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Berkeley, California

Leslie Benet
The Transporter: Dr. Les Benet and the Evolution of the Biopharmaceutical Sciences at UCSF, 1965-2015

Interviews conducted by
Paul Burnett
in 2014 and 2015

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Leslie Benet, 2006, courtesy Christine Krieg Photography

**Dr. Leslie Benet** is Professor and former Chair of the Department of Bioengineering and Therapeutic Sciences, in the Schools of Pharmacy and Medicine, University of California San Francisco. Over his 50-year career, he has published over five hundred articles and six books, has written eleven patents, and founded four companies. He has served as a board member, adviser and consultant for numerous government agencies, corporations, professional associations, and scientific societies, and has received dozens of honors and awards from many universities and professional associations.

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Interview History

While doing the preliminary research for Dr. Les Benet's oral history, I was struck by the breadth and depth of his scientific interests. Not only is he one of the most prolific biopharmaceutical scientists in the world, he has also been one of the most highly cited. Evidence for his influence is everywhere, in the numerous celebrations of his research accomplishments and those of his students, and in his own central role in the promotion of the biopharmaceutical sciences at UCSF, in the United States, and across the globe.

However, these accolades pointed to a more fundamental level of inquiry for a historian of science. Dr. Benet has been both a witness to and an agent of the development of a new scientific discipline: pharmacokinetics. New sciences do not necessarily come into being as the next logical step in a research program from a parent discipline; they emerge in response to a confluence of historical forces— political, social, economic, and scientific. The purpose of this oral history then is to document the perspectives and experiences of one individual who encountered and shaped these forces from the 1960s until the present day.

Pharmacokinetics, as the word suggests, has something to do with the movement of drugs. It is the study of drug "disposition," in what manner and how fast drugs are absorbed by and eliminated from the body. This stands in contrast to a much older scientific traditions of the study of the biochemistry of drugs in the body, which is called pharmacology, or the action of drugs, which is called pharmacodynamics. Dr. Benet was the first to further distinguish pharmacodynamics, which studies what the drug does to the body, from pharmacokinetics, which studies what the body does to the drug.

There are many reasons why pharmacokinetics emerged alongside pharmacology in the 1970s, but there is a larger context worth bearing in mind as you read this history. First, important changes in the role of the state in the pharmaceutical industry and in the medical profession during the 1960s placed a premium on the investigation of the behavior of drugs in the body. In partial response to the disastrous birth defects caused by the drug Thalidomide, the Kefauver-Harris Amendment to the Food and Drug Act in 1962 required drug manufacturers to provide proof of the safety and effectiveness of drugs prior to the award of FDA approval. Then, in 1965, the Federal Government enacted the Medicare and Medicaid programs. Although a prescription drug benefit would not become part of these programs until 2006, the cost of prescription drugs was already a significant topic of political debate by the mid-1960s, as it already constituted by that time ten percent of national health expenditures. As one example of the political furor over drug costs, President Lyndon Johnson asked the Secretary of Health, Education and Welfare to convene a Taskforce on Prescription Drugs in 1967. The taskforce report concluded that the number and cost of prescriptions had risen sharply over the previous two decades, and strongly recommended more research and better education to improve the prescribing practices of physicians.[1] At the same time, the National Institutes of Health came to support much more research on how drugs are absorbed, distributed, metabolized, and eliminated from the body under different conditions.

[1] Thomas R. Oliver, Philip R. Lee, Helene L. Lipton, "A Political History of Medicare and Prescription Drug Coverage," *Milbank Quarterly* 82.2 (2004): 293-94.

The University of California San Francisco responded to these national concerns by building its own unique institutions for biomedical research and innovation. The model was one of enlightened agnosticism, which favored institutional experimentation to complement experimental research programs. The Ninth Floor Program in the Moffitt Hospital inaugurated a trend toward interdisciplinary clinical care to complement the unique interdisciplinary research programs that continue at UCSF to this day. Bridges were built across the schools in teaching at UCSF. Students in the professional Dentistry, Medicine, Nursing and Pharmacy curricula and in the various graduate programs would come to learn basic science from faculty based on their expertise rather than their school affiliation. The silos of Pharmacy and Medicine research were gradually bridged as well, and soon clinical pharmacists assumed a new role in supervising the prescription of medication for hospital patients; pharmaceutical scientists performed the assays for the clinicians in both Pharmacy and Medicine; and senior medical faculty found themselves involved in animal experiments for pharmaceutical research. And as Medicare and Medicaid programs grew in cost, clinical pharmacists were increasingly able to justify their presence on the hospital floor as a kind of cost-control measure.[2] Revenue for the Medical School and Pharmacy tipped away from fee-for-service and tuition and toward government research grants and revenue from Medicare and Medicaid.[3]

It was in this emergent center for interdisciplinary research that Dr. Benet distinguished himself. He, Malcolm Rowland, and others developed a set of methods to allow researchers and clinicians to predict the correct dosing of a drug. In an iterative process of gradually rationalizing unruly clinical and experimental data, they were able to elaborate new concepts to measure drug disposition during the 1970s that were both simpler and more accurate than previous methods.

While Dr. Benet researched the disposition of drugs in the body, he and his colleagues were also concerned with the disposition of their research through the academy. To that end, he and others founded a journal devoted specifically to pharmacokinetics in the early 1970s; in the 1980s, he created and led the formation of a new independent, dedicated association for pharmaceutical scientists, the American Association of Pharmaceutical Scientists. Consequently, this oral history also focuses on Dr. Benet's involvement in institution-building that paralleled the formation of the discipline of pharmacokinetics.

There are many paeans to the "cutting edge" nature of research of both UCSF and the Benet Lab that can be read elsewhere. This oral history is most definitely about borders of many kinds, however. It is perhaps only an illustrative coincidence that much of Dr. Benet's career has been devoted to the nature of substances that carry drugs across membranes of cell tissues and organs. Like these drug transporters and enzymes, Dr. Benet has often stood at the edge of institutions

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[2] Robert Day, *Associate Dean of the School of Pharmacy, UCSF: An Oral History*, (Oral History Center, University of California, Berkeley, 2013), 92-108.

[3] Until 1962, grant-supported research scientists did not even have faculty privileges in the University of California system. Reforms in this period, driven in part by lobbying from UCSF's leaders, made the university a center for innovation in research. Henry C. Bourne, *Paths to Innovation: Discovering Recombinant DNA, Oncogenes, Prions, In One Medical School, Over One Decade*, (Berkeley: University of California Press, 2011) 33; Kenneth Ludmerer, *Time to Heal: American Medical Education from the Turn of the Century to the Era of Managed Care*, (Oxford: Oxford University Press, 1999) 221-30.

and ways of knowing, bringing knowledge and concepts from one domain to another – from chemical engineering to pharmaceutical research, from the academy to the courts, or from industry to government and back again. His lab has been a center for many different forms of inquiry, as Dr. Benet has consistently brought in fresh questions from outside, and has selected and mentored students who do the same. Lest anyone consider this to be "merely applied" research, you will see that Dr. Benet has worked assiduously to use these interactions with the world beyond his lab to probe our understanding of fundamental biological processes. It is his insistence as a biopharmaceutical scientist, however, that this research be undertaken in order to produce healthier outcomes for sick people.

Many background interviews were conducted with Dr. Benet's students and colleagues, and the consistent refrain in most of them described his enthusiasm for his work and for life. However, one informant observed that although Dr. Benet's baseline comportment was one of joyful animation in wrestling with new puzzles, he reserved his greatest professional satisfaction for the accomplishments of his students. Mentorship and teaching were essential components of Benet's identity as a scientist, and this oral history explores how mentorship served as one more way for him to move knowledge from one domain to another, in order to beget yet more fruitful experiments and new scientific knowledge.

Although the discussion ranges over Dr. Benet's research, administrative, and teaching career, I was also very much concerned with the theme of innovation, the drivers of personal scientific curiosity, the balance of work and family life, the institutional mechanisms that foster or hinder creativity, and the evolving and sometimes blurred relationships among scientific research, clinical service, government regulation, intellectual property regimes, and industrial drug development. Throughout, Dr. Benet exhibited thoughtful patience with my questions, and contributed valuable testimony to all of these subjects for the ages.

Paul Burnett
Berkeley, CA

Interview #1 September 3, 2014
[Audio File 1]

01-00:00:07
Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Medicine and Technology Series for the Oral History Center of the Bancroft Library. It's September 3, 2014 and this is our first session and tape one. So, Dr. Benet, you're a very accomplished pharmaceutical scientist and we're going to range over your life and career and talk about, of course, your life as a scientist, as an educator, as a mentor, and as an entrepreneur, as well. So there are many different features of your life that we need to cover. As is customary with life histories, we begin at the beginning. So I wonder if you could tell us a little bit about where you were born and your family and we'll start from there.

01-00:01:04
Benet: Okay, good, thank you, Paul. I was born in 1937 in Cincinnati. My family was a drug family. Both my Uncle Harry and my father Jonas were pharmacists. As kids they worked for delivery boys for pharmacies and got interested in that and also formed a drug company. They had pharmacies in Cincinnati that were in those days what we called professional. It was only prescription pharmacies. And they formed a drug company which was really the first hypoallergenic dermatology company to make dermatological products for allergic people.

01-00:01:49
Burnett: Period?

01-00:01:50
Benet: That was all the company did, those kinds of products. And it was quite successful and I was supposed to come back and run it.

01-00:02:00
Burnett: Okay. So this was the family business.

01-00:02:01
Benet: This was the family—

01-00:02:02
Burnett: The specialty, the drug company?

01-00:02:05
Benet: Right.

01-00:02:06
Burnett: Dispensed those products exclusively through the family pharmacies?

01-00:02:11
Benet: No, no. Any hypoallergenic store or selling hypoallergenic products would have those products. The company was called Dara products. And you can still find the products in markets, in specialty pharmacies. My family doesn't

own the company anymore but the products are still there. And the same products that I knew when I was a boy are still there on the market.

01-00:02:37
Burnett: So take us back to when you were a boy growing up. When did you first become aware of the family business and was it just something you grew up with?

01-00:02:52
Benet: Yeah. I worked. I was supposed to work in the family business in summers, which wasn't a bad deal because—

01-00:02:59
Burnett: So you did work in the summers.

01-00:03:00
Benet: I worked as a stock boy in the pharmacies and sometimes in the company during summer vacation. I wouldn't say I was that interested in it but it was always implied, or more than implied, that this was my responsibility, that I was going to have to come and take this over and make it continue to go. They gave me a lot of different experiences in terms of that.

01-00:03:31
Burnett: So you learned about not just stocking stuff, but you learned about the higher functions of the business or—

01-00:03:40
Benet: Well, I don't know. One summer, but I think I was already in pharmacy school in that time, one summer I actually worked as a detail man, going out and talking to doctors about what are the new products. But when I was in high school I just worked in the pharmacies. I would be a delivery boy. My uncle owned a green convertible De Soto and when I took the deliveries I got to drive it. So I was always ready to do the delivery. [laughter]

01-00:04:13
Burnett: Right, right, right. [laughter] That's a nice car so—

01-00:04:16
Benet: Yeah, right. It was a fancy car in those days. Yeah.

01-00:04:19
Burnett: That's right. So when were you doing the detail man work?

01-00:04:23
Benet: Oh, that was after I was in college, one summer early in college. I think maybe even my first summer when I came back from school. But we're getting ahead. Okay. So we're getting ahead. So I sort of liked science. I never thought it was that wonderful but I liked it.

01-00:04:43
Burnett: It was okay.

01-00:04:44
Benet: Yeah. And I liked math. But I really liked English. I liked literature and I went to a preparatory high school in Cincinnati. It was a public school but very fine high school that you had to pass a test to get into. And you started in the seventh grade. And you took Latin. So I took Latin throughout the time that I was there and it was a very classical education. But probably what I was best at was math and English. Because of Latin I'm a fantastic grammarian.

01-00:05:23
Burnett: And a good writer on top of that, yeah.

01-00:05:24
Benet: Well—

01-00:05:25
Burnett: Well—

01-00:05:25
Benet: I found that out later. And in my senior year was when they started the first advanced placement courses for students in high school that you could get credit in college. And that was funded by the Ford Foundation. And they were called the Ford Foundation courses. And the faculty was funded and a faculty member named Professor Edwin Sauer from Harvard, in the education school, came to our high school, Walnut Hills, to teach the advanced placement English for the first year. And it had an unbelievable influence on me. Well, first of all, you had to be selected to be in there and I was very—

01-00:06:11
Burnett: Enthusiastic.

01-00:06:11
Benet: —happy to be selected. And they also had math, too. And I was selected for that also. So you had advanced placement math and you had advanced placement high school. And it was the first year it was ever offered. And it had a big influence on me. And I was really taken by Professor Sauer and wanted to become an English major. And that was my goal, to go to college and be an English major. Now, my principal was Howard Howe the Third. Howard Howe the Third was the commissioner of education in the Clinton—not the Clinton, from Georgia.

01-00:06:49
Meeker: Carter.

01-00:06:50
Burnett: Oh, Carter Administration.

01-00:06:50
Benet: From the Carter, yeah, in the Carter Administration. But his brother, Arthur Howe, was the director of admissions at Yale. And so we had this big pipeline from our high school going to Yale.

01-00:07:00
Burnett: Right, of course.

01-00:07:01
Benet: So every year about fifteen or sixteen kids went to Yale and that's exactly what I wanted to do. I wanted to go to Yale. But you had to take the advanced placement courses. Now, in those days, your parents had to sign. You couldn't just take the advanced placement courses. Your parents had to agree. My parents said, "Absolutely not." They would not sign. Yale didn't have a pharmacy school and I was going to go to a university that had a pharmacy school because I had to come back and run the business.

01-00:07:35
Burnett: How did you feel about that?

01-00:07:37
Benet: Well, had no choice. [laughter] I had no choice. So I looked around to see what I thought was the best university that also had a pharmacy school.

01-00:07:48
Burnett: And also had a good English program.

01-00:07:50
Benet: Yeah, right. And that was the University of Michigan. And I actually was not aware of Berkeley in those days. But I wasn't aware that Berkeley had the connection with the pharmacy school. So I went to Michigan. And I was the first freshman at the University of Michigan not to take freshmen English. We were the first advanced placement students that came to Michigan.

