I **<T: 40 min>** want to do an experiment," and I'd say, "Well, let's think about it." I mean, we were wise in how we spent, but we spent a lot of money because that's what it took.

SCHNEIDER: And if you had any time outside of your very busy work, what kinds of things did you like to do outside of work or in Ann Arbor? What else was happening in your life beyond the workplace?

DIXIT: Well, I was very occupied with my children because they were young then. And that just took a fair amount of juggling. My wife was in practice a distance from Ann Arbor, so that required a lot of coordination. So it was, sort of, a blur of keeping the lab going and keeping the home front going, making sure they went to their after-school activities. I . . . one of the positives was that when I think back, my wife, her practice was some distance from Ann Arbor, so she could never really go for the school activities of the kids. They were like seven and ten. And they had a lot of activities like going to the zoo, going to the museum, etc. And so that fell on me. And looking back, I'm so glad it did. But I also realized—different from today—that I was the only dad there. You know, it was the spouses—I mean, the women who did that thirty years ago. And now I'm sure if you go to such an event, there's a better mix of genders in terms of parents. But yeah, no, that was a blessing in disguise. I enjoyed those trips immensely. I could be a guide at the Toledo Zoo still. Went so many times. Yeah. But between that, there wasn't time for anything else.

SCHNEIDER: And I know that in 1994, it looked like you became a naturalized US citizen. And I'm curious, what led you at that time to pursue that? And if you could talk a little bit about anything you remember from becoming a citizen.

DIXIT: Well, it was a very special day for me—I mean, and I think I may have said this before—for me, America was the promised land and lived up to its promise. It was the land of milk and honey. It really rewarded me very handsomely, and I was really beholden to the country, to its values, to democracy. And it was a really proud day to become an American citizen. I remember it well. I have a very poor memory, but I remember becoming a citizen well. It was a wonderful day for me because I just felt that this is a country where if you work hard and you don't break the law, you know, you'll get a fair break. I'm not saying that we don't have societal problems, but I'm just saying that from a very personal experience, I was just so incredibly in debt to America that it was a very special day to become a citizen. Yeah.

SCHNEIDER: Do you remember the ceremony, and did . . . was your family there as well?

DIXIT: Yes. My wife was there. I remember the ceremony. I remember the judge. I remember really the, sort of, tapestry of America: people from many corners of the world. And yeah, I thought it was a special day. This was at the . . . we had to go to the High Court, I think, in Detroit, [Michigan], so it was . . . yeah. And <**T: 45 min**> also I felt that America is a country where it's very easy to fit in. I mean, there are other countries that have very long traditions that have been around for a thousand years or so, and it's very difficult to go to them and fit in. I think . . . Japan is a wonderful country, but I think it would be very difficult for an immigrant like myself to go to Japan and fit into society there and be considered Japanese. I just found that America was very, very accommodating in that sense.

SCHNEIDER: And you list your citizenship on your CV, and I'm wondering if that's logistical for when you do travel or if there's . . . what your thinking is as to why you choose to list that on your CV?

DIXIT: Well, I'm proud to be a naturalized American. But also, you know, surprisingly, it's much easier to travel if you've got an American passport. When I had a Kenyan passport, unfortunately, travel was quite an undertaking. I was questioned at every border.

SCHNEIDER: Yeah. And so is there anything else about your time at Michigan that we haven't delved into that you wanted to share as well?

DIXIT: No, I think we've covered the bases. I think, you know, we loved Ann Arbor. It was, sort of, the quintessential college town. It was . . . a lot of activities. The kids were very happy there. Career was going great. Everything was . . . . We didn't care much for the weather. But other than that, it was really a wonderful place.

CARUSO: I just have two questions. Since you mentioned responsibilities for taking your kids to field trips and things like that, I was curious to know whether or not you ever brought them into your lab to show them the work that you were doing.

DIXIT: Not really. Not really, no. I mean, they came on occasion, but never like did I say to them, "Look down a microscope. Do you see that thing wiggling?" No, I didn't.

CARUSO: Okay. And did you have any impressions about the science that they were learning in school? I know they were relatively young at this point in time, but I'm always curious to know what scientists think of science education in the United States in relation to how concepts are being conveyed to children and getting . . . stimulating their interest in science.

DIXIT: Yeah. That's a great question. I mean, I thought that what they were exposed to was very well-taught. And I did think, though, that later in the school years, when you go to like the AP classes, there are a lot of concepts there that are introduced to students that they master through rote learning. And I think they're better—those sort of concepts—are better delayed to college years. So I think this love for doing AP classes, I think that is . . . it reaches a point of diminishing returns. I think there are concepts in there that are probably better introduced later with a more conceptual understanding of the work. Yeah. So I think it's very important in science to have an understanding and not to resort to memorization of facts and that. And I think that for some students, it's fine in high school, for others, it comes better in college, but I think there's maybe too much pressure on AP classes.

SCHNEIDER: So **<T: 50 min>** when the position with Genentech came about, how did that come about, and what led you to decide that that was the next step that you wanted to take?

DIXIT: Well, you know, it was quite . . . when I look back, it was a series of very unlikely events that transpired. I got called by a headhunter, and they said that Genentech was looking for a person to head up their cancer group—director of cancer biology—and would I be interested? And I really . . . I thought . . . . I'd known the work at Genentech. I had known David Goeddel. I had enormous respect for Genentech. It was . . . a lot of the foundational work in biotechnology was done at Genentech. The production of recombinant insulin growth hormone. So I had wanted to visit, but the furthest thing from my mind was working at Genentech or going to industry or leaving Michigan. I was a dyed-in-the-wool academic, I felt, and the work at Michigan was going well, and I was very appreciated there. But my brother lived in the Bay Area, and I thought, "Well, this is a free trip to the Bay Area. I'll go interview and spend the weekend with him." But after I interviewed, I was very impressed with the people I met. I met with Art [Arthur D.] Levinson, who was the CEO of Genentech. I met with Sue [Desmond-] Hellmann, who was the chief medical officer. And even though at that time in the nineties Genentech didn't have a foothold in the cancer space, there was a real commitment being made by them.

And they said to me, "If you come, you'll head up cancer biology. And you'll make a difference." Because they wanted to make new sorts of medicines, antibody drugs in cancer. And so I was very impressed with that sort of commitment. I also realized and they made it abundantly clear that if I came, I could still maintain a research lab. So I thought, "Boy, I could have my cake and eat it too." I remember I talked to David Goeddel and who had that . . . he had left Genentech. He was at Tularik at that time. And he said—and I trusted Goeddel completely—and he said, "You should really give it serious consideration. Art is a straight

shooter. It is what they tell you." And that really got me thinking. And I think what eventually, sort of, swung the deal was I realized that this is not like getting a chairmanship offer or . . . that this offer may not come around again. I mean, they needed a director of oncology. They were building up oncology. It's not like they would do that every third year, right? And I also, you know, given my background in medicine, had an interest in drug development and so decided to take the plunge and move to Genentech, '97.

SCHNEIDER: And what were the discussions like with your family or with your wife? Did she end up moving and starting a new practice in California, or what was her perspective on the situation?