01-00:08:16
Burnett: To be granted—

01-00:08:16
Benet: Three of us came that year that had taken these Ford Foundation courses. And we took a test and I remember taking the test. And one of the three got selected and it was me. I was selected as the person who didn't have to take freshmen English but I had to take sophomore English. I had to take English classes. So I was pretty much along in the curriculum. I didn't get credit for math but I got credit. Rightly so I didn't get credit for math. But I did get credit for English.

01-00:08:48
Burnett: So you felt you weren't quite as strong in math as you were in English?

01-00:08:52
Benet: Well, actually, I thought I was pretty strong but I screwed around or fooled around a lot.

01-00:08:57
Burnett: It didn't inspire you the way that English did.

01-00:08:58
Benet: Yeah, it didn't inspire. But I liked it. I liked math and always did. Always liked mathematics. But I went to Michigan and took advanced math classes and stuff like that. But I didn't get waived out of anything. And I had to go to pharmacy school, so I signed up to go to pharmacy school.

01-00:09:21
Burnett: But you have an AB [Bachelor's degree] for—

01-00:09:24
Benet: Right, okay. I was in pharmacy school for about a year and a half and while I was there I figured, "Since my parents are paying for me I better start working because I really want to drop out of pharmacy." So I started working outside jobs, waiter and stuff like that, and at the end of my sophomore year I felt I could probably support myself if my parents refused to support me and I came home and said, "I'm dropping out of pharmacy. I'm going to go into English."

01-00:10:01
Burnett: What was the reaction?

01-00:10:03
Benet: Not good. It was not good. They actually didn't cut me off but they were really upset because it was really the family plan to—

01-00:10:12
Burnett: Did you feel conflicted?

01-00:10:14
Benet: I don't remember feeling conflicted. I remember feeling, "This is what I want to do."

01-00:10:19
Burnett: Passionate, right.

01-00:10:20
Benet: And, "I'm enjoying this." I got a lot of feedback, positive things in English. I did very well and was a creative writer and did very well in all the English courses and especially in the writing courses. Took poetry courses and would sort of win little awards and things like that as an undergraduate of Michigan. Nothing really special. And I also had at that time as a faculty person Donald Hall. Donald Hall became the poet laureate of the United States but at that time he was just an assistant professor at the University of Michigan. I was graduating in English and started to apply to graduate school. Because, actually, what I wanted to be was a university professor. When I was a kid, that's what I thought—

01-00:11:18
Burnett: That was your idea of a good life?

01-00:11:19
Benet: Yeah, a good life.

01-00:11:20
Burnett: Of a meaningful life.

01-00:11:20
Benet: Yeah, that's right. I wanted to be a university professor. In high school I don't think there were many kids that said that's what they want to do. But that's what I did want to do. I thought that would be a very interesting and enjoyable life. And I had a lot of good models to look around in terms of Dr. Sauer and other people that I had seen. So I applied to graduate school in English at Michigan and a few other places. I went to see Mr. Hall. I asked him for some advice. I asked him would he give me some advice. I had had the class. I'd done very well in his class and I was going to apply to graduate school. And he says, "Okay, give me your portfolio." And I had a portfolio book of stuff that I had done. And I gave it to him. And he said, "Come on back in two weeks and we'll talk about it." So came back in two weeks. And he said, "Les, I've had you in class. I think you're very dynamic. I know you want to be a faculty member." He says, "I think you'll be an excellent faculty member. You'll really be influential on students and you'll enjoy your life. But I have to honestly tell you, you'll never be a poet."

01-00:12:32
Burnett: Wow.

01-00:12:33
Benet: Pretty grateful. I knew it. I needed him to tell me.

01-00:12:38
Burnett: Yeah?

01-00:12:38
Benet: Yeah. I knew it at the time but I needed him to tell me. Because in some sense I really thought academia was sort of a fooling around. And you could really sort of enjoy yourself, really good life.

01-00:12:56
Burnett: And explore, yeah.

01-00:12:57
Benet: And you didn't really have to be that great a poet and you still could do well and teach. But he told me that and I knew it and I said, "Thank you, Mr. Hall." In retrospect, pretty unusual that somebody would be that honest.

01-00:13:14
Burnett: It is. But it's kind of the way he phrased it. He could have said, "From my experience, I think you—." You appreciated the directness but he also had the confidence that he knew about your future. I don't want to jump ahead too far but you're a mentor. You have been a mentor to people for decades.

01-00:13:45
Benet: Yeah, I would do that.

01-00:13:45
Burnett: You would do that?

01-00:13:46
Benet: I would do that. But I had had him in a class. I was not his graduate student and somebody that he had a lot of responsibility for. He was somebody that I really admired. So he could have just said, "Looks really good and go ahead." But I was pleased that he did it, in retrospect.

01-00:14:10
Burnett: Well, but what's interesting to me is because you've just said what was important to you is you wanted to be a professor and being a poet is not a prerequisite of being an English professor. So there's something else that was meaningful to you there that you wanted validation for, you wanted to find a path in. And he said no to that.

01-00:14:34
Benet: Right.

01-00:14:35
Burnett: And you felt it yourself, though. That's a rapid set of transitions to go through.

01-00:14:40
Benet: But, as I said, Paul, I think I knew it. So, for example, my wife, who was also an English major, who I met at Michigan, had attended some of my—when I would present to the class. She had attended those. She wasn't my wife yet but she was all into that this is what I was going to do. And I would read my poetry and be involved and so I think she would have accepted that. And we've talked about it. She sort of pictured herself on a porch at some little school in Ohio, Kenyon College or someplace like that, or Antioch or something like that, with students around you talking. And I had had an experience like this with a biology professor named Marston Bates, who I had a very close relationship with. I had had that interaction, of being at his house and spending time with his family and being sort of accepted as a professor/student relationship. So that's what I wanted to do. But I guess, now that you bring it up, yeah, I wanted more. I wanted to be a poet and I wanted to be a successful academic in addition to being just a teacher. Successful outside of the university itself. Yeah.

01-00:16:01
Burnett: Yeah, yeah. It wasn't just literary criticism or reflection upon some author or poet. You wanted to *do* that in the world.

01-00:16:11
Benet: Right, yeah.

01-00:16:14
Burnett: I don't know. So in other words, you have that honest conversation and then what's the next step?

01-00:16:24
Benet: Well, I went back to pharmacy school. I needed another year. And, in fact, in those days you couldn't get two degrees. You had to be a full year in the field. So I had to go back and do a full year in pharmacy. I had done enough that I could finish it in a year and a half, and applied to graduate school in pharmacy and went on to graduate school at Michigan in pharmacy.

01-00:16:47
Burnett: Did you apply to other schools or did you—

01-00:16:49
Benet: No, just Michigan. Actually, I don't even remember. In English I applied to other schools because I thought it would be competitive and I might not get in. In Michigan I was pretty sure I would get in so I probably only applied to Michigan.

01-00:17:03
Burnett: Well, let's talk about the graduate work that you did.

01-00:17:15
Benet: Okay. So I went in to Michigan as a graduate student. It was a pretty good program. Today I could rank all schools in all fields. I think as a student then I had no idea. I had no idea how good a school it was compared to other schools. But it was a good school overall, University of Michigan. It wasn't the best graduate program in pharmaceutical sciences but it was good and respectable as a university. And my first year in graduate school I had to make a decision of who my major professor would be. And that was an interesting idea also. So I had taken this class from Jere Goyan, who had come from California, was an assistant professor, and I also took a class from Ara Paul and I actually did my first research in Dr. Paul's laboratory at Michigan. He eventually became the dean and is still a very good friend at Michigan. Basically pharmacy, a lot of pharmacy in those days was just memorization. You memorized stuff and then you went and passed the boards and then you went out and practiced.

01-00:18:35
Burnett: Dispensed, yeah.

01-00:18:36
Benet: Dispensed and things like that. But Goyan was really strong mathematically and did all his course – which was called physical pharmacy, which was physical chemistry applied to pharmacy – in terms of mathematical ideas and derivations and treatments. And I was really intrigued. I really liked it because this is my math side. And I liked it a lot. And if I think back, I might have been the only person that really liked it in the class.

01-00:19:12
Burnett: This is something that education experts are agonizing over. What is this excitement around math? And it seems to be rare. Can you talk a bit about your enthusiasm for math?

01-00:19:30
Benet: Well, I like to solve things and math is relatively quick solving things. Maybe I didn't know I liked to solve things but I did at that time. Taking all these courses where you learned about drugs and you learned about ointments or capsules or tablets, it was just routine stuff.

01-00:19:54
Burnett: Yeah, yeah, rote learning.

01-00:19:55
Benet: Rote learning and routine type things. But you had to actually think about this. You had to think of why this did this or what was the derivation of this or even try to come up with a hypothesis why this would happen in terms of interactions that were going on with these pharmaceutical systems. And I was just so intrigued. And it was mathematical and you could solve it. And if you were clever enough you would figure it out. It was a solvable problem. Later on when I went into graduate school, I had the same feeling. I didn't have any feeling that I was creative in that class. It was just that I could solve the problems. It's sort of like doing a Sudoku today. You're not very creative but you can do it and you can think it out and you can work it out. So I never thought I was creative in doing this. It just was so intriguing to be able to think about it like this.

01-00:20:54
Burnett: Did you have a sense of Dr. Goyan's creativity or Dr. Paul's?

01-00:20:59
Benet: Yes, yeah, yeah.

01-00:21:01
Burnett: In the teaching there was a spark of—did they lay out narratives of how they approached experimentation?

01-00:21:12
Benet: Not so much with Dr. Paul. It was sort of fun research to do but it was not where I was going to go. But Goyan, later on, I could see myself doing these kinds of things. I didn't really at the time but I could see them later on and, of course, that's what I eventually did. But I had an issue first because the famous man at Michigan was named Dr. Mattocks, Al Mattocks. He was a pharmaceutical manufacturing person and so all of the people that came out of Michigan that did really well came out of the Mattocks lab. Goyan was a new assistant professor. Paul was a new assistant professor. So they had no credibility.

This is a really interesting thing. Mattocks's class was at night and you'd go to class. And once the class got canceled. There was a notice, "Class canceled tonight, we'll meet on such and such a date." When we came back he said why it was canceled and I recall going home, because I was married now, telling my wife, "Guess what? You know last week when Al Mattocks's class

didn't take place? The reason was because he went to Chicago to consult for a chewing gum company," because he was interested in formulations and so forth then. "And, Carol, guess what? They paid for him, first-class in the train, and he even got paid for the consultation and then they brought him back first-class in the train." I said, "I didn't know faculty members did stuff like that." I thought that's pretty neat.

01-00:23:01
Burnett: In the space of a couple of years you've gone from an image of the academy as ivy covered, genteel, perhaps—

01-00:23:10
Benet: Right. Yeah, yeah.

01-00:23:11
Burnett: —ennobling—there are all kinds of adjectives that come to mind in describing sort of the old college image of the professor—to something new for you.

01-00:23:23
Benet: Right, yeah.

01-00:23:24
Burnett: Well, how did you feel about that?

01-00:23:27
Benet: Okay. So I thought that was really interesting. I said, "I didn't know faculty members did that. I didn't know faculty members got paid outside of the university for their expertise and did things like that." So then I had to make a decision. "Am I going to work for Mattocks who was the famous guy or am I going to work for Jere Goyan who did this?", and I would have been his first student, or I was his first student, who had this intriguing mathematical background and stuff like that. And I went around and talked to a lot of people and got a lot of different advice and then decided, "No, I'll do Goyan." It was just much more interesting and the projects are going to be more interesting.

01-00:24:09
Burnett: Scientifically stimulating.

01-00:24:11
Benet: Right, yeah. Yeah.

01-00:24:13
Burnett: So just to get a little bit larger context, the immediate context is you got married. Can you tell us a little bit about that?

01-00:24:28
Benet: Okay. So I had a little brother in the fraternity from Buffalo, New York in my fraternity and he told me that, "Next year there's a woman transferring from Skidmore, from Buffalo, who is perfect for you."

01-00:26:44
Burnett: Wow.

01-00:24:46
Benet: Yeah.

01-00:24:49
Burnett: So it's kind of almost arranged through the fraternity? [laughter]

01-00:24:51
Benet: Right. Showed up. Showed up. She showed up, I met her on November 19th and—

01-00:25:01
Burnett: Of what year?

01-00:25:02
Benet: Of '58.

01-00:25:04
Burnett: Well done. [laughter]

01-00:25:06
Benet: [laughter] But she was very popular, I was very popular, so we didn't have a date until January of the next year, something like that. But I went home at Thanksgiving, told my mother, "I met the woman I'm going to marry."

01-00:25:23
Burnett: Wow.

01-00:25:23
Benet: I said, "I haven't had a date with her yet. I met the woman I'm going to marry."

01-00:25:27
Burnett: Wow, wow. That's pretty inspiring.

01-00:25:30
Benet: Yeah.

01-00:25:36
Burnett: How did the entrepreneurial possibilities – did that make a light go on in terms of the family business or did you think of it in those terms?

01-00:25:49
Benet: No, not at all. Not at all. Because I was really trying to escape from the family business. Because the family still expected me to come back now. Okay, so here I am in graduate school studying the kinds of things that would lead me to come back and run the company. Not the pharmacies but the manufacturing company. And to do the research that would develop the new products. So the family is still thinking I'm going to come back and run the company. And that's when I worked as the detail man, after the first year in graduate school.

Or, no, maybe in pharmacy school. It's a little hazy when that was. But the family now still thinks I'm coming back.

01-00:26:31
Burnett: Right, right. Well, this is the 1950s, right?

01-00:26:35
Benet: Early sixties. I entered graduate school in '60.

01-00:26:37
Burnett: Okay. So this is the early 1960s. And in the 1950s, obviously pharmaceuticals had become very political, right, and pharmacists had become active and they were complaining about having to stock me-too drugs from the pharmaceutical companies and they wanted to stock brand substitutes, for example. And so a National Pharmaceutical Council was established to improve relations between doctors and pharmacists, to raise the profile of modern pharmacy. And this is 1953. And so that's the history books. Is any of that in the air at the time for you?

01-00:27:26
Benet: Yeah, okay. Yes, it is. But I have a different view of it. As I started to do research I began to think more that what was exciting was the discovery. Yeah, yeah. And a couple of things. One, my father was really good at making new products. And I *never* thought I had that skill. So I think in some sense I was afraid to go back and do that because I wouldn't have the same skill. My uncle was fantastic at business, my father was very good at developing new products. And so I didn't think I had either of those skills. But what I thought I did have was being clever and coming up with new ideas, new scientific ideas, and solving problems that hadn't been solved in the past. So that was there, but I wasn't paying much attention to it because I was going to be sort of strictly research. I don't think I told my family that yet but I had moved away from that aspect of it in terms of deciding that just didn't interest me. Now, later on I got very involved in all of those issues. But at that time I wasn't paying attention to it. Yeah. Yeah.

01-00:29:03
Burnett: Right, right, right. But you're in the middle of graduate school at that time. It's the early 1960s and your advisor if Jere Goyan. Right. And you would have graduated—

01-00:29:21
Benet: From Michigan.

01-00:29:21
Burnett: —from Michigan.

01-00:29:22
Benet: Yeah. I would have graduated in 1964 from Michigan. Yeah.

01-00:29:25
Burnett: Yeah. So what happens to change that course?

01-00:29:29
Benet: Okay. So he got recruited here.

01-00:29:32
Burnett: Okay. UCSF. Yeah.

01-00:29:32
Benet: Well, there's an interesting aspect before this.

01-00:29:36
Benet: Troy Daniels, who was the dean, came out to visit Michigan and visit Jere, or just visit the University of Michigan because he was actually a University of Michigan graduate. And he asked me if I'd be interested, when I graduated, in coming on the faculty at California.

01-00:29:51
Burnett: Really?

01-00:29:53
Benet: Because I was thought well of, certainly by Jere and those people. And in those days, the dean sort of made the decision of who was going to come out.

01-00:30:00
Burnett: Yeah, that's right. That's right.

01-00:30:02
Benet: And I told him, "Yeah, I'd be interested." He said, "I know you're still a couple of years away." "Yeah, I'd be interested in it." And so I already sort of thought about that, or he had put it in my mind of whether I would be interested in this. And then Jere got recruited back on the faculty member. So I had to make a choice. I actually had three choices to make. Well, first of all, I could have just stayed at Michigan and probably finished the experiments and graduated from Michigan and communicated back and forth with Jere. I could have come to California with Jere but still graduated from Michigan. Or I could come to California and graduate from California. Okay. So the bad part about coming to California and graduating from California is I had to take my qualifying exams over again and I had to take the German and French language again because in those days you had to do that. Well, that wasn't so bad because I was pretty good in German and French, so I didn't mind that. But taking the qualifying exam. Michigan was strictly the physical chemistry approach. And California was the biological approach. So if I was going to take the qualifying exams here I had to learn some biology. Now, in pharmacy there's biology but in Michigan you could have got through pharmacy and sort of faked your way through most of the biology courses. And everything was based on physical chemistry and manufacturing and all those aspects. So I made the choice to come to California and graduate from California and to take the qualifying exams. Boy, I remember I really said, "Boy, am I stupid!"

you know when I'm out here that first year—because it took me an extra year to be able to do it.

01-00:31:50
Burnett: So there are qualifying exams to be granted the doctorate?

01-00:31:55
Benet: To get to the PhD, yeah. Yeah.

01-00:31:57
Burnett: To get to the PhD?

01-00:31:57
Benet: Yeah, to get to the PhD. So basically—

01-00:32:00
Burnett: To become ABD or all but dissertation—

01-00:32:02
Benet: Yeah, that's right. That's right.

01-00:32:02
Burnett: Equivalent. Yeah.

01-00:32:04
Benet: Yeah. When you finish your coursework, then you take the qualifying exams, and then all you need to do is finish your research.

01-00:32:08
Burnett: Right. Can you talk about the research that was part of Jere Goyan's lab and did he—

01-00:32:15
Benet: Okay, so yeah. Here's something else that's really amazing and it's in those books that you maybe read about. Jere believed that every instrument you worked on you should make yourself. Because he was very handy. He was electrically handy, he was handy in all aspects of it. And so I was working on pH, trying to understand how the pH, the acid-base balance, and how to understand different aspects of it. And so he thought I should make a pH meter. And that wasn't so bad. You could buy a Heathkit in those days and you could make your own pH meter. My pH meter wasn't so good because I couldn't get it grounded properly, so you had to work barefoot on it so it could be grounded. So it had a sign on it that says, "The no-shoe pH meter," something like that. But it worked fine. [laughter] Except for those grounding things.

01-00:33:20
Burnett: So that wasn't a voltage consideration, was it? Were you in danger if you—

01-00:33:24
Benet: No, I wasn't in danger. I wasn't in danger. Just didn't have the right grounding. And it's partly because of all the instruments here in the hospital. Okay, so I got that to work. But that wasn't that hard. But then what my major thesis was on was the thermodynamics of chelation of tetracycline. Because in those days it was thought that the way tetracyclines worked, these antibiotics worked, is they would attach to a metal ion, calcium in the bacteria, and they would break the wall open of the bacteria. So that was the theory. And so I was going to do the thermodynamics of that interaction. So I had to build a calorimeter to do this, to measure like .0001 degree changes. That took me a long time. That took me a long time to do.

01-00:34:13
Burnett: Well, this is not just jerry-rigging something. These are precision instruments.

01-00:34:16
Benet: Oh, no. Yeah, yeah. When I built this thing there was no better calorimeter. You couldn't buy a calorimeter that was more accurate than the one I built at that time.

01-00:34:29
Benet: And, in fact, of the two years I was here, it took me two years minus two weeks to build the thing and then I got all my data in two weeks.

01-00:34:41
Burnett: Did they give you a degree in engineering as a good—

01-00:34:43
Benet: No, no. It was just something that Jere expected that you—no, I have no expectations of that of any of my graduate students. That is crazy. You buy the best instrument you can and you make it—but that was what he believed and so I had to do it. It was very challenging. And I'm not so sure I would say it was very educational or worthwhile. I got through it. I got through it. I don't think it really had a major impact on me in terms of later years. It just was something really hard to do. But I got it to work and I got a couple of papers out of it. What my real papers, that were really important, were my pH papers. Those got pretty well cited, even in those days. And they're certainly the most cited papers that Jere published. And I did make some advances. And I began to realize I could think on my own. And that I could come up with it on my own. And Jere was terrific at back and forth, ask each other the right questions and try to go solve it. This was all theoretical and then I would run the experiments to see if I could prove that what we thought was right was right. It did. It turned out to be right. But the really interesting thing about this, and I'm not sure that this is anything written before. Is that what we did in Dara products was change the pH of the formulations. That was our innovation. We changed the pH, because the allergy was to soap-type things.

01-00:36:30
Burnett: Right, right. So it's alkaline, you make it a little more acidic.

01-00:36:31
Benet: Yeah. And we changed the pH and so the major advance in those products and the big secret in those days was changing the pH. And then here I am five years later or something doing theory related to pH, which I probably didn't even realize at the time. But I've thought about it in the past, isn't that interesting.

01-00:36:57
Burnett: Well, was the pH research program already going when you joined Jere's lab?

01-00:37:07
Benet: No, it was brand new. I was his first student.

01-00:37:08
Burnett: So you're his first student?

01-00:37:10
Benet: His first student and how do you solve this problem? It was multi-particulate ionization and how do you solve for it? And how do you get the right pKa of drugs and stuff like that.

01-00:37:23
Burnett: So it's just a coincidence.

01-00:37:28
Benet: Yeah. It's a coincidence. But the further coincidence is when I went to Washington State, my first biological research was pH in the intestine. So pH, at least in my early career, was essentially sort of all from a different aspect.

01-00:37:49
Burnett: Did that set you on a path to—

01-00:37:55
Benet: Well, no, it didn't set me on a path. It didn't set me on a path.

01-00:37:59
Burnett: In terms of thinking about how you think about problems or how you think about—

01-00:38:02
Benet: Think about problems, yeah. But not that it was pH. That wasn't the reason of it.

01-00:38:10
Burnett: I'm thinking more of styles of reasoning or approaches to problems, that you're influenced by Dr. Goyan and you're influenced by Dr. Paul a little bit.

01-00:38:23
Benet: Right. I'm always interested in – this is the dogma. Is it right? Is it correct? And can I prove to myself that it's right or not right. And the dogma about pH wasn't right and the dogma about thermodynamics of chelation wasn't right.

And the pH in the intestine wasn't right. So all of my projects are always "I don't necessarily believe that and let me prove to myself that it's true." And that is sort of a lot of times the basis of what I do. I read something and I say, "That doesn't sound right. I don't believe it. Yeah."

01-00:39:12
Burnett: Is it because something doesn't ring true for you or is it because it sounds too simple? Is a dogma by definition a reduction?

01-00:39:20
Benet: No, not necessarily too simple. My stuff is simple. Everything I do is simple. It's just you haven't thought it correctly through. You haven't put everything together correctly.

01-00:39:34
Burnett: Yeah. And there's a negative instance of something. If someone says, "It's always like this." There's, "Here's a case where it doesn't work and here's a suggestion as to why."

01-00:39:43
Benet: Right, yeah. So I've written this a couple of times later and I've used it in speeches, graduation speeches. What I try to teach clinicians is to suspend disbelief. And we can come back to that later. But what I try to teach scientists is to suspend belief. Yeah.

01-00:40:03
Burnett: Yeah. That's important.

01-00:40:05
Benet: And that's sort of what I do. I don't believe it necessarily. I want to prove it to myself.

01-00:40:14
Burnett: Challenge the conventional wisdom.

01-00:40:14
Benet: Yeah, right, yeah. Yeah.

01-00:40:15
Burnett: Yeah, yeah. So you're conducting experiments on pH and completed those with your instrumentation and that gets written up and you have your doctorate from Berkeley.

01-00:40:37
Benet: No, from here [UCSF].

01-00:40:41
Burnett: Your advisor –

01-00:40:41
Benet: During the period of time I was here, the graduate program at UCSF was established. Okay. Although I had to have a Berkeley faculty member on my thesis committee.

01-00:40:55
Burnett: Okay. For that to be okay. Right.

01-00:41:06
Burnett: Okay. Can you talk a little bit about the transition to your first position?

01-00:41:16
Benet: Okay. I had a bunch of offers to do post-docs. Because I think I was viewed as a star graduate student. Les Benet is a California graduate and he's got real potential.

01-00:41:36
Burnett: The word got out.

01-00:41:37
Benet: Yeah, right. So I had a bunch of offers. But I thought, "Why would I waste my time doing that?" because I could get a faculty position and make much better money and have complete control over what I do. Now, my colleagues at UCSF at that time, if they did post-docs what they did was to go to Europe. And that was pretty neat. But I had a new baby and stuff and I wasn't interested in doing that. And so I had two offers. One was from Kansas and one was from Washington State for a faculty position. And what happened at Washington State was the previous people who were there—there was an NIH grant—they were leaving. The senior guy was still there but he really wasn't doing the work. The people who had left, one had gone to Iowa, one had gone to Ohio State, they were the guys doing the work. And so there was an NIH grant that I could immediately move in and it was on pH. Okay. And it was on intestinal pH. It wasn't exactly—

01-00:42:40
Burnett: It was different.

01-00:42:40
Benet: —that but there was enough of it that was that that I could do and so that's why I went to Washington State.

01-00:42:47
Burnett: So not only did it have this position, it had this research money that was already attached to it.

01-00:42:50
Benet: Right, right.

01-00:42:52
Burnett: And you could complete the work.

01-00:42:54

Benet: Right. So I was hired to teach analytical chemistry because I was a good chemist and to teach physical pharmacy, which is what my PhD was in. Physical chemistry applied to pharmaceutical systems. And this grant, though, was in biological systems. Pharmaceutics and biological systems. Now, Professor Riegelman told me when I was a graduate student, I don't remember saying this but I remember him telling me, that I had told him once that I would never do any work with biological systems because they were too inexact. [laughter] He told me that later on when I came back to UCSF. And I said, "My God, did I say that?" [laughter] He said, "You definitely said that. You said you would never do that. You couldn't believe any of the data from biological systems."

01-00:43:47

Burnett: The body is not reliable? Or the measurements of the body aren't—

01-00:43:48

Benet: The measurements and reproducibility. Reproducibility. That's what I told him. It's just impossible to have trust in the reproducibility of that data. That's what he told me I said. I don't remember saying it at all but he told me I said that. [laughter]

01-00:44:05

Burnett: I think that's something that's striking about this kind of research, is the modeling. When I first looked at these papers, they seemed so very removed from the body, right. So very abstract. This is calculus. These are statistical formulae. Can you talk about your comfort with the kind of work that you do and how this is—

01-00:44:38

Benet: Let me tell you another really interesting thing about writing my PhD thesis.

01-00:44:40

Burnett: Of course.

01-00:44:41

Benet: Because there was no copying machines or anything when I wrote my—I got my PhD in '65. There was a Selectric typewriter. That was the big advance. And so you could use carbon paper and do it. But I had all these equations in my thesis and I was going to hire somebody but nobody could do it. So I actually had to type my thesis myself because I had to get the equations and get the superscripts and subscripts the same way. You couldn't hire anybody to do that. And I can show you the thesis later on. It's pretty terrible when I look back at it now. [laughter]

01-00:45:19

Burnett: Well, you had to build your own calorimeter, you had to do your own —

01-00:45:24
Benet: pH meter and I had to type my thesis. And I tell my students today, in fact, you couldn't copy it. If you made a mistake you had to go back and white it out.

01-00:45:33
Burnett: So there's this enthusiasm for abstract representation of functions in the body that you're undertaking.

01-00:45:48
Benet: But not anywhere near what I ended up doing. Okay. And so the break is I read some of Riegelman's papers and Malcolm Rowland's papers and I was reading it because of the mathematical stuff in it. In the first place this is wrong. They've got it wrong. They've got the math wrong. And there's much easier ways to do this than the ways they're doing it. So that's how I started to get interested in that stuff. So I wrote Riegelman. I said, "This is wrong. These equations aren't right. Here's the correct way to do these equations and to do this." And we published a paper on that. So that was sort of my first pharmacokinetic paper, along with Riegelman and Rowland, in terms of just correcting something that they had done before. And then I sort of looked at all of this math and said, "God, boy, I know how to do this so much easier than the way these guys are doing it."

01-00:46:45
Burnett: So it was overly complicated in their approach?