DIXIT: She didn't have a position, but we decided to take the risk and move with the understanding that she would try to find a position. And in the end, that did work out. She did get a position at Menlo Medical [Clinic]. She had qualified as an allergist, so she was an allergist at Menlo Medical, and she worked part-time there. And that wasn't too far from where we live so that worked out rather well. But initially when we moved, we didn't know **<T: 55 min>** that that would happen. And yeah, the move was revealing in the sense that the cost of living in the Bay Area is so much higher than it is in the Midwest. And that was a bit of a revelation for us. A bit of sticker shock there. But I think the kids in particular, they did quite well. They accommodated to the new surroundings. And I was really busy with my job, so yeah.

SCHNEIDER: And was there anything else other than that sticker shock of transitioning into, you know, more of an industrial setting or transitioning to California? Was there anything else that was a big adjustment, or did you . . . or how did it feel to make that transition?

DIXIT: You know, it was a big adjustment in the sense that I'd never developed a drug. I didn't know what drug development was about, to be honest. I was an academic researcher, and here I was leading a group of very talented researchers that created this department, and it had that, and they had recruited people from other parts of Genentech. So, for example, Napoleone Ferrara, who did antiangiogenic therapies, he came into the department. Mark Sliwkowski, who had . . . went on to develop therapeutics against HER2, came into the department. Fred [Frederic] de Sauvage, who developed a small molecule inhibitor to sonic hedgehog pathway, came in. Avi Ashkenazi, who worked on death receptors. And then I recruited Paul [G.] Polakis, who had . . . was amongst the first to implicate WNT signaling in human cancer. So it was, suddenly, I had a really great department and very talented, gifted researchers. Paul Carter, who had brought in antibody therapeutics. And so I have to . . . I would say I learned a lot more from them than I think they learned from me. And I worked very closely with some of them, especially Paul Carter, because I was very interested at that time in antibody therapeutics and the possibility of arming antibodies. And, you know, it was a . . . on the . . . from the outside, it seemed like an incredible mountain to climb. But when you got in there, you realized that you

had a lot of helpers. And this was, sort of, different from the academic setup, where each lab is its own island, its own small business entity. But here, we actually work together.

I mean, their success is my success. And the sort of resources that one could bring to bear to a problem were significant. And so it took me some time to adjust my thinking and to learn about new fields. I had to learn about WNT signaling. I had to learn about antibody therapeutics. But I really enjoyed that. I just enjoyed learning that new biology. And then the successes came. And even though the boats on these projects were launched before I joined, you know, anti-HER2 therapies were approved when I was director. Anti-VEGF [anti–vascular endothelial growth factor] was approved when I was director. So there was a lot of positive reinforcement, again, on antibody therapeutics. And again, I should say that I don't take the credit for that. These boats were launched prior to my joining Genentech, but just that the successes were coming in while I was there really added to the atmosphere that this was a brave new world for cancer therapy. And I think Herceptin, which is the anti-HER2, has had a significant impact. Anti-VEGF has had a significant impact. Anti-CD20 was **<T: 60 min>** licensed [as] Rituxan, had a significant impact. We did an alliance with AbbVie and the WEHI [Walter and Eliza Hall Institute of Medical Research] on a BCL-2 small molecule inhibitor. We did an alliance with another company for a kinase inhibitor, Tarceva. So all of a sudden, a combination of in-house research, in-licensing, alliances gave us a very respectable—in fact, more than respectable—we were suddenly top dog in oncology.

And again, I can't . . . I don't take credit for that. I must emphasize that. I just happened to be at the right place at the right time. But it was a . . . it opened my eyes in the sense of what synergy meant. You know, when you think of big projects like the Manhattan Project—and obviously we weren't operating on that scale—but it . . . what it means to be thinking outside—at least for me— thinking outside your own narrow focus, right? I was completely focused on my research lab, and now I had to attend business development meetings. I had to attend meetings with lawyers on patents. I had to attend . . . . You know, it just opened up the scope for me, so it was like an opening up of the world, sort of, a removal of blinders that . . . . And I found these people were very capable. Goodness. The patent lawyers, the people in marketing, the people in all these other areas were exceptional people, but people I'd never interacted with before. So it was a real education for me in that. Manufacturing. When you have to manufacture, you have to do cell culture, mammalian cell culture, twenty-four thousand liters, CHO [Chinese Hamster Ovary] cell culture. You go and see this thing, it's three stories high, and it's an engineering problem. So it was all of those things that really . . . that I got exposed to. It was like a torrential rain of information. And I was there drinking from a . . . as much as I could.

SCHNEIDER: So it sounds like maybe your time was used to address different things versus, I know you were saying at Michigan, at a certain point you had lots of grants and you were really focused on the grants and funding. Did working at Genentech allow you to focus more on these other elements of the work like collaboration and patents? Or do you think the grant work was . . . was the grant work still a big part of what you were doing?

DIXIT: So at Genentech . . . no, Genentech, there was no grants, right? So they . . . so we're a . . . so, remember . . . so the grants were gone. I left them, so I walked away from them. That's what people were incredulous that you walked away from them. So at Genentech, the work was funded by Genentech itself. And I worked for the company, and I had all these hats on. All of a sudden, I wasn't just thinking about my work, but I was thinking about the portfolio, the pipeline, projects, new ideas, evaluating business development opportunities. It was a whole other world for me. So it really at . . . and I have to say at one level, it was a massive learning experience. But it did take me away from my research lab. You can't . . . it wasn't like Michigan where I was completely focused on my research. You know, I was . . . I had to . . . I had other responsibilities.

SCHNEIDER: Yeah. And so could you talk a little bit more about patents and maybe your perspective on the role of patents in this phase of your work with drug development and also just in general if . . . what your perspective is on the role of patents?

DIXIT: Well, I think—and I'm no scholar in this area—but I think it's very difficult to have innovation without patents because that really incentivizes industry. I can't imagine us **<T: 65 min>** having a biotechnology industry if we didn't have patent protection. So I think that's . . . that to me is first and foremost the most important function of patents. I think that when you talk about patents, it's a very complex area. I mean, there are . . . and it gets into things like patent extensions. Should patents be extended on minor improvements or not? Can . . . should genes be patentable? But I think as society evolves, patent law evolves—sometimes slower than we wish. But I think patent law is something that is always evolving. And it should evolve with societal needs, but it should always be there because that's the only way to foster and protect innovation.

SCHNEIDER: And so I know in 2011 you had a *Nature* article about caspase—please correct me if I'm pronouncing that incorrectly—11.[8] And I'm wondering if you could talk a little bit about what went into that article and the impact of that research.

DIXIT: Yeah, you know, so I'll start . . . . So when I joined Genentech, and I would say that the outline of the death pathway was, for what I was interested in, which was death receptor-induced cell death, was pretty much . . . had been worked out, right? I mean, there were people, like I said, who did structural work. There was a lot of structural work going on. But that wasn't my forte. And that, sort of, confirmed our biochemistry. And so I was looking for other areas to investigate. And one of the areas we started working on was NF-kappaB, so NF-kappaB is a signal transduction pathway that impinges on the activation of NF-kappaB transcription factors that drives inflammation. And so I was interested in this pathway. Quite surprisingly, the NF-

[8] Nobuhiko Kayagaki et al., "Non-Canonical Inflammasome Activation Targets Caspase-11," *Nature* 479 (2011): 117-121, https://doi.org/10.1038/nature10558.

kappaB pathway also drives cell survival. So I was like, "Huh. How does that work?" And so we started working on antigen receptors—this is the T-cell receptor and B-cell receptor—and started asking ourselves, "How do these receptors that are very important in immunology, in the adaptive immune system, how do they engage NF-kappaB?" And we discovered a three-component bridge between the receptor and NF-kappaB. It's called the CBM system. It's an adapter CARD11, BCL10, a bridging molecule and then MALT1 of paracaspase. I think the most surprising thing was that we discovered this molecule that we called paracaspase, also known as MALT1.