01-00:46:47
Benet: Right, yeah. And not using higher math. So when I was a Michigan graduate student, when I was there—since then, Dr. Amidon, who's at Michigan, got a master's in math – but I took the most math of any Michigan pharmaceutical chemistry graduate student. I took some of the advanced courses in math. Operational mathematics and that's how I did Laplace transforms and things like that and was able to really simplify much of what people were doing. There was a whole bunch of papers that were just wrong in terms of the conclusions that they were making and it was because they didn't understand the math.

01-00:47:29
Burnett: Okay. Can you walk through an example of an inappropriate use of mathematics that you then corrected?

01-00:47:38
Benet: Yeah. Okay. So what Riegelman was famous for was realizing that if you were going to model the body, you needed to use more than one compartment. So pharmacokinetics was compartmental and everything up to Riegelman's time was really saying the body is just like one big bathtub. And Riegelman said— and there were clues in the literature but he mathematically did it—that you can't do that. You got to have at least two compartments. So you have the compartment you can sample, the blood, and you have another compartment.

It actually is a hypothetical compartment but people didn't realize that. So if you look at those two compartments, and they interconvert, okay, because one's sort of a—you could think of it being a tissue or the muscles and the other one being the blood and the organs. But how does drug get eliminated from that? It could be eliminated through the blood compartment or it could be eliminated through the other compartment. Okay. So there's actually three mathematical models that can fit them. One where the elimination only comes out of the blood compartment. One where the elimination only comes out of the second compartment, the tissue compartment. And one where it comes out of both. Okay. You can solve those. And the way people were doing it, they were using something called micro-constants, where they had little constants on each of the parameters. And people were writing papers trying to say that it goes this way or it goes this way or it goes both. And there were more than three. There were a bunch of papers in the literature. I looked at it mathematically and said mathematically it's impossible to tell the difference. It's all just how you're fitting the data if you get an answer one way or another. It's impossible mathematically to tell the difference between these and you don't want to use micro-constants. They aren't the correct way. You have to use these macro-constants. And that's sort of my 1972 paper on pharmacokinetics and stuff, saying, "Okay, this is how you approach it." But those were a whole bunch of papers just completely wrong. The conclusions that, okay, well, then it's happening here and therefore the way LSD works is it's out in the tissue and it's having its effect there and so on – all nonsense. It was just mathematically nonsense.

01-00:50:06
Burnett: Right, right. And experimentally—well, in terms of—

01-00:50:10
Benet: Impossible to tell experimentally.

01-00:50:13
Burnett: Right. Right.

01-00:50:18
Burnett: Okay. And the compartmental model has to do with the—the proxy for measuring the drug is the—

01-00:50:35
Benet: Blood or plasma.

01-00:50:37
Burnett: Right, the blood or plasma.

01-00:50:39
Benet: Or urine actually.

01-00:50:40
Burnett: Right. But that represents the impact at the receptor, the—

01-00:50:49
Benet: Right. Everything that's going on is represented by that concentration. And you're trying to mathematically figure out what's going on as a result of those single-place measurements that only allow you to measure in blood. Yeah. If you want, I could give you another really good example of this.

01-00:51:06
Burnett: Sure, sure.

01-00:51:06
Benet: And this has clinical relevance and this was one of my early advances in pharmacokinetics from a mathematical point of view. The aminoglycosides, which are a series of very strong antibiotics that you take with really serious disease, okay, they sort of all work the same way. There's a bunch of them – gentamicin, amikacin – there's a lot of them. If you were going to prove efficacy for these drugs you definitely—they were killing the bugs that are in your blood, so you just look at the blood and you want to get the concentration right. Okay. So everybody knew that. So here's how we decide to give these drugs so we kill the bugs, because we know what concentrations will kill the bugs and we need to get up to that level. But they have two toxicities. One is ototoxicity. You become deaf. You become deaf from these drugs. And the other is kidney toxicity, which kills you. Okay. So what people were trying to do was develop dosing regimens to keep blood levels in this range to be efficacious but not to be toxic. Okay. But mathematically the toxicity was not in the blood. It was someplace else in the peripheral compartment. So when I first looked at that I said, "That's impossible." You can't do it because 86% of the way the body gets rid of the drug is in the plasma and you're trying to predict the toxicity that only represents 14% of the thing. You'll never mathematically be able to do this because you're trying to use something that really is the blood and think you're going to predict something that's 14% over there. And that was one of the earliest sort of clinically relevant things that I did, using mathematics to say, "No, you're not doing it the right way. This isn't the right way to approach it and mathematically here's the reason it won't work. You'll never get this right." And labs all over the world were doing this because they're trying to get the efficacy right and the toxicity wrong. And so people would publish nomograms that this is how you should dose and this is how you should do your dosing and basically they were based on the results that this hospital got that said, "Okay, these guys were okay and these guys weren't." But anybody else that tried that nomograph, it would never work. It was only that set of data. And that was just because they had the mathematics wrong. It wasn't that they hadn't thought it out; they'd never thought about it at all. They just thought you should be able to develop a dosage regimen that would allow you to predict this and I could mathematically show absolutely you'll never be able to do this.

01-00:54:09
Burnett: And was there a spur then to develop some other measurement for where it was—

01-00:54:16
Benet: No. I knew how to dose it. I told them how to dose it. What I said was the toxicity never depends on the plasma levels. Okay. Only efficacy depends on the plasma levels. So they were worried they were getting too high in the plasma levels. I said, "What you want to do is to prevent the drug from accumulating in the tissues. So what you want to do is give the biggest dose you can immediately. A *huge* dose. And stop! And you won't get the toxicity and the drug will be around for long enough." And that's basically what we do today.

01-00:54:50
Burnett: Right, a wallop. Right.

01-00:54:52
Benet: Yeah, yeah. With all of these compounds. But I knew mathematically from putting the things together that you'll never be able to get the concentration in the ear or the kidney—it didn't make any difference what the concentration was. You wanted to get as much as you could. And they wouldn't have any toxicity. And I did that in the early seventies. Yeah.

01-00:55:14
Burnett: Wow.

01-00:55:15
Meeker: We should probably change tape.

01-00:55:17
Benet: Okay.

01-00:55:17
Burnett: Yeah.

[Audio File 2]

02-00:00:13
Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Medicine, Technology series. This is session one, tape two. Dr. Benet, I wanted to go back and talk a little bit about—going all the way back to Cincinnati and talking about your family background. How did the Benets end up in Cincinnati and can you tell us some of those stories?

02-00:00:37
Benet: Okay. Sure. It's just one family. So my mother and father were related. My mother's grandmother and my father's mother were sisters and so I'm my own cousin and every one of my relatives is my cousin in addition to being everything else. And I'm actually very good at that, about once removed and telling you how to define what relationships are because in our family it's something that should be done. They were Jewish and came over in the pogroms in Lithuania in the late 1880s and I think essentially the whole family—different parts of it came over. My mother's family and my father's

family, because they're the same family. My father's mother came. All she had was a wooden paddle for washing clothes in a stream. And we have that and it says the year on it, 1889, that she brought from Lithuania when she came over.

02-00:01:49
Burnett: That's incredible.

02-00:01:50
Benet: She was about twenty when she came over. My mother's father came over when he was three and he was the second boy in a family of six boys and a girl. And they came to Cincinnati. I'm sure there was some relative that I don't know about but that was what was the driving force, the Cincinnati. And they all came to Cincinnati and then we have North Platte, Nebraska, and Denver, Colorado, and Los Angeles.

02-00:02:23
Burnett: The branches –

02-00:02:24
Benet: The brothers sort of moved out from Cincinnati but at one time or another they all came over. Like many Jewish young men, early in the century, they were all boxers, the men. And so I have pictures of grandfathers and great-uncles and things like that, boxers.

02-00:02:44
Burnett: Wow.

02-00:02:46
Benet: That's what you did. That's how you got out of the gutter. But my mother's father was a very successful printer and same printing family was in Denver. So they were printers really.

02-00:03:02
Burnett: Right. That was the trade.

02-00:03:06
Benet: My Uncle Harry, who never had any children, my father's older brother, and my father—their father was a peddler. So they sold newspapers. I have a picture of them selling newspapers on a corner in like 1905 or something like that, and then working in pharmacies. They worked in Millers Pharmacy, I think, I can't remember the street but someplace in Cincinnati, as delivery boys and assistants and decided this is what they want to do. My Uncle Harry went to University of Kentucky and was a graduate pharmacist from the University of Kentucky and my dad went to the University of Denver and was a classmate of Hubert Humphrey's—

02-00:03:57
Burnett: Wow.

02-00:03:59
Benet: —at the Denver College of Pharmacy, which doesn't exist anymore. And basically he went out to go fishing or something like that and decided, well, he might as well go to school at the same time. [laughter] Come back and joined his brother in the business in Cincinnati. So that's the basis. Now, they became very successful because they entered pharmacies—it's very interesting, too, because of the life timing in my family. Until my son, who was an officer in the Marines, none of my forbears were in the service because there wasn't—they were too young for the First World War, they were too old for the Second World War. Same thing for me. I was too young for the Second World War and by Korea and Vietnam I was already in graduate school with a family. So nobody was really in the service. But what really helped them, and, of course, helped all pharmacies at that time was the Volstead Act, because the only people who could have alcohol licenses were pharmacists. And there's no doubt that our family did well in terms of—

02-00:05:19
Burnett: For the medicinal properties of—

02-00:05:20
Benet: The medicinal properties of alcohol. I don't remember because I wasn't old enough but I've been shown some of the warehouses they had on the river where the boats would come and bring the alcohol, which they were allowed to have. It wasn't illegal, but it was a very successful business.

02-00:05:46
Burnett: Yeah. High-volume business.

02-00:05:47
Benet: Right.

02-00:05:50
Burnett: And did you have any siblings?

02-00:05:51
Benet: I have a brother who's five years younger than me. He went to MIT. Started off in electrical engineering, finished in electrical engineering. But like me, then got a double degree, got a biology degree. And then he followed me to Michigan and got a master's in computer sciences and then he followed me to Washington State and was in graduate school in computer sciences in Washington State and then he went and worked for the University of Alberta and then he went—

02-00:06:23
Burnett: Were you there at the same time?

02-00:06:24
Benet: Yeah. He came while I was there. He sort of followed me around. [laughter]

02-00:06:28
Burnett: You are obviously close.

02-00:06:31
Benet: Yeah, we're close. He lives in Greenbrae now. And then he went and worked in computers and then he was at Simon Fraser University. And when Oracle started, he's a hardware person, he's a machine person. And Larry Ellison tried to recruit him very early. I think when he first made an offer to him he would have been like the seventh or eighth employee at Oracle. And he didn't accept it. He stayed. But I think he came maybe about the sixty-fifth or seventieth, eighty and he still works for Oracle.

02-00:07:06
Burnett: Fantastic.

02-00:07:07
Benet: It's been a very good career for him, too.

02-00:07:10
Burnett: Wow. So was your family active in the Jewish community in Cincinnati?

02-00:07:18
Benet: Yeah, very active.

02-00:07:19
Burnett: Because it's a very active community in Cincinnati.

02-00:07:22
Benet: Right. And my mother was president of Hadassah, which is the Jewish Zionist organization and she was president for the Midwest. My father was very active in the American Zionist organization. And they were very active in terms of when Israel was formed and being involved in that.

02-00:07:41
Burnett: Is that something that you have continued to be involved with?

02-00:07:44
Benet: Not so much. I am. I'm involved but not to the extent that they were. I've interacted very strongly over the years with schools in Israel, in the field, and have had post-docs from there. But I haven't been to the same degree that they were.

02-00:08:07
Burnett: And you've mentioned in passing your own family and so you married your wife, whose—

02-00:08:14
Benet: Carol.

02-00:04:15
Burnett: —name is Carol. And you said in the early sixties you had a young family. Can you talk a little bit about your family?

02-00:08:23
Benet: Okay. So I'll give her family background. Her mother was from Watertown, New York, and her father was from New York City and their family came from southern Russia, okay. Her father was an encyclopedia salesman and very knowledgeable guy. Never graduated from college. Ran away from home to join the army, to be in the army in the First World War, just like his son did in the Second World War.

02-00:09:07
Burnett: Wow.

02-00:09:09
Benet: But a very good family in terms of learning and valuing education. My wife grew up in Buffalo. She went to Skidmore the first year because, when she visited Skidmore, she saw skis on the steps of one of the houses and she thought this would be a good place to go. She was supposed to go to Vassar but when she went there there were no skis on the steps so she went to Skidmore. But she didn't like it and so she transferred to Michigan and then I met her. And she was an English major. But really in French and since has got a PhD in comparative literature at Berkeley and taught at Berkeley for a while. Yeah.

02-00:09:56
Burnett: Wow, great.

02-00:09:57
Benet: My son, Reed, was born in 1962 in Ann Arbor. We know the day, August 16th, because it was my advanced physical chemistry final exam and she had a final exam in one of her literature courses. I had a downstairs neighbor who took the exam. I told him to tell Professor Cated I was up all night and the child was born but he didn't tell him. He was going to tell him after the exam. So in the middle of the exam he calls me because I'm not there and I'm actually in the hospital or I must have been at home sleeping because the baby was born. And he said, "Why aren't you there?" I said, "Didn't Mr. Allen tell you that my wife had a difficult birth last night and I was up?" He says, "Oh." He says, "Oh, no, he didn't tell me that." He says, "Okay. When you're rested come and see me." He says, "What was it? Boy or girl?" I said, "Boy." "Yeah, congratulations. When you're rested, come and see me." So I did. I went to see him about a week later and he pulled out his grade book. He says, "You've done pretty good." He said, "I don't think you need to take the exam." But my wife, she had to retake her exam even though she was the one that—so we remember that day [laughter] well. Just celebrated it, August 16th. So he was born in '62. I came here in '63. So '63 to '65 and then we went up to Washington State and my daughter was born a couple of months after we got there, August 27th. So she was born in Pullman, Washington. Pullman was

a very nice town. When your kids were young it was a good place to be. But I got recruited back here, came here in ’69 and had the really good fortune—my wife made the decision to buy a house in Belvedere in 1970. Wow. I wouldn’t have had to do anything else in my life but buy that house. [laughter]

02-00:12:18
Burnett: Right, right. The way things have turned out. Yes.

02-00:12:20
Benet: Yeah, to buy that house in Belvedere. So it’s been a good life since then. And I have six grandkids.

02-00:12:28
Burnett: Wow, great.

02-00:12:30
Benet: My eldest, of my son, my son lives in Birmingham, Michigan outside of Detroit. He’s a senior at the University of Michigan studying pharmaceutical sciences and is going to apply to graduate school in the next couple of months, including here. Worked in my lab three summers ago. I thought that would be a pretty neat thing.

02-00:12:51
Burnett: Without any pressure, presumably.

02-00:12:53
Benet: No, without any pressure.

02-00:12:58
Benet: All my nephews and my kids, and everybody worked in my lab but nobody wanted to be here until this kid. But it looks like maybe my eldest grandson, who’s a sophomore in high school, of my daughter may also want to be a pharmaceutical scientist. They both think that looks like a pretty good life. Yeah.

02-00:13:13
Burnett: Right. Well, we’re more or less caught up with the family and personal side of things. We can launch into your return to the University of California San Francisco. Can you talk a little bit about how that took place and what you encountered when you arrived. Things had been happening in the interim while you were gone.

02-00:13:41
Benet: Sure. Oh, yeah. Yeah, yeah. Well, first of all, they wanted to recruit someone in physical pharmacy and they went after one of the leading guys whose name is George Zografi, who was out at the University of Wisconsin, he was actually a Michigan graduate. When I was a first year graduate student he got his PhD. But he turned them down, luckily, and they offered it to me. From my years as a graduate student, no one thought I knew any biology. So I was recruited back here to teach the same thing I taught at Washington State,

which was analytical and physical pharmacy, even though I had started doing this biological stuff. The school was in turmoil in terms of what to do with the curriculum and how to interact with the accreditation agency when I came back. In fact, we had already not passed our accreditation visit, UCSF. And we did a couple of things that really the agency didn't like. One of the things is Dean Daniels was a real leader in believing that you bring in scientists to teach scientists, not necessarily pharmacists to teach scientists. So all of our basic-science faculty at UCSF, when I was a graduate student here and when I came back, were non-pharmacists. And the accreditation agency didn't like that because basically it was pharmacists who taught pharmacists all aspects of all of the things at that time.

And the other thing is we were in the process of creating this new paradigm of clinical pharmacy and changing the curriculum and changing what people would do in terms of their training. There was much less emphasis on the physical aspects of it but that was still what was the primary relationship of pharmacy and the accreditation agencies. The school actually was going to fight it and I came back—I was already hired but I wasn't here yet when we had an all-school faculty meeting about how we should respond to the accreditation agency. And I took the position – very vocal – took the position that we shouldn't really fight it. Let's just paper it over. And that's what the school did. We just said, "Okay, yeah, we'll do—," but we ended up still doing what we were going to do. But we sort of papered it over in terms of what we presented to the accreditation agency instead of fighting it. Jere actually wanted to fight it. He felt that it was really important for pharmacy that we break away, with a strong break, from what had happened in the past and that clinical pharmacy was where we should go. I'm sort of amazed sometimes that I did take that position because I've been known not to take positions like that.

02-00:17:29
Burnett: Earlier on you had a more diplomatic—

02-00:17:32
Benet: I was more diplomatic. Actually I'm still diplomatic.

02-00:17:35
Burnett: Yeah. Yeah, yeah, yeah.

02-00:17:35
Benet: I'm still diplomatic. And we got through it.

02-00:17:44
Burnett: And the accreditation agency was the American Association of—

02-00:17:47
Benet: No. The ACPE, American College of Pharmaceutical Education. American College? It's ACPE, yeah. Yeah. [ed. note: American Council on Pharmacy Education]

02-00:18:06
Burnett: So you alluded to the path that UCSF was on towards clinical pharmacy. And others have talked about this. There's an interview with Bob Day about the development of that. Can you talk about your understanding of the development of—

02-00:18:25
Benet: Yeah. It sort of happened while I wasn't here. It happened in the four years I wasn't here. Really the impetus to make it happen was in the four years I wasn't here. We started the curriculum in '66 of offering a Pharm.D at UCSF as our only degree. Four years at UCSF and theoretically you could get in after two years. In the early days you could but you can't anymore. You really have to have an undergraduate degree to get in today. And an emphasis on clinical practice. We got rid of a number of the physical dispensing courses and got rid of some of the pharmaceutical administration courses and did it related to the clinical practice. In other words, bringing it out of the basement up into the floors of the hospital. The leaders were Sid Riegelman, Don Sorby, and Eric Owyang. Eric was the chief pharmacist in the hospital at that time but his academic appointment was in our department.

The big impetus was to get the ability to have a service in the School of Medicine agree that we could work together with them on the floors, and Surgery allowed us to do that. And the clout that Riegelman and Sorby and Jere had allowed that to happen. They didn't really do it. Who did it were the clinical pharmacy people. And Bob Day was among them but not—Bob is still more of a formulations person than a really clinical pharmacist. But Toby Herfindal, Bob Miller, people who really led what was going on, established the ninth floor practice. And it was very successful and the School of Medicine liked it. Department of Surgery really liked it and it gave, for the first time, the pharmacist the ability to interact with physicians and to be able to make recommendations and to be involved in the decisions about drug dosing of patients. And so it was a major change in the world of pharmacy, in the world of therapeutics, and it happened here and we're all very proud of it. It's really interesting because when I came back here, when I first came on the faculty, all of those people were still seniors. I taught a bunch of them so I had really a good feeling about interacting. Mary Anne Koda-Kimble was a student. I taught a lot of them.

02-00:21:30
Burnett: Great, great. But as far as your work was concerned, how did this change, affect the kind of research you did or not—

02-00:21:42
Benet: No, it didn't.

02-00:21:44
Burnett: It didn't.

02-00:21:45

Benet: It didn't. It didn't have an effect. It sort of had an effect on teaching. And we didn't really have that impact until clearance concepts, which I've written on quite a bit. We were there but it was just different rote learning. It was now rote learning that was more biological and more physical and understanding the applications of drugs. But in my mind we weren't bringing a unique aspect of information that didn't exist in the medical community. There were many physicians here who really opposed clinical pharmacy and said, "There is no pharmacist that knows as much about drugs and patients than me." And really challenged them. And what was happening then is that our people were spending a lot more time paying attention to it and learning it and being involved in it. But in my mind there was no unique aspect to it. I think we started the unique aspect with pharmacokinetics in terms of our ability to make drug-dosing decisions that were rationally based on theory that could be explained in terms of pathology and physiology, that would then lead to a rational decision of drug-dosing recommendations. And so that was a major impact. As you know, that happened in the early seventies. Yeah. And the clearance concepts, coming from the paper in 1973, was really important. We didn't realize it at the time but it certainly had an unbelievable impact in terms of the practice of not only pharmacy but clinical pharmacology in medicine in terms of how we treat patients and being a rational way to understand drug dosing and how you can take a blood sample and use that blood sample to make some correct decisions of how you're going to dose a patient.

02-00:23:59

Burnett: Well, when you got there in '69, can you talk about that work that led to the clearance concepts?

02-00:24:13

Benet: Well, okay. What was I working on in '69? I was working on intestinal absorption.

02-00:24:16

Burnett: That's right, yeah. Intestinal drug absorption.

02-00:24:19

Benet: I was still working on intestinal absorption, of pH effects in terms of understanding intestinal drug absorption. Malcolm Rowland was in the offices next to me and because of the mathematical things I started dabbling in pharmacokinetics and started writing papers about how you could do these things mathematically much easier than were being done and here's simple ways of approaching this. And Malcolm and I just started talking. How can we explain what happens in terms of drug elimination in the liver? What are the characteristics? Can we mathematically talk about that instead of putting it into a compartment? Can we mathematically understand what's really happening in that? And it was hard. I remember. His office was next to mine. We would sit and talk and think about it. He was the major person I think in terms of putting the conceptual concepts in there. I was just part of sort of the

sounding board and the interaction in terms of understanding it. But I can remember sitting there and saying, “Well, how do we deal with the fact that blood comes back from the heart and also comes from the hepatic portal vein and that it mixes in the liver and are we going to be able to treat that? Do we need to treat it? Is it going to be mathematically important in how we approach this and how we approach the different aspects of it?” And we thought, “Gee, okay, here’s a way to do this.” We were intrigued with what the chemical engineers were doing. I had taken a course in chemical engineering at Michigan, unit operations, so actually knew some of that stuff. And Malcolm was very good mathematically in it and we said, “Well, let’s take these papers that these guys Bischoff and Dedrick were publishing and see if we can understand what they’re talking about and apply it to pharmaceutical systems. They were trying to predict what’s going on in all the tissues and things and using what we call physiologic-based pharmacokinetics. But Malcolm and I were trying to get down to much more basic things. What changes to make this change? What happens when blood flow changes? What happens when the enzyme changes and can you predict what’s going to be the outcome? Whether it’s going to be important or whether it’s not going to be important.

02-00:26:55

Burnett: There are various biographical descriptions of this period of research. In the late sixties, early seventies, so you’re studying intestinal drug absorption, starting with an in vitro mechanistic model, then migrating to in vivo animal models and healthy human volunteers. This sounds like much more concrete experimental practice. For someone not familiar with the science of pharmacokinetics, can you talk about the various kinds of scientific experimental practice that go into producing the research that you’re doing?

02-00:27:41

Benet: Okay. So what we were doing in terms of the intestinal membrane and the transporter—I thought, okay, the pH effects but also there’s electrical effects. And so I had this very complicated machine. I didn’t build it but I contracted for the service here to build this very complicated machine so we could measure all the electrical aspects of what was going on in an intestinal tissue and things like that. Some of our early papers related to that. But we didn’t think that was good enough. So I wanted to get an in vivo model that I could use. And in those days you could work on monkeys. And so I had monkeys that I got the GI surgeons and the urologists to operate on my monkeys to put in the right kinds of catheters so I could feed them where I wanted to feed them and sample where I wanted to sample that I couldn’t do in humans. Okay. And so those were the experimental protocols.

And, in fact, at that time Michigan tried to recruit me back. So this has to be mid-seventies. But when they found out what I was doing with monkeys they didn’t like it. They thought it was just too much and it was too difficult, the kinds of things that we were doing. They still made me an offer but they

didn't want me to come and I didn't want to go there anyway. I didn't want to go back anyway. But I recall that they looked at the monkey model that I had in terms of saying that's really more—because they were still physical [physical chemistry]. It was still a physical place. And that was not something that fit in.

So I became an experimentalist. In fact, I've always been an experimentalist. I do the theory stuff when I can't explain something and then try to figure it out. It's usually my experimental results that don't fit what's going on that lead me to the new hypotheses that are mathematical. And so that's sort of understanding the enzymes in the intestine, for example. Okay. So what happened was one of my clinical pharmacy fellows said that all these transplant patients that have TB, they're getting out of control in terms of their immunosuppressant drugs and the clinicians don't know what to do in terms of how to dose the drugs. But obviously it's not working. They're not getting the right doses, these patients. And when she told me that I said, "I know what's going on." If they have TB they're taking the three-drug cocktail that's available in the market at that time. Still available. And one of the drugs is an inducer, Rifampin. And what's happening is these TB patients are inducing their enzymes and therefore if you give them the normal doses they're metabolizing it much faster than anybody expects and therefore you need to give them higher doses. So let's prove it. And, in fact, let's go and test it and see if we can then say how you should make the adjustments. So we did. We took healthy volunteers and gave them oral and IV cyclosporine before and after they had taken a course of Rifampin like they would in the TB drug to induce their enzymes. We got the data back. We're in the nineties already. But it's sort of an example. We got the data back and said, "Hey, the theory doesn't work. We can't explain any of this data by all of the theory that's presently there in terms of how the body eliminates drugs." And we said, "Well, why not? What could else be happening?" And at the same time a colleague of mine named Paul Watkins at the University of Michigan had taken two liver transplant patients and got the clinicians to agree that when they had taken the old liver out, before they put the new liver in, he could slip a dose of cyclosporine into the sleeping patient and then get one blood sample. And he found in one of these people, that 50% of what he found in that blood sample were metabolized and in the other sample, 25%. In the other patient, 25% were metabolized. But they didn't have any livers. So the question was, well, if they don't have any livers what's making the metabolism? Because the enzyme that makes this is in the liver. And so we said, "Well, where else is the enzyme?" "Well, it's in the intestine but so little of it in the intestine, nobody pays any attention to that." We said, "Well, maybe that's the answer though." So we went back and tried to figure out if the intestine was doing it and what would happen and what the results were. It perfectly explained our data. We could explain it. Then we went and did it the opposite way. We inhibited the enzyme and showed that we could explain it because the major route of metabolism for an oral immunosuppressant was the gut. And that was completely new. But it was really sort of based on somebody saying, "Why

doesn't this happen? Why doesn't this work?" and then running the experiments to try to prove it.

02-00:33:44
Burnett: It's classic experimental physiology.

02-00:33:50
Benet: Right, yeah. And since I had discovered it I could patent it.

02-00:34:01
Burnett: Oh, now we're getting way ahead of ourselves.

02-00:34:03
Benet: Yeah, way ahead. Yeah.

02-00:34:04
Burnett: Yeah. But this is later.

02-00:34:06
Benet: This is the nineties. This is the early 1990s.

02-00:34:07
Burnett: But these are just examples of kinds of experimental practice.

02-00:34:13
Benet: Right, right. That's why I was bringing it up. The sort of things that I look at. And so I have a whole series of papers on what are called acyl glucuronides**.** Nonsteroidal anti-inflammatories causing immunologic toxicity. Nobody could explain that. We interacting with people here in the liver center found that they were looking at bilirubin and bilirubin was in people that had liver cholestatis, was doing things different in terms of its metabolism than would normally happen, and those people would get jaundice. And we said, "Wow, maybe that's happening with drugs." And maybe the reason that people are having toxicity with things like aspirin and other non-steroidal anti-inflammatories is that what we think is a detoxifying mechanism could be a toxification mechanism. That's one of my famous papers. Where we said could you explain something that you thought was completely different is in fact doing something differently and we had this explanation from the guys in the Liver Center looking at bilirubin and we said, "Well, drugs might do the same thing. Let's look at drugs."

02-00:35:40
Burnett: I'm sorry, bilirubin?

02-00:35:40
Benet: Bilirubin. Yeah. It's part of your blood. It's the way you make blood.