Now why we called it paracaspase is that when we first looked at its sequence, it looked like a caspase, and we predicted that this is a protease. So it seemed that a protease was again involved in signaling. And this protease paracaspase was dysregulated in a human malignancy called MALT lymphoma. So there was some clinical interest in it as well. And working with Eugene [V.] Koonin, we found that this family of paracaspases likely has a different substrate specificity—this was on molecular modeling—but had counterparts in fungi and plants. And we called them metacaspases. And we wondered—though we didn't provide proof—we wondered if these were the long sought-after death proteases in the plant kingdom. So this was of great interest to us—the NF-kappaB pathway. And for a long time, we tried to find the substrate for the paracaspase: what was it cleaving? But that was in the end solved by others. We were **<T: 70 min>** unable to do that, but our attention was drawn to a family of kinases called the RIP [receptor-interacting protein] kinases. And again, we were drawn to this because RIP kinase 1 has a role to play in NF-kappaB activation. But it also has a role to play in cell death. So get this, you have a kinase that's doing two diametrically opposing things. It's giving you cell survival on the one hand and cell death on the other hand.

And we are like, "How can that be possible?" And this is a problem that Kim Newton, who joined me, took up. And it's a problem we work on today. It's a very complex machinery that determines how RIP kinase 1 acts. And we're still deciphering it. But I should say that at this time, we were . . . . I had done about ten years at Genentech, so '97, 2005, 2007. And I was itching to get back into the lab. And so I proposed . . . and it was approved that I set up a small group. And it was a small department—still is there—termed physiological chemistry, called physiological chemistry. And it had two faculty other than myself, Kim Newton and Nobuhiko Kayagaki, who were former postdocs. And we decided together that we would work hand in glove with each other, and we would collaborate and we would study this axis of cell death and inflammation. Because now it was evident that the other form of cell death—necrotic cell death where the cell essentially explodes—is related to it. It can propagate inflammation. So now I could go back to the lab and spend a lot of my energies not thinking about the pipeline that much, but really thinking about my own work. And so we branched out into a number of new areas. So one was the RIP kinases, we started working on this form of necrotic death, cell death, termed necroptosis, which is an inflammatory cell death.

Kim Newton showed the involvement of a kinase, RIP kinase 3, there. We also started looking at ubiquitin modification. And this is the wonderful thing about Genentech is you could do curiosity-driven research. We were wondering why, just from reading, that there is an E3 ligase in plants that runs the photomorphogenetic program. So this is a program that allows

plants to respond to light and fix carbon dioxide and is responsible for the life of plants. That's how you get photosynthesis, chloroplasts, etc. It's responsible for life on the planet. And so this regulator of plant photomorphogenesis was found in mammalian cells, and we were just—I had a postdoc—just started wondering, what is it doing in mammalian cells? And it turns out that this E3 ligase COP1 in mammalian cells is a regulator of transcription factors. It's a regulator of c-Jun and ETV transcription factors that also have a role to play in cancer. So I guess I was feeling about different areas again. I wanted that . . . I wanted the, sort of, the aura, the . . . I wanted to relive Michigan, the breakthrough of Michigan. So I was exploring different areas. That led to the study of a deubiquitinase BAP1 that's mutated in familial cancers. It's involved in histone modification.

And we did a lot of work on **<T: 75 min>** defining receptors for B-cell mitogen BAFF, we discovered with other people, very competitive. But I wouldn't say I was floundering, but I would say I was exploring areas that would become . . . that would allow us to have another burst at inventive, creative, exciting textbook, sort of, science. And, you know, often these things happen when you least expect them. So we started working on the inflammasome, and the inflammasome—this is a term coined by the late Jürg Tschopp—is the upstream apparatus that controls caspase-1. Now if you recall, I said caspase-1 was also called interleukin-1 converting enzyme. And this protease, which cleaves pro-IL-1β and pro-IL-18 to give you the mature cytokines, is highly regulated by an upstream machinery that responds to inflammatory insults. So you could imagine if you are infected with the pathogen, this machinery is going to detect that infection, is going to activate caspase-1, and you are now going to make pro-inflammatory cytokines IL-1β, IL-18 to mount a host defense response. And when you think of this apparatus, the key part of the apparatus, the effector portion, is caspase-1. But you have to have sensors that detect the inflammatory insult. And there's a family of such sensors, a dozen or so such sensors. And when we started working on it, we were . . . we wanted to define the nature of the inflammatory insults that were being sensed by each of the sensors.

And this turned out to come as . . . we had a mouse in the lab, NLRC4 knockout. NLRC4 was a putative sensor. We had knocked it out, but the mice . . . mouse lived to old age, and there was nothing of consequence. And we were quite disappointed. But one day we ran . . . . So what is the use of such a mouse? We used to use it for negative controls for other knockout animals, right? So we were once examining caspase-1 knockout animals in response to salmonella. And so we said, as a control, do NLRC4 knockouts because they will respond. The caspase-1 won't respond. And lo and behold, the caspase and the NLRC4 knockouts did not respond to salmonella, but they responded to other inflammatory insults. So we realized that there was a specialization in sensors. You had some sensors that only responded to certain inflammatory insults. So NLRC4 responded to intracellular pathogens like salmonella and shigella. And then following this work—I think it was published in 2004—it was a paper in *Nature*.[9] It received a . . . it surprised the field that there was such a sensor. But then it dawned on everybody that the other sensors must also be specialized. And then I think there were three papers back-to-back.

[9] Sanjeev Mariathasan et al., "Differential Activation of the Inflammasome by Caspase-1 Adaptors ASC and Ipaf," *Nature* 430 (2004): 213-218, https://doi.org/10.1038/nature02664.

One of them was ours that showed that another sensor, NLRP3 sensor, is a sensor that recognizes membrane damage and responds to the presence of crystalline material. So crystalline material is very important in sterile inflammation because remember, sterile inflammation is the inflammation that you get in the absence of an infection, like with an atherosclerotic plaque, or in Alzheimer's disease, where you've got protein aggregates, and they're propagating inflammation. So that's sterile inflammation, and an NLRP3's mediating that. So that was a paper in 2006, and that suddenly got us excited in the inflammasome.[10] And **<T: 80 min>** I would say that I had a postdoctoral fellow come from Belgium, Mohamed Lamkanfi. And he started working on NLRP3, and he found that it was a druggable target because you'd want to drug the sensor because you'd want to dampen the inflammation in atherosclerosis and in Alzheimer's. And so he found that glimepirides, analogs of glimepirides, an antidiabetic drug could, in fact, inhibit this axis. And that, I think, set off a real race to drug NLRP3. And now there are a number of NLRP3 inhibitors in the clinic. So that was an exciting area to get into. So more and more, I guess I was drawn—even though I sent out feelers in a number of areas, ubiquitination, NF-kappaB—I was drawn back to cell death and inflammation.

And part and parcel of that was the inflammasome. So we decided that this is what we would do. We would work on cell death, and we would look for therapeutic targets. And then Kim Newton, working with Domagoj Vucic—was a former postdoc and was a scientist at Genentech—decided that for the necroptosis pathway, they would see if they could come up with an inhibitor to RIP kinase 1. And indeed they did, as did other companies. And those are being tested in the clinic now. But so this is how, looking for the promised land here and looking for the joy of science, I sent out a lot of feelers, a lot of areas, and then, sort of, coalesced back into working on cell death and inflammation. So that is the backdrop to this 2011 paper. Okay. So now the 2011 paper turns out to be quite important, but it's a bit of a detective story. So Nobuhiko Kayagaki is a very rigorous scientist, and we were working on the caspase-1 knockout mouse that had been generated. And so this mouse had become the workhorse in innate immunity. Everybody who used the caspase-1 knockout mouse used it as prima facie evidence for the involvement of their pathway. They'd say, "Look. My pathway stimulated it, and I used it in the caspase-1 knockout, and it did not respond, so caspase-1 is involved."

So it was used to legitimize the involvement of caspase-1 in many pathologies. But Nobu realized that the caspase-1 knockout had a problem. It also lacked caspase-11. It was also a caspase-11 knockout. People hadn't realized this because the mouse strain in which the caspase-1 knockout had been done had a null mutation in caspase-11. So unbeknownst for fifteen years, thousands of papers, people had, in fact, been using a caspase-1/11 double knockout. So you could take all the conclusions and throw them in the trash. You could say it was caspase-1 or caspase-11 involved, but you couldn't say which. So that was very interesting. Like wow. And that . . . I remember I gave the presentation in Italy. And there was just pin drop silence. I mean, people realized that they'd have to revisit their work. So then the question

[10] Sanjeev Mariathasan et al., "Cryopyrin Activates the Inflammasome in Response to Toxins and ATP," *Nature* 440 (2006): 228-232, https://doi.org/10.1038/nature04515.

became, what does caspase-11 do? So we made a real caspase-11 knockout, then we started testing it. And **<T: 85 min>** again, frustration. We couldn't . . . it was . . . the caspase-11 knockout mouse did fine, died of old age. It responded to every inflammatory insult we could throw at it till one day we tried gram-negative enteropathogens: Citrobacter rodentium, Vibrio cholerae. And all of a sudden, now the mice didn't respond.

So caspase-11 was dedicated for gram-negative enteropathogens. That's what it seemed to us. Well, that was interesting. But what is it about gram-negatives that caspase-11 is sensing or what activates caspase-11? So you've got a gram-negative intracellular pathogen. Shigella. Citrobacter rodentium. Salmonella. But what is it about those pathogens that is being recognized? So we went on a search, and this was the second paper. So the paper in 2011 that you mentioned was the one where we said the caspase-1 knockout everybody has been using is the caspase-1/11 double knockout . . . is the double knockout. But then I think in 2013 in *Science*, we published that this pathway that we called now—we coined the term the non-canonical inflammasome pathway because it was . . . it responded to gram-negative enteropathogens—that this pathway was engaged, activated by LPS in 2013.[11] So this was very surprising. Because in 2011 they'd given the Nobel Prize for the LPS receptor, it was toll-like receptor 4. But we showed in this paper that the response to LPS was independent of toll-like receptor 4. So people are like, "What gives? We just gave the Nobel Prize for the LPS sensor. And now you're coming in saying that in the absence of toll-like receptor 4, your mice are responding to LPS. How can that be possible?" Now what we realized was that in our setup there is no questioning the work that establishes the importance of toll-like receptor 4.

So the way those experiments were done, is if you take a mouse that's wild-type and inject it with LPS—so remember LPS is this cell wall component of gram-negative organisms—you inject it with LPS, that mouse will die by the end of the day. If it's toll-like receptor 4-, it will live. So how did we do the experiment? Because I just said in our setting, the toll-like receptor 4 mice were susceptible to LPS. Well, what we found was that the noncanonical pathway was inducible, so that if we took toll-like receptor 4 null mice and engaged another toll-like receptor like TLR3—the specifics aren't important but another toll-like receptor or another inflammatory pathway—this led to the induction of caspase-11. So now caspase-11 was induced in the cells of the innate immune system. It was there. And then when LPS was delivered, **<T: 90 min>** it was ready to respond. So our experiment was a priming experiment. And the reason we did it—you would say, "Well, why did you do it?"—is that when you are infected with a pathogen, you're not being injected with pure LPS. Multiple toll-like receptors are being activated. So we wanted to mimic a situation that more resembled a real infection, albeit using purified molecules.

So what we decided to do was not just engage toll-like receptor 4, but to engage another receptor prior to that. And so then the . . . so what they said was that in a toll-like receptor 4-animal, they would respond to LPS. Not only would they respond to LPS, but they would die on exposure to LPS. So these toll-like receptor 4 knockout animals, the only difference from

[11] Nobuhiko Kayagaki et al., "Noncanonical Inflammasome Activation by Intracellular LPS Independent of TLR4," *Science* 341, no. 6151 (July 25, 2013): 1246-1249, https://doi.org/10.1126/science.1240248.

previous experiments to this experiment was that we had primed them by giving them an initial TLR agonist. Now, this, of course, really surprised the field. Again, because, as I said, it went right against what had been recognized, what had been recognized in Stockholm, [Sweden]. And so one way was that we made the mice immediately available to everybody in the community because, you know, if you're going to come out with an outlandish claim like that, you need to make the reagents available. And I have to say that's been my modus operandi. Everything we publish is readily made available, often at our own cost, because I want people to be able to reproduce the work. Otherwise, it's not worth it. And then there was acceptance that this indeed is the case. Now, I should say that there is work from Feng Shao in Beijing, [China], that suggests that caspase-11 itself is the LPS sensor, that the protease is the sensor.

So that's not our work. This is different work. And whether that's the case or not, I think more studies will tell. But what is clear is that there's another LPS sensing pathway. Well, now you may say, "Well, why is that important?" It's important because the, sort of, plague on modern medicine is septic shock, especially gram-negative endotoxic shock, right? It's responsible for more deaths than all the cancers put together. The statistics are shocking. Yearly death statistics from sepsis are just [. . .] it depends on the WHO [World Health Organization] figures that you take, but there's somewhere between seven to eight million a year. And the morbidity's considerable. And yet, there has been no therapy for . . . effective interventional therapy for sepsis. There is supportive care, and there's a lot of good supportive care. And so agents that were tried with much excitement was like the TLR4 antagonist because they thought you have the TLR4 is the receptor so the TLR4 antagonist should work. But that's not the case. The clinical trials failed. In fact, there have been over fifty consecutive failed clinical trials in sepsis because you can imagine this is a huge problem. Pharmaceutical industry is interested in it, obviously. But when you have so many failures, then it is either because the pathway or the disease is complex—and there's an element of that to sepsis—or you are targeting the wrong pathway.