02-00:35:50
Burnett: I guess what I'm still wrestling with a little bit is your early passion for solving mathematical problems and your work as essentially physical chemistry at Michigan. And was it when you worked on the NSF grant in

Washington where you started doing experimental work or has this been going on the whole time when you were doing—

02-00:36:22

Benet: No, no. That was the first biological experiment. I was doing experimental work in my thesis. I built the calorimeter and stuff like that. But the experimental work I did in Washington State was trying to explain what was going on in the intestine in terms of this absorption and different formulations in terms of pH changes of what could be happening there. But I was doing other stuff at the same time that was more physical related and more mathematical related. But that sort of got me into biological data, being able to carry out biological experiments. Rats. We were doing rats. We would take rat intestine and make little tubes out of it and look and see what happens in the intestine of rats.

02-00:37:10

Burnett: So Dr. Riegelman's opinion of you changed? Would you—

02-00:37:19

Benet: I don't know. No, because when they brought me back here, live teaching assignments were all physical pharmacy. They were afraid to put me into any biology.

02-00:37:29

Burnett: So you said you had an office across from Malcolm Rowland's or beside. So can you talk about how the culture shaped this kind of experimental—

02-00:37:42

Benet: There were three young guys who looked like they were going to change the field. Tom Tozer, who actually was not here when I was a graduate student because he was at the NIH working with B.B. Brodie and teaching Brodie in terms of some mathematical techniques of how to analyze data. He came back on the faculty. He was strictly a physical chemist but he was a Pharm.D trained here. Malcolm, who *was* a pharmacokineticist and trained in the UK and then came to work with Riegelman as a post-doc, and me. We were the young faculty members and we were the assistant professors in the department. And the more senior people were some physical-related but there was a lot of pharmacokinetics expertise in the department. Sorby and Bert Ballard and other people who were interested in that. Except for Riegelman, the department didn't have much of a reputation. The reputation would have been in pharmaceutical chemistry here because those were the people Daniels brought in. So except for Riegelman and some of his predecessors, pharmacy was not very influential in the school. But as time progressed, and the faculty in terms of the data that we were generating, really allowed us to make important advances. And the thing that Sid did that was really influential was to work together closely with Ken Melmon, who became the chief of clinical pharmacology at UCSF. *And* we became sort of the laboratories of clinical pharmacology. So the clinicians in clinical pharmacology were clinicians and

they didn't really have laboratories. So if you were going to do experiments and you were going to work on animals or even humans in terms of measuring blood levels and things like that, you had to do it in the Department of Pharmacy, which was us. And so Sid and Malcolm and Tom and I—I think Tom—all had appointments in Clinical Pharmacology also.

I haven't brought this up but this is really important. The way pharmacokinetics had an impact was because we could develop the analytical methods that would allow us to measure the drugs. Because you can do all the theory you want. If you can't measure the drugs you're not going to be able to do it. And you have to be able to measure the drugs in blood. And so measuring the drugs in blood means you have to have very sensitive assays. And so pharmacokinetics became a really good field because the people who were doing it had the analytical expertise. And I had the analytical expertise. Malcolm did. Sid had. Tom. We had the analytical expertise. And so we could take that data from these experiments and interpret it and then use it to develop the new theories.

02-00:41:07
Burnett: But you also had a group of people who were experimentally inclined or they had the ability to marshal resources? I'm thinking of technicians, for example, who can get the requisite number of monkeys to—

02-00:41:23
Benet: Yeah, right. Although it wasn't so hard. I went to Washington State because there was an NIH grant but six months later I had my own NIH grant. So in those days about 50% of grants got funded.

02-00:41:37
Burnett: The good old days.

02-00:41:40
Benet: In the good old days. Every grant I wrote for twenty-one years got funded on its submission. I never had to rewrite a grant. Then it got tougher. So no, I generated that money. The individual faculty member generated that money. But it was the UCSF collaboration. That's what I talk about in the video. That's what's really unique about UCSF. The collaborative – I mean, I got the head of GI surgery to work on my monkeys. He had never done surgery on a monkey before. I wanted to put in a Thomas cannula and stuff like that and he was willing to do it. And I got another guy who was a urologist to work on the kidneys and he had never worked on a monkey before. But he was willing to help me out and do the surgery and try to develop the techniques so that I could make the measurements that I wanted to make.

02-00:42:36
Burnett: So a more open culture, less siloed.

02-00:42:42
Benet: Oh, yeah, yeah. This is the hallmark at UCSF. Yeah. It is really interactive. People work together and help each other. I couldn't have done this at Michigan. I couldn't have done what I was doing at Michigan. You just didn't have the right context in terms of where your influence was in those days.

02-00:43:07
Burnett: Right. At the time I imagine you encountered a lot of folks from other universities out East and went to conferences and so forth. Did you get a sense that this was pretty unique or were there other models that were interesting in terms of the level of collaboration, the level of interdisciplinarity?

02-00:43:32
Benet: Well, Buffalo was the other place where probably leading pharmacokineticists were—and they had good collaborators. But their collaborators were more their technicians, where here our collaborators were also thought leaders and were able to really make their contributions of their own in addition to our contributions. Buffalo had all the access that we had and ran the same experiments that we did and made major contributions. But I don't think they had the level of the strength of the university that we had here in terms of the comparable people who would work with you.

02-00:44:14
Burnett: Going back to this, the experimental results, you had this research question, this mystery about the intestinal absorption. Can you talk a little bit about how your theoretical acumen became important in this research?

02-00:44:42
Benet: Okay. Well, what I was going to tell you is that I was wrong. My original hypothesis of what I thought was wrong with what was going on in the intestine was wrong. My hypothesis was wrong. I thought the original thing that was—couldn't be supported by physical chemistry. But there's some weird things that happened and it looks like it did support it. But that didn't bother me and it's never bothered me to be wrong because it just leads you to the next question of saying, "Okay, well, now I know this and here I have all this data. And how do you answer this question?" So what drove me initially and what I wrote my original NIH grant on was not a correct hypothesis. But I ran all the studies that led to a new hypothesis because those were the studies that I was running. It never bothers me when the students or the post-docs run stuff, it doesn't come out like we expect. In fact, I prefer it not to because that means there's something we don't know that we can make a contribution to understanding. So that's the real fun of it. I particularly enjoy it when, and the graduate students and post-docs love it, too. They make their presentations once a quarter of their research and, boy, they don't tell me ahead of time the data that they're going to show me that proves I'm wrong. Then they present it to me, and I say, "Oh, wow! Pretty good." [laughter]

02-00:46:15
Burnett: So that drives you, in a sense. A new mystery is opened up for you.

02-00:46:21
Benet: Right, yeah.

02-00:46:22
Burnett: There's a new puzzle to solve and you take it to the next level.

02-00:46:27
Benet: Small levels, Paul. That part is all right but this part is wrong.

02-00:46:33
Burnett: Right, right. So should we talk then about—

02-00:46:41
Meeker: About ten minutes.

02-00:46:41
Burnett: About ten minutes, okay. So to set up talking about clearance concepts in greater detail next time, when I spoke with Dr. Rowland about this era it coincides with some other institutional pieces. So there's a new journal, for example, the new *Journal of Pharmacokinetics and Biopharmaceutics.*

02-00:47:11
Benet: That we founded, yeah.

02-00:47:13
Burnett: Yeah. So could you talk a little bit about the genesis of this journal and what the drivers were and who was involved?

02-00:47:24
Benet: Okay. So there was no journal for the field. You published your papers in really the *Journal of Pharmaceutical Sciences*, which was really the only respectable journal at that time that really had basic pharmaceutical science advances and that was interested in those kinds of things. And so we felt here's a field that is really progressing rapidly and we should have a journal. I think we were approached by a publisher or Sid was approached by a publisher and Sid asked Malcolm and me if we wanted to do the work. And we said, "Yeah, that sounds like it'd be good to do." And he was the editor and Malcolm and I were the associate editors. And we founded the journal in 1973, and it was a moderate success. [laughter]

02-00:48:21
Burnett: And can you talk a little bit then—if there's no journal of record for pharmacokinetics, can you walk—

02-00:48:30
Benet: That was the first one, yeah.

02-00:48:30
Burnett: Yeah. And so can you talk about the identity of pharmacokinetics, where it resides if it doesn't have a journal of record, and how it's being discussed as a discipline?

02-00:48:44

Benet: Okay. Well, you would publish those papers in *JPET, Journal of Pharmacology and Experimental Therapeutics*, or you could publish it in your medical discipline. So a lot of the pharmacokinetic papers were published in the medical discipline journals because it was directly related to a drug in that medical discipline and how you understand that drug. So the first really important papers that applied to pharmacokinetics, and I have this in the history of the department, was a paper that Ken Melmon was the senior author on, on lidocaine. Malcolm, I think, was the first author on that. Where we understood this anti-arrhythmic and what the pharmacokinetics were and how it was important in drug dosing. That had a major impact. I don't remember the second drug that I listed that we—salicylic acid. There was a lot of papers published on acetyl salicylic acid and the reason all those early papers were published on aspirin and salicylic acid was because we can measure it. And you took large doses of it. But when you got to lidocaine you had to have a really good analytical method. So those were published in—the lidocaine paper was in a cardiology journal. Yeah. So that's where that stuff was published. But there was no sort of general place that people would come together and say, "Okay, if it's going to be pharmacokinetics and you're going to make an advance in pharmacokinetics, where do you publish this?" And that was the impetus for founding the journal, Yeah.

02-00:50:25

Burnett: And I suppose the larger context, too, is in the early sixties there's a concern about not only the effectiveness of drugs but the safety of drugs. Was there an uptick in NIH funding for this kind of research that—

02-00:50:42

Benet: Oh, yeah. Oh, yeah, very much so. Very much so. And the center grant that I had here that began in 1979 and a grant at Vanderbilt which was the other major clinical pharmacology and probably the leading clinical pharmacology place, was funded from the NIH. And NIH became very intrigued with pharmacokinetics and its application to clinical medicine and improving drug dosing. And I became chairman of the Pharmacology Studies Section. I was the first pharmaceutical scientist to become a chairman of an NIH—not a chemistry but a non-chemistry. A medicinal chemist had been chair of the study section but I was chair of the Pharmacology Studies Section. First time. That's kind of interesting.

When I went on the pharmacology studies section I was the second pharmaceutical scientist on the Pharmacology Studies Section and after two years NIH asked me to be chair for the next two years. And when the chairs of the departments of pharmacology and the medical schools found out about that they sent a delegation to the NIH and they said, "We know Les Benet. He's a good guy. But if he becomes chairman of the pharmacology studies section that's the death knell of traditional pharmacology because what he does is not traditional pharmacology. He does pharmacokinetics. Which is okay, we'll say it's part of pharmacology, but it's not real pharmacology."

NIH told them to go to hell and I became chairman of the Pharmacology Studies Section and also the pharmacological sciences and that influence went on. So that was an important breakthrough but not so much my doing. NIH's doing. Yeah.

02-00:52:40
Burnett: Giving the green light and saying this is legitimate. But you can see that people are policing boundaries at this time and after, as well. Perhaps if there had been that solid break that Sid Riegelman had wanted, the confrontation would have been more out in the open. But—

02-00:53:06
Benet: Yeah, maybe. Jere wanted it. Sid didn't want it. Jere wanted the confrontation.

02-00:53:10
Burnett: But there are little skirmishes here and there that emerge to deal with this emerging science. But it seems to have support in these other domains. And the National Institutes of Health has this value, especially—well, what about the—I don't want to open up a new chapter and we'll—

02-00:53:37
Benet: I can tell another anecdote that is kind of fun.

02-00:53:41
Burnett: Okay, sure.

02-00:53:44
Benet: The guy who founded the American Society of Pharmacology and Experimental Therapeutics was a faculty member here at UCSF. Grand old guy. And the Western Pharmacology Association had a meeting in Vancouver and he invited me and Lew Sheiner to come up and present pharmacokinetics to the Western Pharmacology Society. And they lambasted us. They just took out after us and said everything we were doing was terrible. And I said to him afterwards, I said, "If you were going to invite us up here to talk about this field, why'd you invite us if you're just going to tell us nothing is useful and nothing—" And he says, "Well, that's the way it is." But pharmacology did not like pharmacokinetics but clinical pharmacology did. And that was a new field, clinical pharmacology. They liked it because it was their vehicle for making their advances. And so what we did was align with clinical pharmacology and that first really started here. Yeah. And that was really important for moving everything forward.

02-00:55:11
Meeker: Do you mind if I ask a question?

02-00:55:12
Benet: Sure.

02-00:55:12
Burnett: Yeah, no, please do.

02-00:55:21
Meeker: Why was it, kind of in layman's terms, that traditional pharmacology disliked pharmacokinetics so much?

02-00:55:24
Benet: Because it was not the rote learning, this is what the drugs are, this is what they do, this is the doses. We were trying to say, "No, the doses could be wrong." And this is the—

02-00:55:35
Meeker: So it wasn't traditional chemistry but it was interaction between chemistry and biological systems or—

02-00:55:42
Benet: Yeah. I don't know. They saw it as a threat. And here's another story. In 1980 I did the pharmacokinetics appendix in Goodman and Gilman. Okay. So Goodman and Gilman are: Al Gilman, who was a professor at Yale and Arthur Goodman, who was at Utah, And their son, Alford Gilman, who I knew from pharmacology study section because we roomed together for four years, who got convinced pharmacokinetics could be important. So he tried to convince his father and Goodman that they should have pharmacokinetics in Goodman and Gilman. And senior Al Gilman was against it. He did not want it in there.

02-00:56:26
Burnett: In 1980.

02-00:56:28
Benet: Yeah. He did not want it in there. He thought it's a different field. Those are different guys doing different things. But Goodman and the younger Gilman overruled him and so it got in there. And it really had a big impact on how pharmacology—I think the pharmacologists just saw it as a threat. It was completely different. We weren't working with organ baths. We were working with humans in terms of understanding and trying to model what was happening and they didn't really do that kind of stuff. But I don't know why. Chauncey Leake was the guy who was the founder of the American Society of Pharmacology and Experimental Therapeutics. I don't know why Chauncey didn't like pharmacokinetics. Maybe he didn't like me. I don't know. Yeah.

02-00:57:15
Burnett: And the organ baths, those were the in vitro.

02-00:57:19
Benet: In vitro.