But here we had discovered another pathway for LPS, a pathway that was important and worked independently of TLR4. So **<T: 95 min>** the question is, can this pathway be targeted? So that was now the state of affairs 2013, and we actually started looking for the LPS sensor. We started looking for the LPS sensor. And we did this with a forward-genetics approach with collaborators in Australia. And so here you take mutagenized mice or strains of mutagenized mice, and you examine the signaling pathway of interest. So in our case, it's a very large undertaking, but we developed over ten thousand strains of mutagenized mice. They're exposed to a mutagen called ENU, which is . . . introduces single nucleotide changes. There are about twenty to thirty per strain. So we can survey quite a bit of the genome. This is ongoing. It's been ongoing for years. And we removed the innate immune cells, bone marrow-derived macrophages, and we simply stimulate them with LPS. And we ask, "Is the pathway broken?" If it's broken, then something is mutated, which we can then discover. And indeed, we found something was broken in one of the mice. It was a strain called B11. And that's, I think, is the 2015 paper. And what we discovered was a protein called gasdermin-D. It's a fascinating protein.

I have to backtrack now. And I have to say, one of the major questions in innate immunity—a question that exists in cell biology—is that there are entire families of secreted molecules—in many instances, cytokines—that don't have a signal peptide so they don't go through the ER Golgi apparatus. And yet they are secreted, these are referred to as leaderless cytokines. So how does that happen? One hypothesis is that it happens when membranes get perforated. So when cells are dying and membranes get perforated, these cytokines, like alarms, leak out of the dying cell and activate the immune system. But how are these membrane pores through which this leakage happens actually formed? So it turns out that those pores that allow for the leakage of small cytokines or IL-1, 17—it's about 17 kDa—those pores are formed by this molecule, gasdermin-D. And what's really remarkable is that gasdermin-D is in all our innate immune cells. But when you activate the inflammasome, gasdermin-D gets cleaved by caspase-1 to give you a fragment p30 that oligomerizes in the plasma membrane to give you a large pore of about eighteen to twenty nanometers. So this is the mechanism by which IL-1β and IL-18 exit the cell. And this is the mechanism by which, if not repaired, the cell dies because the pore leads to electrochemical collapse, collapse of the gradient, and death of the cell. So in the search for the sensor, we actually discovered a very interesting molecule gasdermin-D.

And it turns out—not from our work, but from the work of others—that gasdermin-D-like molecules are there in fungi, are there in coral, and are there in bacteria. And in bacteria, they're a part of the innate defense system in bacteria. So this, sort of, pie in the sky research uncovered a whole new vista in biology. **<T: 100 min>** This is the 2022 paper this year about the bacteria work in [*Science*].[12] And so very . . . . But what it says is that if you could specifically target gasdermin-D . . . . I should say there are some gasdermin-D inhibitors that have been published, but they have a number of targets. But in the pharmaceutical industries, it's important to be as specific as possible. If we could specifically target gasdermin-D and prevent this form of death that's termed pyroptosis that leads to the leakage of IL-1β and IL-18 and subdue this response to LPS—this inflammatory response to LPS—then maybe this is a therapeutic entry point for having another go at sepsis or other syndromes where the immune system is overactivated. And a very good example, unfortunately, of that is COVID where you have cytokine storm. That is in large part being mediated by overwhelming pyroptotic inflammatory death of cells. So if you could subdue that, then it would help. So there's a lot of interest in gasdermin-D. So that's the 2011 paper, and I tried to put it into context.

SCHNEIDER: Yes. Thank you. That's wonderful to hear that whole trajectory of how you moved through and how the different findings built on one another. So I'm wondering how some of those decisions get made about which new area to pursue and also, if the . . . you were talking about clinical trials and clinical applications of the research and how . . . what does that look like in terms of . . . are you at all talking with clinicians, or . . . ? I'm just, kind of, curious about how these research decisions come about and are made and then also how they're translated into the drug development or the practical applications.

[12] Alex G. Johnson et al., "Bacterial Gasdermins Reveal an Ancient Mechanism of Cell Death," *Science* 375, no. 6577 (January 13, 2022): 221-225, https://doi.org/10.1126/science.abj8432.

DIXIT: You know, it's . . . the history of Genentech has been that we favor our internal discoveries. And once you make a discovery like this RIP kinase 1, gasdermin-D, you go to essentially a review committee, and you present the data. And the review committee considers it in terms of all the other opportunities. And based on that, they will make suggestions. They may need more data. They may say, "Come back after you've done this." But they'll make a decision. It's like a grant submission in real time because they give you the feedback in about a week or so. But generally they will . . . they want to help. So they will be . . . if the project gets a green light, then there are certain milestones that have to be hit. Because remember, when you get a green light, you're . . . the company's committing a lot of resources to it. And as I've said many times, the making of a drug is a miracle because you can never predict where things will go awry. And so the milestones that you hit and then . . . and the project is funded, is peopled appropriately based on the progress and the promise of the project. And so the wonderful thing about being at a place like Genentech is you can go from a lab concept all the way to a phase 3 clinical trial, all on the same campus. So, yeah, you're talking to all of the people. You know, you're talking to chemists, you're talking to people in PK [Pharmacokinetics] and metabolism, you're talking to clinicians, you're talking to . . . a huge aspect of it is biomarker group. You're talking to a lot of people, and yeah, yeah.

SCHNEIDER: Yeah. Very interesting. And so as you're doing this—the trials and the research—I guess what . . . . Well, since you took us through to 2022 a little bit, what do you see as some of the next areas of interest or areas **<T: 105 min>** emerging in the field that you think have a lot of promise or you might be interested in?

DIXIT: One of our own area of interest is we made a, I think, a discovery last year that I'm really, really excited about. And it's a discovery of this molecule NINJ1 that violates a lot of basic biology that we've been taught. So when you were in junior high and you put cells under osmotic pressure, they would burst. So it's almost we think that if you poke a hole in a cell—a large hole—then it's going to burst, much like poking a balloon with a needle. It's just going to burst, right? And all the experiments we do from junior high onward say that that is indeed the case. If you poke holes into cells, then they burst. They spew out their contents. They spew out small molecules, large molecules. Boom, it happens. And that's been ingrained in us. But we found, through a forward-genetics approach, a molecule NINJ1. And I should say NINJ1-like molecules are conserved in prokaryotes, eukaryotes, archaebacteria, so it may be a general finding, is that once you have poked a cell and you've got holes in it, the cell is dead. There's no question there. And we've always assumed that the bursting is a passive event. Boom. But we find that that bursting is actually greatly facilitated by this protein NINJ1. So, to give you as an example, if you take cells and you poke holes in them, then they will burst in a matter of many minutes. If you take a cell that's deficient in NINJ1 and you poke holes in it, it's dead.

You've poked holes in it. You can keep it overnight without bursting. So what that says is that what NINJ1 does is it accelerates the bursting process maybe by generating mega pores. And you would ask yourself, "But hold on a second here. This is an event that happens after the

cell is dead. So what's the evolutionary pressure to keep it around?" And we think the evolutionary pressure may be defense because intracellular pathogens require a living cell to replicate. But as soon as the cell is dead and if the dying cell ruptures and exposes the intracellular pathogen to the external milieu, which in mammalian cells is often very toxic with its complement and neutrophils, etc., then you're going to accelerate immunity. So we think it's part of the immune response, this accelerated bursting of cells, a response to intracellular pathogens. Now what's exciting is that some of what I've said is suggested by experiments, some isn't, but it's an exciting area to explore. So we are very excited about that prospect but also because this, sort of, bursting of cells and spewing of contents, which promotes inflammation and may be helpful in fighting an infection, in cases of sterile inflammation may be harmful. So if we could inhibit it in its sterile inflammation, then there may be a therapeutic entity there. So I think from our own research, that's what I'm really excited about pursuing.[13]

SCHNEIDER: Great. And you mentioned collaboration, I think. It sounds like you collaborate with a lot of different people in different ways, and you **<T: 110 min>** specifically mentioned some collaborators in Australia. And so I was wondering how . . . what is that like to collaborate with another group, even in another country? And what do you think are maybe the opportunities, and what are maybe the challenges of that . . . those forms of collaboration?