02-00:57:20
Burnett: So you're taking organ tissue and it's perfused—

02-00:57:24

Benet: Putting drugs on it and you're finding what happens. Yeah. Good work. I'm not saying it's not good science. But, boy, what we did they didn't like. So, there used to be a big split between Pharmacology and Medicine, Pharmacology and Pharmacy. Okay. And the pharmacology guys in the School of Medicine didn't teach pharmacists. This was an exception. This was an exception at UCSF. And that, again, was one of the real strengths of UCSF, which was to say "we are not going to have separate departments of the same thing. We're going to have one department and it's responsible for everybody." So Pharmacology or Physiology here teaches the nurses, it teaches the dentists, it teaches physicians, it teaches to everybody. Now, you may hire separate faculty to do this but they're in your department to do this. We're not having separate departments in that. So I think it was just the feeling that this was Pharmacy pharmacology and it was the School of Medicine chairs. But there was a real break there and I just think this was Pharmacy School pharmacology. Yeah. It really had no place in Medicine pharmacology.

02-00:59:06

Burnett: Well, we'll talk more about disciplinarity and perhaps this tension between professional silos and disciplinary silos and maybe we can bring that up in future instances as we go through the interviews.

02-00:59:19

Benet: Yeah, good.

02-00:59:20

Meeker: Good.

Interview #2 September 30, 2014
[Audio File 3]

03-00:00:04
Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Technology, and Medicine series of the Oral History Center. This is session two, tape three, September 30, 2014. So, Dr. Benet I was hoping you would talk a little bit about the history of clearance concepts, certainly about the beginnings of pharmacokinetics at UCSF. And in my research I came across this 1937 paper by Torsten Teorell and others have pointed to this as important in the history of pharmacokinetics and I looked at the paper and its impressive for the—

03-00:00:50
Benet: Hand-drawn figures.

03-00:00:51
Burnett: For the sophistication.

03-00:00:52
Benet: He drew the figures by hand in that paper.

03-00:00:55
Burnett: It's a physiologically based, pharmacokinetic model looking at the passage of a drug through the body, and it divides the body up into different compartments and it talks about the complexity of what happens to drugs as they pass through the body. It's not just a question of dissolving. There's all kinds of chemical and electrochemical reactions that happen at each step that he's defined. In the history books it talks about this paper as being ahead of its time. The mathematical formulae were extremely sophisticated for this model. And Teorell himself talks about it being impractical to solve. And so he did it as a kind of thought experiment to establish how you might go about doing this. So that's 1937 all the way to the 19—

03-00:01:52
Benet: Year I was born.

03-00:01:53
Burnett: Right. All the way to the 1970s. Can you talk a little bit about what made this kind of work practical and possible by the late 1960s?

03-00:02:08
Benet: Okay. So what Teorell did in '37, and we often call him the father of pharmacokinetics because there had been some papers, the Bateman function, and there were a couple other papers, that considered the body sort of as just one pool, like a bathtub and you stirred a drug around in it and you looked at its disappearance. And what Teorell did in that paper was say, "No, no, it's much more complex than that. You can't consider it as a single bathtub compartment. You have to consider all the other possibilities of where the drug can go and all the various aspects of things that can happen in that." And, yes, he did present a number of equations that were unsolvable at the time, or

basically unsolvable because he had no data. You had to be able to measure the drug to be able to get that and so he had no drug. But he was a physiologist, very interested in that, and he came to many of the initial meetings on pharmacokinetics. I knew him very well and he did attend in 1987 when I got an honorary degree from Uppsala University. He was in attendance and we spent a couple of hours together following that.

03-00:03:18
Burnett: Did he have any kind of recognition by the pharmacokinetics community? Was he celebrated?

03-00:03:23
Benet: Yes. Yeah. He definitely was recognized and would come to these meetings. That paper was definitely, well, actually, there were two papers that were recognized as being very influential and certainly influential on UCSF because Riegelman and Loo and his colleagues and Rowland basically said, "You can't do one compartment. You have to do multiple compartments if you're going to explain drug kinetics." So it was very influential.

But still at the time pharmacokinetics, leading up to the early seventies, late sixties, pharmacokinetics couldn't explain anything. All it did was *describe* the data that was there. There was no predictability to pharmacokinetics and it was very complex and unbelievably complex models. A very famous NIH scientist, Mones Berman, who was a computer guy, really built models that did these very complex pharmacokinetics but completely useless, completely irrelevant to a clinician in terms of applying pharmacokinetics and treating a patient. So that's where we were in the early seventies.

03-00:04:39
Burnett: So could you talk a little bit then about how the evolution of computer processing power has to do with the development – I guess in pharmacology. This is prior to pharmacokinetics. This is what people in the discipline of pharmacology, people would be doing these kinds of complex—

03-00:04:58
Benet: Yeah, but it was really sort of pharmacokinetics. Pharmacologists, as I think we talked about last time, didn't like pharmacokinetics. They didn't like the mathematical basis. There was a drug-response measurement and efficacy as opposed to a concentration-time thing. And that's why it was not applicable to patients, because in patients drug levels go up and down. So it wasn't pharmacologists. Mones, he was a physiologist also.

03-00:05:29
Burnett: Physiology, okay. So it's inside disciplines such as physiology?

03-00:05:31
Benet: Yeah. Right.

03-00:05:32
Burnett: Right.

03-00:05:33
Benet: He was trying to model things like iodine and what would go into the various organs and things like that that were physiologically relevant.

03-00:05:44
Burnett: Okay. And so these would be linear differential equations?

03-00:05:47
Benet: They were all linear differential equations. There were some non-linear equations. But, again, you didn't have the data to say you needed non-linear equations in those days. It was hypothesized that you would and there were certainly some toxicity issues that you knew drugs were following non-linear kinetics.

03-00:06:04
Burnett: So where does the data come from? What's the history then of the data collection to get to the point where you could use those calculations?

03-00:06:15
Benet: Okay. We may have talked about this last time. But theophylline and lidocaine were the two drugs that were very much looked at in various disease states in trying to look at the model, the pharmacokinetic models. Not only the pharmacokinetic models in healthy subjects but the pharmacokinetic models in congestive heart failure patients and patients with MI for lidocaine and renal failure on top of congestive heart failure, and looked at all these changes and said, "Look, everything's changing here. All these parameters are different." But we didn't know what to do with it. We couldn't apply it. And we could describe it but we couldn't apply it. And so what we needed was some way that you could use that information to make a prediction. And that's where we were.

03-00:07:03
Burnett: Right, right. And in order to solve a series—let's not talk about your clearance contributions. But prior to that, to solve the messy/incorrect series of differential equations, what would you have to do? What kind of equipment would you need to solve –?

03-00:07:27
Benet: Okay. So first of all, just to do the mathematics, they were writing these unbelievably long papers where they would solve the mathematics. Because I had taken courses in operational mathematics and came in and said, "No, there's a much easier way to do this. Here's how you solve it and here's how you write it all down." But that didn't do anything but solve the equations. You still put the equations into a computer program to fit the data. Okay. And so the first really big computer program was developed at the Upjohn Company by a guy named Carl Metzler. Can't even remember the name of the program at the time. But that was the original effort trying to fit the data. And

John Wagner, who had come from Upjohn Company and then went to University of Michigan, was the leader in these very complex equations, fitting the data, solving it with these non-linear models, with these computer fits, and then saying, "Okay, here's the answers. Here's what the rate constants are." But, again, no application to how you would translate this over into making a decision in a patient, in a clinical patient.

03-00:08:42
Burnett: Do you think there was an enthusiasm because computer time becomes available during this period, more readily available at the universities?

03-00:08:50
Benet: Yeah.

03-00:08:50
Burnett: Was there a kind of technological enthusiasm?

03-00:08:51
Benet: Oh, yeah, definitely. Definitely. When I came here as a graduate student—as a graduate student or—no, as a graduate student in 1963 I actually was one of the most competent computer people. But we were doing it with these huge card decks that we were taking down to the computer center, which actually was right here. This is where the computer center was in those days. Huge machines taking up big rooms and solving these problems and trying to fit the data. Yeah. It was exciting. You had data. We now had the data. We had good enough analytical methods we could start to have some data. We could actually measure the drug in patients and we could see the differences and we could fit the equations, and we could see what changed and what didn't change and we could get answers and we could draw the curves. And from the curves you could predict what's going to happen here and you could use something called superposition, which just says you put one curve on top of another and predict what's going to happen in multiple dosing. And so the computers could do all that. It could predict what concentrations were going to happen in this situation but it couldn't predict what was going to happen in congestive heart failure, what was going to happen in renal failure, those kinds of things. All it could do was describe the data at the time.

03-00:10:06
Burnett: On a universal body.

03-00:10:07
Benet: Right, yeah.

03-00:10:08
Burnett: Right. A universal human body that is kind of—

03-00:10:11
Benet: Right. And so fitting average parameters. Individuals would be fit and then average them all off and look at six to eight people and follow the data. Sometimes one or two people and follow the data.

03-00:10:24
Burnett: And so a research program evolves around the comparison of the pharmacokinetics of a given drug between a healthy body and a diseased body of a particular kind?

03-00:10:37
Benet: Right, right. Yeah, yeah.

03-00:10:38
Burnett: And you would say lidocaine with congestive heart failure, lidocaine with renal failure, or both?

03-00:10:42
Benet: This is what's going to happen. This is what's going to happen in terms of the blood levels. But not based on a prediction, based on having the data and coming back and saying—

03-00:10:50
Burnett: Clinical data.

03-00:10:51
Benet: —"Okay, we now know that this is what happens and therefore this is what the curve's going to look like in a congestive heart failure patient." This is what theophylline's going to look like in a smoker. Those were the kinds of data we had. Yeah.

03-00:11:06
Burnett: And so this physiological spirit is about scientific investigation of the complexity of the human body in all of its manifestations, in all of its states?

03-00:11:19
Benet: Right.

03-00:11:20
Burnett: So getting as much sort of "truth-to-nature" as the historians say?

03-00:11:25
Benet: Right. It's sort of the stem-cell situation now. There are a lot of people working on stem cells and you get this data and you see it and you publish it. Well, that was what we did in pharmacokinetics. You take a patient, give them the drug, measure the blood levels, and publish it.

03-00:11:40
Burnett: Right, right. And so there's this tremendous burgeoning of research and papers surrounding the complexity of the body. And you go in a different direction. Can you talk about what's different about your approach? You had this initial—you were "bothered" by the mathematics. That was the—

03-00:12:08
Benet: Okay, so yeah.

03-00:12:08
Burnett: Right.

03-00:12:08
Benet: But that part, I could solve that. That was just simple, different ways to do the mathematics, much simpler ways to do the mathematics and looking at what was impossible to solve, which people thought they could, and what could be solved, and doing all that. That was really sort of straightforward math applied to pharmacokinetics. But, again, no predictability. And so what happened was Malcolm Rowland, who was in the office next to mine up in HSE, we started talking about how can you predict what's going to happen. How could we predict? And we knew that the liver is where most of the metabolism took place and we knew that there had to be blood flow to the liver and we knew that under certain conditions, under congestive heart failure, we might change the blood flow and under liver disease we might change the enzymes. Can we take this data and develop some kind of approach that would allow us to say "this is what's going to happen?" And I still can remember trying to think about it and sitting and talking various days, sort of interrogating each other, going back and forth, what about this? And what of the fact that two sources come to the liver, 20 percent comes directly from the heart and 80 percent comes from the gut? And how do you handle that and how do you put the two things together? And how do you deal with that? And what kind of mixing do you have to do? And what's going to happen with blood flow? Why is blood flow important in some cases but not in other? Why is the enzyme important in some cases but not in others? Enough protein-binding relationships? Those were the kinds of discussions we were having.

03-00:14:01
Burnett: And that's obviously a very inspiring climate to be in, that there was a lot of enthusiasm around bold thinking, it seems at UCSF, and in your immediate milieu, as well. What was the dogma that suggested this was—for example, I'm thinking of what might have been a negative reaction to this kind of thinking or this kind of research? Were there people who said, "This can't be done," or that this is—

03-00:14:39
Benet: No, I don't think people said it can't be done. Just they didn't have the tools to do it. I think people thought it was useful. And we didn't actually understand it. You got it right in the beginning. We didn't understand all the implications and how you could translate it and how it could be useful. It really sort of transformed us, too, in terms of being able to think about it. But once we had it – and we developed the relationship considering unbound drug because we believed unbound drug was what was active and what was metabolized and then Shand and Wilkinson actually took our equations and they added protein binding to it and their paper got a lot more—they took our equations, just they added protein binding. But it was an important addition.

03-00:15:28
Burnett: That's the Wilkinson-Shand 19—

03-00:15:29
Benet: Yeah, Wilkinson Shand, yeah.

03-00:15:30
Burnett: —75 paper?

03-00:15:32
Benet: Paper, right. And that was important because we didn't have the implications in there and they raised that implication. So they took the issues that we had sort of invented and added the protein binding to it and it was really an important addition to the literature. But the thinking was what was the important part. Could you parse out what was going to happen if protein binding changed? If enzyme activity changed? If blood flow changed? And predict it. And therefore you would then be able to say, "Ah, in congestive heart failure where I know blood flow changes, this is going to be important or is not going to be important." And that really was the transformation of pharmacokinetics because now there could be a predictive basis that then you could go test and see if it was right and then you would find all the things that didn't fit and it would lead to—

03-00:16:30
Burnett: Refine it.

03-00:16:30
Benet: —refining different measures and understanding different aspects of it. So it was really the transformation of pharmacokinetics to being useful. That it now would allow a clinician to actually say, "Okay, here's the rationale for changing the dose. It's not some rate constant in a model that I don't understand. I can understand exactly that clearance times the steady state concentration equals the rate in," because that's how simple it is. And if—

03-00:16:59
Burnett: For a single organ, right?

03-00:17:00
Benet: No.

03-00:17:01
Burnett: No?

03-00:17:01
Benet: You can do it for the whole body. We did it for a single organ but then you combine them all. So you have clearance of the kidney, clearance of the liver, possible excretion in the air and stuff like that. The two major routes. Clearance in the kidney, clearance in the liver. And you could break up what would happen: predict if renal failure was going to be important for this drug or if not, if congestive heart failure was going to be important, if protein

binding was going to be important. All of those things then led to, “Okay, now I understand. Now I understand how to adjust doses.” And so it was really important.