DIXIT: Yeah, no, this is a collaboration with Ed [Edward] Bertram and Chris [Christopher] Goodnow at the Phenomics Institute [The Australian Phenomics Facility] that . . . this is an offshoot of the Australian National University, and it is a for-profit institute, so it's actually a business deal with them. So it's very large-scale screening. But we have a lot of academic collaborations too, and I think Genentech really likes to foster them really. In the Bay Area, we have collaborators at Berkeley, at Stanford, but we have collaborators at other institutions. And I think there's a real appreciation, understanding that, you know, it's an effort that crosses boundaries, and we're all better for it. Yeah. Yeah, there was . . . sometimes it can get . . . matters can take longer than they should, but I see that happening less and less. So I'm very optimistic that industry and academia and institutions will work closer together because they see it's in their best interests.

SCHNEIDER: And I know you've . . . have a lot of different roles and things that you're doing through your work, one of them being serving on journal editorial boards. And so I'm wondering if you could talk a little bit about that service and if you have any thoughts about the kinds of articles you see to review, maybe changes in the field over time, or just reflections on that work of doing journal editing?

[13] For more about Dixit's research and discoveries he has made throughout his career, see: Vishva M. Dixit, "The Road to Death: Caspases, Cleavage, and Pores," *Science Advances* 9, no. 17 (April 26, 2023), https://doi.org/10.1126/sciadv.adi2011.

DIXIT: Yeah, I mean, it's a laborious task. I think the problem one is faced with is, sort of, the deluge of manuscripts. It's very difficult to maintain quality control. We talked about the *Cell* editor, how he had the luxury of looking at the manuscript and developing an opinion, a learned opinion. I think it's very difficult. There's just not enough hours in a day these days to do that. And I think the whole publishing industry's undergoing change. There's a lot of the bioRxiv publishing that is happening, which I think is a positive. But I think something's got to give and I don't know what it is, but I see the number of manuscripts that are being generated is just extraordinary. And you do fear that there is an impact on quality. I mean, I don't have a ready solution for it. I mean, I've thought a lot about it, but it's not like I can say, "This is what we should do." I think that it'll have to be a community decision of how we evolve our publications. So yeah, that's . . . . I wish I could be more enlightening, but I'm just flummoxed by the number of papers that comes out.

SCHNEIDER: And looking back also at Genentech as an organization over the years you've been there, have . . . is there anything that strikes you as some way in which the work has evolved over time or the organization has changed? Or just any reflections about the organization through your . . . through the lens of somebody who's had a lot of experience there.

DIXIT: Well, I think it's become a lot more competitive. You know, when I joined Genentech, in terms of antibody therapeutics, we were pretty much the only game in town, really. And now it's a huge industry. There is just enormous amounts of money in the biotech VC [Venture Capital] sector. A lot of startups. I think it's good overall. Overall, I think it's great that we're investing in this. But I think that when **<T: 115 min>** you have so much money sloshing around, you're going to go through some . . . there are going to be investments that are not productive. But that's the nature of the beast. But overall, I think it's good. But I think for Genentech, for Roche, it means that it's a much more crowded field. I mean, much more crowded. It's very competitive. We are looking, understandably, a lot externally. So we're looking at a lot of biotechs, alliances, collaborations with other companies, buyouts. So I think that . . . the business has changed. It's also become riskier. It's almost like the low-hanging fruit is gone, and the targets are riskier. They are more multi-component. You have cell-based therapies now, which are very expensive. So there's an evolution that's happening. There's a lot of promise, I think, with CRISPR-based therapies, maybe sickle cell disease, possibly, at least in the West, in the First World, may well get treated. There are still major problems.

I think the big advance in cancer when I look at it, has been cancer immunotherapy. No question. But there's still a lot of malignancies that don't respond to immunotherapy. So I think that's open to investigation. But it's an exciting time, too. I think you . . . . I just look at the last ten years, and I look at cryo-EM [Cryogenic electron microscopy] come up and, you know, we can now do structures that we didn't . . . couldn't contemplate. And then also, you look at the computational tools that we can now predict protein structure from primary sequence to enlarge quite accurately. This is work that has recently been highlighted. So I think that technology is also progressing by leaps and bounds. And our challenge is to marry the two, to marry the, sort of, really difficult clinical problems. I mean, if you got glioblastoma multiforme a hundred years

ago or you got it today, prognosis is the same. So difficult problems like that with the amazing technology that's coming about. So I think that that's the challenge but overly . . . but I'm optimistic. I'm glad to have been part and observe the revolution in medicine that has happened since I went to medical school. It's beyond . . . I wouldn't have . . . couldn't have dreamt of it really. But yeah, the world has totally changed, and our pharmaceutical industry has totally changed.

SCHNEIDER: Well, and through your work, you've received a number of awards and recognition for all that you've done. And I'd like to highlight just a few of them and just hear a little bit more about that experience of being recognized. So I know you received the G.H.A. Clowes Memorial Award from the American Association for Cancer Research for Outstanding Basic Cancer Research, and that was in 2016. And yeah, so I'm wondering first if you could talk a little bit about being recognized with that award, and, you know, just what was your reaction when you found out?

DIXIT: You know, I'm always surprised to get the awards. I mean, I have to say that it's wonderful to get the accolades, but for me, the work that's been in many instances recognized was done early on in my career. Like the death receptor signaling was done in the mid-nineties, and I thought it had been, sort of, long forgotten. But it's nice to get recognized. I think cell death is one of the hallmarks of cancer. And certainly there are therapeutics emerging in the cell death field that **<T: 120 min>** have . . . are of consequence to cancer therapy. So, yeah, it's wonderful to get the accolades. It's, sort of, ironic to get it so late in one's career for work that was done so early. But, you know, it's wonderful. It allows me to relive memories and the exciting times. And the ACR is a special organization. They're just tremendously committed to using advances in basic science to further cancer therapies. I mean, and they have done a ton in making sure through conferences, through meetings, through scholarships that that happens so to be recognized by them, very special.

SCHNEIDER: And you also are involved as a Foreign Member of the Royal Society, Foreign Member of the Royal Netherlands Academy of Arts and Sciences and have received the Dawson Prize in Genetics from Trinity College. And you mentioned a little bit about some international collaboration, but I'm curious if you could share a little bit more about what you think about . . . how you see maybe international collaboration or the community of sciences, you know, across different countries playing a role in your career or why . . . yeah.

DIXIT: I've just always found that the community of scientists is one without borders. I've had . . . when we get together, it is really as a community, and it's such an international undertaking. I do feel that we could be doing a lot more in the US in involving minorities. If you look at the number of African American or Hispanics who are represented, I think that does our society a disservice. Similarly, I would say that when we look at the developing world, there's enormous potential there and that it would be wonderful to embrace them as well. But it's the . . . coming

to the European work or the European institutions, I mean, I think historically there has been a very close collaboration between the US and Europe. And being recognized by the Netherlands and by the UK is, you know, was really special. I . . . that was quite unexpected. I know a number of Dutch and UK researchers and have enormous respect for them, but to get recognition from their learned societies was very special. I mean, I was really, "Wow. Like did they get the right person on this address?" So it was great. And it does, I think it does also underscore the internationality of science. And Ireland, too. I've been to Dublin, [Ireland], for the Dawson Prize, which was wonderful. I just . . . yeah, and when you go for these things, you meet with students, and that's always a highlight.

SCHNEIDER: And I also wanted to mention the Vilcek Prize in Biomedical Science awarded in . . . you know, you were awarded for the 2022 prize. And that organization specifically focuses on raising awareness of immigrant contributions to science and to other fields like the arts. So I'm curious if . . . I know you're highlighted on their website and have been recognized in this way. Did you give a lecture as part of this, or are you involved in any way with the organization?

DIXIT: Well, I should . . . so first, say that the Vilcek was a very special prize for me. Being an immigrant, it meant a lot. I just . . . . You **<T: 125 min>** know, it recognizes immigrant contributions to the United States and being selected was very special. And I think it says a lot about the country and the fact that we have such a prize that recognizes immigrants, given that there is, unfortunately, fairly strong anti-immigrant sentiment across many nations. So that was very special, and I think it was also in regards to what it means for scientists, I think that it says that the community is accepting of scientists from other places. But the celebrations for the Vilcek, they have . . . the major celebration is on hold because of the COVID. But I've done a number of interviews, I've done some videos for them. And that is a very special prize for me because . . . given my background and given what I'd said earlier.

SCHNEIDER: And I also . . . you brought up COVID. I'm curious if or how COVID impacted your research or the day-to-day work that you do at Genentech.

DIXIT: Yeah, no, it did impact my research because I had to work from home, and I have to be thankful for the people who worked at the bench. They didn't miss a beat. They went to work and with appropriate precautions. But I think it said a larger thing. I said . . . I think that on the one hand it said the enormous importance of science and research. And really, this is research that has gone over the decades that we were able to make a vaccine in a timely manner that literally saved millions of lives. And it's very difficult for people to appreciate prevention. You know, if you say a million people died, that has a different resonance from saying a million people were prevented from dying, but that's what vaccines do. And so it was just so incredibly powerful testament to the importance of biomedical research, to the importance of institutions like the NIH that have funded much of the basic research behind the COVID vaccine. But on the

other hand, it highlighted a more disturbing aspect, which is the aspect of propaganda and social media. And I think a failure of us as scientists and a failure of our educational system to underscore basic biology in our schools, just to say to people that do you know that 99 percent of native populations in the Americas and in Australia, 99 percent died of smallpox? And today smallpox is history because of a vaccine. And the last thing you want is for issues like this to become political. And I'd venture to say that if we had had a broader vaccine program in the US that was more widely accepted, you'd have had fewer deaths, and it would have been over sooner. So I think those are the two contrasting forces—macroforces at a societal level—that it exposed: the importance of biomedical research to a society and then the importance of education and the understanding of how distorted social media can actually cost people their lives.

SCHNEIDER: Yeah. And have you in your work been involved in any efforts to, you know, to be part of that dialogue with the public or share your scientific findings with the public in ways that you hope can . . . the public can better understand science and its impact?

DIXIT: You know, I'd **<T: 130 min>** love to. I have locally, but I think the problem is that when you run into people who don't want to get vaccinated—and I did run into one such person—it's like a religious belief. And you quickly realize that it's a losing battle. And so I think that in some ways, the damage is done when this, sort of, propaganda gets out with the anti-vax movement. And I think society—you know, there'll be another COVID equivalent, there's no question about that—but society will have to then debate whether the freedoms that we so cherish, at what level do we contain them in the interest of public health? I think that's a debate that I think needs to happen. Otherwise, we'll lose many needless lives when the next epidemic, pandemic hits because the vaccines is the answer, and once a vaccine is developed . . . . Now, thanks to COVID, the silver lining is we can develop vaccines very rapidly. So now maybe the battle is really a social battle, is acceptance of those vaccines because a timeline for development will be rapid, and will people accept them?

SCHNEIDER: Interesting. Yeah. All right, so I'd like to switch gears a little bit. And I'm curious if you've—you talked about international collaborations and work—if you've been involved at all in scientific advances or work in Kenya or in India. So, yeah, I'll start there. Have you had any research collaborators in Kenya or gone back and presented at conferences or anything of that nature?

DIXIT: Yeah, you know, in both instances, yeah, I have. I worked for the . . . as an external advisor for the Department of Biotechnology in India for maybe for a period of about twenty years where we would meet every year and discuss, really serve as a sounding board for that department, that ministry, because they want to foster biotechnology in India. And I think that was a great experience. While they have some ways to go, the Indian pharmaceutical biotechnology space is one that has grown. As you know, a lot of the vaccines are made in

India, and they can have significant impact. And I think quite rightly, the Department of Biotechnology wants to move away from India being a generic manufacturer to the next level. And I think that's the challenge a country like India faces is how do you go to the next level and be competitive in making new medicines? So those were discussions. In Kenya, and I've always given talks at . . . when I visited India at their institutes. And in Kenya, I go back every year except during this time of COVID, and I always give a talk at the institutes in Kenya. Often now these are institutes that are run by the Wellcome Trust and the Kenyan Medical Research Institute—KEMRI and Wellcome Trust—it's a joint, and they have research institutes.

I give them talks. I think in many instances the talks are to say that look, if I could make it, anyone can make it sort of talk to instill confidence in them and their . . . . I wish I could do more, but that's what I've been able to do. Yeah. Yeah. You know, it's . . . . I also work on a scientific review board for the Gates Foundation. I'm on the Science Review Board for the Howard Hughes Medical Institute. And at those forums, I try to make the case for investment in diseases **<T: 135 min>** that afflict the developing world. Obviously, Gates is committed to that, I'm talking more about the Hughes. But with the Gates, make the case more for the development of indigenous capabilities in the developing countries, rather than seeking solutions for the problems that afflict those countries on the West Coast of America, really try to propagate researchers in those . . . and develop, foster researchers in those countries. So those are the sorts of issues that I influence to varying extents.

SCHNEIDER: And I know you've been involved in some, I believe, some philanthropic work as well, perhaps with the Cheetah Conservation Fund in Kenya and some other work so I'm wondering if you could speak a little bit about that.

DIXIT: Yeah, I have. I don't know. I just really have an appreciation and love for wildlife, and I am afraid that with the number of humans that we have on the planet—I think it's nine billion by 2050—that the environmental impact may be irreversible. And in that includes the loss of many species. And so I work with the conservation funds, with Elephant Conservation, Cheetah Conservation, and World Wildlife Fund. In many instances—I also have a love for dogs—so in many instances, it's channeled through that. So there's a dog program that the Cheetah Foundation runs, and these are dogs that they keep with the flocks. They're . . . it's like a Turkish wolfhound. It's like a Turkish hound. It blends in with the wild stock, but it's actually quite an aggressive dog, and it chases off the cheetahs so that the farmers don't have to shoot them. With the World Wildlife Fund, I support a dog program that trains tracker dogs that have been disproportionately effective in keeping poaching down in Africa. So, in fact, we're going to visit the place this year—this program we've been funding for a few years now. So yeah, I try to do our bit. I just think it's . . . when I look at the environmental impact, it's huge, and it may be controversial, but I think the biggest problem the planet is faced with is that we just have too many human beings. And when you have that dominant a species on a planet, speaking as a biologist, things have got to give. And I'm afraid it's the environment. Because I grew up in . . . right next to the national parks—you can imagine seeing all these wonderful wildlife—that I think it's . . . one is honor-bound to preserve them.

But I realize the battle. I was just really shocked to see that the introduction of wolves in the western United States is such an uphill battle. I mean, they've opened up hunting season on them. You know, livestock losses to wolves are minuscule, and that's an exaggeration. And yet there is this visceral need to hunt them—so difficult. So we're talking about the richest country on earth, it's very difficult, very wealthy people, to introduce wolves. So you can imagine in Africa where you're desperately poor, and you've got an elephant with a tusk that's the equivalent of a gold bar. That's like winning the lotto if you hunt it down. So the temptations are huge, but I think we have to stop it at the source. You have to . . . there has to be education in China that really, you don't want to be doing this, the rhino horn is not an aphrodisiac. Tusks belong **<T: 140 min>** to the elephants. They don't belong to your mantelpiece. There's a huge hunting industry in America which, you know, that goes out, and you have to tell people, hunting for the joy of killing an animal? Come on. There has to be education. But I think the . . . I think it's a race. I think the younger generation is more sympathetic of having an environment, of environmentalism. And so it's a race between this younger generation being more dominant in politics and the older generation who are opposed to wolves and want to go to Africa to hunt lions and elephants. And Biden administration just approved elephant imports yesterday. So I think it's a generational . . . I think it's a race between the two.

SCHNEIDER: And I know another thing you're involved in . . . at least according to your LinkedIn page, it mentioned the Indian Scientists Abroad LinkedIn group. And I'm just wondering if you're engaged in the Indian American community, or how you see . . . if that part of your identity plays a role?

DIXIT: No, definitely. I feel that a country like India, which is the largest democracy, has a lot of potential but has a lot of problems as well. And so I talked about my work with the DBT. I also run a yearly conference—or I should say help run a yearly conference—that one of my former postdocs actually runs in India. With the local community here in the Bay Area, there is interest in helping institutions in India through philanthropic donations, and I'm often asked to advise on that. So, yeah, that's a . . . and I think that I would say, I think one needs to be a global citizen and be, sort of, when you think of countries, they're such artificial boundaries. And I think if we think of ourselves as that, and we can say that we need to help our brothers and sisters in the developing world and whatever your profession, if you can do that in any way, that's great. You know, do it. So it's more in that spirit. And that's . . . when I do the work or help with the work in Africa or in India, it's more with that sense. It's very minuscule in the scheme of things, but I think if everybody did some of that, it would amount to a lot.

SCHNEIDER: Yeah. So it sounds like you . . . mentorship is a big part of what you do in some of those instances and I would imagine with your own students and colleagues who have . . . who you've worked with as well.

DIXIT: Oh, yeah. No, I think that's . . . I think when you think of the legacy, I think this happens as you grow older, I think it's . . . we talked about the excitement of doing science and that was in the excitement of discovery. And that's amazing. But there's another aspect to that, which is the legacy you leave behind, the people you train, people like Arul Chinnaiyan and others, very, very . . . and you're proud of them and you want the best for them. And I think at times I'm a hard taskmaster in terms of the trainees I've had. But it's always been done with wanting the best. I think I've always seen it as—when I have been demanding—is trying to get the most out of everybody. It's not always easy, mentorship. But I think people are very, very capable and I know myself, I lacked confidence early on in my career and that can be debilitating. And if you lack confidence in yourself, <**T: 145 min**> that can be really difficult. And so I try to instill confidence in trainees: be brave, be confident, swing. And if you fail—we all fail—get up and try again. You know, that sort of thing.

SCHNEIDER: Yeah. So on that note, what . . . if you could talk to some people who are going into science or interested in science, what would you tell future generations about science or about our world or what kinds of lessons would you like to impart for somebody who might watch this interview years down the road?

DIXIT: Well, I think being a scientist is a privilege. I think it's a privilege that more . . . that society has bestowed on a select few that they can do science because it is such a satisfying profession. I mean, it allows you to do curiosity-driven work, and if you're . . . and that just seems an attractive way to live is to seek knowledge, is to do curiosity-driven research and especially if that research can benefit others, if your work can benefit others, then that's very special. But I would also say that you don't want to do it if it's not your passion. And I think you want to . . . whatever you do, it should be your passion. It's something you should really get excited about because there are going to be barricades and road bumps and disappointments in any career, and science is no exception. But if you are passionate about it, then those just will be road bumps. It will be water off a duck's back. It will be . . . you'll go on. But if it's not your passion, then it can really be . . . derail you. So I would say first and foremost, do it if . . . for your passion. And if your passion is being a doctor, being an engineer, whatever is your passion, do that because I think in the long run you want to be able to say, which I'm fortunate that I roll out of bed every morning itching to get to work. Just itching.

And that's great, but it's because I'm pursuing my passion. And the road is long. But it is very rewarding. It's intellectually rewarding. And there's a lot to be said for that. And your colleagues, the people you meet, your ability to learn and your ability to teach are unparalleled. And you're always a student. You're forever a student in this profession. You're always learning. And in a field like mine—molecular biology, biotechnology—you are learning at a ferocious rate. You know, you are really . . . it's a treadmill that's going full blast, and you are doing your best to keep up, but it's so exciting. So I would say pursue your passion. And if it's science, you're lucky. Lucky that you're . . . if you're in the US or in the First World. It's lucky that you have the opportunity to do it and society not only tolerates, but promotes people to

pursue science, pursue research, pursue the pursuit of knowledge. That's a wonderful testament for any society.

SCHNEIDER: Wonderful. Thank you for sharing all of those reflections. And I'm wondering if there's anything else we haven't talked about in the interview that you'd like to talk about or highlight. I know you have . . . you've done quite a bit. So just now is the time if there's anything else you would like to talk about, please let us know.

DIXIT: I think I've touched on a lot. I would say that. Yeah. No, I think I've touched a lot upon . . . . I would say that it's just important as you go through life **<T: 150 min>** is to be generous and to give. You know, you may not be rich, but you can give your time. It's important to have an impact and . . . whichever way you do that. And in that way, we will uplift society. And I'm very optimistic that by doing that, we'll help. You know, two hundred years ago, we had slavery, and today we don't. And so if even day-to-day if things look terrible with the Ukraine war, etc., I think overall, if there's a commitment from the younger generation to be more generous, more environmentally aware, more aware of each other, more aware that the planet is a living thing just like they are and needs care that there's a bright future. And for those who want to go into science, man, this is an amazing, amazing time to be in science. The tools, the rate of progress, the excitement—it's really special. So I wish everybody the best.

SCHNEIDER: All right. Well, thank you so much for taking the time to do this interview with us. We really appreciate it. So thank you.

DIXIT: All right. Thanks.

[END OF AUDIO, FILE 2.1]

[END OF INTERVIEW]

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