03-00:17:37
Burnett: And compared to half-life, the reason half-life is not an accurate indicator is—

03-00:17:44
Benet: Okay. So half-life works, and anyone who’s a chemist knows they can always describe all the reactions with half-life and get it right. And so the initial reaction would be, “Wait a minute. Why do I need clearance?” Because in chemistry half-life always works. Rate constants always work. And the reason is because in chemistry the volume never changes. You have a beaker with an amount of fluid in it. That volume doesn’t change. And, in fact, chemistry’s also looking at clearance but volume stays constant so there’s always the direct relationship between half-life and clearance. In physiology and humans, volume changes also. It changes as a function of disease. It changes as a function of how old you are, whether you’re a male or a female. And therefore there’s two parameters that affect half-life. One is the body’s ability to eliminate the drug and the other is the space in which the drug can distribute in the body. One is volume of distribution, one is clearance. In chemistry it’s all clearance because volume never changes. That’s sort of the big jump that you move from chemistry to pharmacokinetics.

03-00:19:00
Burnett: And did that also make it easier and more accurate? The clearance parameter doesn’t change between in vitro and in vivo?

03-00:19:10
Benet: Oh, no.

03-00:19:11
Burnett: Whereas—

03-00:19:12
Benet: It can.

03-00:19:12
Burnett: It can?

03-00:19:13
Benet: It can. Definitely. That’s still an area of important research, of how you take the in vitro and predict the in vivo clearance.

03-00:19:21
Burnett: But compared to half-life, that would be—

03-00:19:25
Benet: Well—

03-00:19:25
Burnett: No? Okay. [laughter]

03-00:19:27
Benet: All of it can change. All of it can change. Okay.

03-00:19:30
Burnett: Okay. And in terms of inspiration, there was that paper by those two scientists, Detrick [sic]—

03-00:19:43
Benet: Dedrick and—

03-00:19:43
Burnett: Dedrick—

03-00:19:43
Benet: —and Bischoff.

03-00:19:44
Burnett: —and Bischoff.

03-00:19:44
Benet: Dedrick and Bischoff.

03-00:19:44
Burnett: Yeah.

03-00:19:45
Benet: Okay. So what Dedrick and Bischoff did was to take a physiologic-based approach to drugs in the body. Okay, so clearance, you can just say, "Okay, the whole body and it's got clearance." And since rate in equals clearance times the steady-state concentration, you don't have to know where that clearance is. What Bischoff and Dedrick did, from a chemical-engineering perspective, was to say, "Okay, I want to consider all of the different compartments." Okay, now, they actually used clearance in their model because we stole clearance from the chemical engineers. It was a concept that they knew about for petroleum cracking.

03-00:20:32
Burnett: So is this the same as the well-stirred –?

03-00:20:35
Benet: Yes, this is the well-stirred model.

03-00:20:36
Burnett: Okay, so what—

03-00:20:38
Benet: The well-stirred model is the first of the models of clearance. It's the simplest clearance model, the well-stirred model. Okay, now, I don't know if you want me to say. The well-stirred model just says that when you come inside the

reactor the concentration in the reactor is the same as what goes out. That's the well-stirred model. So instantaneously the concentration that comes in goes down to the concentration that comes out after the reaction takes place. That's the well-stirred model. Now, what you might think is, well, I don't want to do that. I want to come down like this. That's a parallel-tube model. Or you might want to do like this. That's a distributive model. So we've developed all those models over the years. But the fine-tuning of the models is not necessary. The well-stirred model from a clinical perspective does fine. You don't need to be more exact in the model in terms of applying it to treating patients.

03-00:21:37
Burnett: So it's kind of a black box in a way?

03-00:21:38
Benet: It is a black box and that's what we got from the chemical engineers. What we borrowed from the chemical engineers in clearance, and Malcolm and I borrowed from the chemical engineers and I took this course, where is it, in unit operations and the book is here, when I was a graduate student. So I don't know. [*looking on shelf for a book*] It's here someplace. It's a green—oh, there it is.

03-00:21:58
Burnett: It's one of your talismans?

03-00:21:59
Benet: There it is.

03-00:22:00
Burnett: McCabe and Smith?

03-00:22:02
Benet: As a graduate student, I took a course, chemical engineering, unit operations, and could understand those processes. Now I lost my train of thought. [laughter]

03-00:22:15
Burnett: But the basic message is it doesn't matter.

03-00:22:16
Benet: Oh, yeah. Okay. Right. So we had borrowed that from the chemical engineers because they were using that process, the black box, to say, "Okay, oil comes in here and gasoline goes out here and what happens inside, that's clearance." Converting the oil to the gasoline, right, yeah. Okay.

03-00:22:40
Burnett: And so when you say that clearance is the area under the blood-concentration time curve, it is—

03-00:22:48

Benet: Okay, okay, so that's true. If you give an IV dose and measure the area under the curve and divide it into dose, that's clearance. Thinking back to what Malcolm and I were doing, it was so strange! We were trying to get this parameter, it was a measure of the body's ability to eliminate drug, but the units were volume per time. It was a *flow*. It was so hard for us to understand how that could be until we realized, okay, what we're doing is limited by blood flow. The body can't eliminate drug any faster than it can get to the organs of elimination. So the upper limit's going to be blood flow. Lower limit's going to be zero. And that's why it's a flow parameter. Clearance is a flow as opposed to half-life, which is a rate constant. Yeah. Yeah, yeah.

03-00:23:37

Burnett: Right, right. Okay. I think I *almost* understand. [laughter]

03-00:23:41

Benet: Yeah. But, you know, it was very hard for us to get that picture in our head. What does this mean? How is this useful? How can a flow measure the body's ability to eliminate drug? It took us years to explain it simply like I just did.

03-00:24:04

Burnett: And Malcolm was interested in this obviously. Was it an intellectual problem or did you start out with the idea that you wanted predictive value to come out of this? You wanted it to be predictive?

03-00:24:22

Benet: No, it was how do we treat the liver? How do we accurately model the liver so we can—which was at that time the major organ of elimination for a drug. How are we going to model it so it'd translate into something understandable, that you could predict what changes? We weren't farsighted enough to realize how important the change was. Yeah. But as time progressed we certainly recognized it, yeah.

03-00:24:54

Burnett: And the liver is a terrible organ to work with when you're talking about flow, right, because you have this hepatic portal vein. You've got this intermixing of venous and arterial blood. So you have blood coming from the heart and blood coming from this portal vein. And so you had to model , well, you black- boxed it effectively? That was your solution.

03-00:25:20

Benet: Right. We did. We did. [laughter] We black-boxed it. But we spent a lot of time thinking about how to do it. I can remember having a whole series of equations that I had worked on at home and bringing them in, putting them on Malcolm's desk and say, "Okay, how about this, this, this?" I can remember that. Trying to do the simulations and saying, "What would happen under this condition? What would happen under that condition?"

03-00:25:44
Burnett: Could we expand on that a little bit? These are two very prominent scientists at the beginning of an important collaboration. Can you talk about work practice between the two of you? How you divided up the work, how you worked together? Is there a way to sort of—

03-00:26:08
Benet: No, it was just the discussion, Paul. We talked about it *every day*. We were in the labs next to each other. We were two assistant professors, so we're not traveling around the world all the time. We're there. And every day we talked about it.

03-00:26:26
Burnett: So it wasn't this sense of you came in with the material, then you'd go away for a while and work on things. You were in constant discourse about—

03-00:26:33
Benet: Yeah. Yeah. As I remember, we talked about it all the time. And Gary was the post-doc working with Malcolm at the time, who was there, too. Gary Graham. Yeah.

03-00:26:45
Burnett: And what were the other demands on your time, as well, for both of you? Were you both teaching a lot?

03-00:26:51
Benet: Yeah, we were teaching and had graduate students and clinical pharmacology fellows and doing research. But it was sort of an overwhelming—we continued to talk about this all the time. [laughter]

03-00:27:04
Burnett: [laughter] At dinner parties. Was that—

03-00:27:06
Benet: No, I don't remember that.

03-00:27:09
Burnett: No?

03-00:27:09
Benet: Now Malcolm and I will sit around and do that at dinner parties but in those days it was in the office.

03-00:27:15
Burnett: Yeah, yeah, yeah. Keep it bounded. This is not necessarily 9:00 to 5:00 but a good sort of work/life balance?

03-00:27:23
Benet: Right, yeah.

03-00:27:25
Burnett: Even though it was that exciting.

03-00:27:26
Benet: Yeah, we both had young kids and had to be home.

03-00:27:29
Burnett: And that would balance you out a little bit?

03-00:27:31
Benet: Right. Yeah. I guess so. Because we were always, with consternation, "What does this mean?" So we're talking about it but then we're trying to think about how can I explain this? This just doesn't fit. What we said yesterday doesn't fit with what I'm thinking today. So it was exciting but I didn't realize how exciting it was at the time because we didn't realize we were there to make that jump. I've had some very similar experiences a number of times like that, where you're sort of progressing and thinking about it and where does it go, what happens the next time.

03-00:28:15
Burnett: Right, right. And so you get to writing the paper together. Did you write the paper together or did you—

03-00:28:21
Benet: Yeah, we wrote the paper together. Probably Malcolm wrote the first draft. And I'm an English major so I spend a lot of time—

03-00:28:29
Burnett: Editing. [laughter]

03-00:28:29
Benet: [laughter]—editing. Yeah. But I know we changed it a lot. And, of course, we put it in our own journals, which Sid would have been the editor for because Malcolm and I were the authors.

03-00:28:44
Burnett: Yeah. I was actually—

03-00:28:46
Benet: Second issue of the journal.

03-00:28:47
Burnett: One of the things I did, I did a sort of OED search, I just wanted to get a little sense of pharmacokinetics. I read some other papers about the history. So I came across Teorell and the first use of "pharmacokinetics" is 1959 in the *British Journal of Anesthesia*. German, pharmakokinetik with a K is 1963 and it's first used as an adjective in 1963. There's a book by Robert E. Notari called *Biopharmaceutics and Pharmacokinetics*, which is just the reverse of what your journal ended up [being titled]. Was this book, I guess it's a text—

03-00:29:27
Benet: Yeah. Bob was trained, well-trained. He came out of Garrett's lab in Florida. He was at Ohio State at the time and he wrote that textbook. I don't think it really had an influence on us.

03-00:29:42
Burnett: It's just the name. It came up.

03-00:29:42
Benet: It was an early textbook. But you've got to go back to Germany. *Grundlagen der Pharmakokinetic*. Yeah. That's the important paper from a guy in Gießen. Now I'm too old to remember his name. The pediatrician.

03-00:29:58
Burnett: And how long ago was that?

03-00:29:59
Benet: This was in the fifties. I reference it in my early papers. He's a pediatrician in Germany that is in the German army, very early gets captured and brought to a prisoner of war camp in New Jersey, okay, for four years. And does all these derivations and writes all these textbooks while he's in New Jersey in the prison camp and then publishes *Grundlagen der Pharmakokinetic*, the basis of pharmacokinetics, and another book called *Der Blutspiegel*, mirror of the blood, something like that, that are two really important early pharmacokinetic books and now I can't remember. Why can't I—oh, that's terrible.

03-00:30:51
Burnett: Well, also the names don't signify pharmaco—so, for example, the journal that Teorell published in, which is volume fifty-seven, so it goes back to the nineteenth century, was called *Archive Internationale de pharmacodynamie*.

03-00:31:04
Benet: Yeah, pharmacodynamics yeah.

03-00:31:06
Burnett: But I guess, translated from French to English, pharmacodynamics is translated as pharmacology, weirdly. But all this to say that some of the words were used but they didn't have the same significance and certainly not the disciplinary significance, which is what you and your colleagues are doing at UCSF at the time. So I was just wondering about influences of stuff that was coming out when you were about to publish this. And then there's one more paper from the *Annals of the New York Academy of Sciences*, J.R. Gillette, "Factors Affecting Drug Metabolism."

03-00:31:45
Benet: Right, Jim Gillette from the NIH.

03-00:31:47
Burnett: Did that have an impact on you?

03-00:31:48
Benet: Yeah, no, a very important contributor to the field. More a metabolism person than just a straight pharmacokinetic person but very influential, Jim Gillette. There's an important symposium. If we just take a second, I know I have the book, that all of these people were at, very early.

03-00:32:13
Burnett: This is in the late sixties or early seventies?

03-00:32:16
Benet: Here's Teorell, Dedrick. Pharmacokinetics and pharmacodynamics.

03-00:32:23
Burnett: Okay. And that's Teorell, Dedrick, and Condliffe.

03-00:32:27
Benet: Yeah. So Dedrick's your Bischoff and Dedrick.

03-00:32:28
Burnett: Right, that's right.

03-00:32:29
Benet: Teorell is your guy. Condliffe was an NIH person, I believe. Let's see what the year this—

03-00:32:35
Burnett: And those are the proceedings.

03-00:32:36
Benet: Yeah. What's the year? Yeah, he's at NIH. Seventy-two.

03-00:32:50
Burnett: Ninety seventy-two.

03-00:32:50
Benet: So we're meeting in 1972. Yeah. And so here are all the people at that meeting. Here's Gillette.

03-00:33:05
Burnett: Luzius Dettli.

03-00:33:06
Benet: Dettli.

03-00:33:08
Burnett: Dedrick.

03-00:33:08
Benet: Well, Dettli is who I did my sabbatical with in Basel. And we're all at that meeting in '72. This is before clearance.

03-00:33:20
Burnett: Okay. And Ken Melmon?

03-00:33:25
Benet: Yeah.

03-00:33:26
Burnett: And Torsten Teorell.

03-00:33:28
Benet: Right.

03-00:33:29
Burnett: And all of these folks. And Sid Riegelman, Peter Condliffe and there you are. Les Benet.

03-00:33:37
Burnett: Bischoff.

03-00:33:40
Burnett: Yeah, and Bischoff. So there's a real—

03-00:33:45
Benet: Julius Axelrod, Nobel prizewinner.

03-00:33:47
Burnett: Julius Axelrod. And so—

03-00:33:52
Benet: He was Mones Berman's. He was laboratory of theoretical biology at the NCI.

03-00:33:58
Burnett: And so this meeting was convened by whom?

03-00:34:03
Benet: Let's go back and look and see who convened it.

03-00:34:06
Burnett: *Pharmacology and Pharmacokinetics*. And it was—

03-00:34:14
Benet: Proceedings and conference held at the Fogarty International Center Advanced Study at the NIH, October 30 to November 1, 1972. It was part of the advanced study program. Professor Torsten Teorell came to the Center in 1970 as one of the first scholars. In '71 and '72 spent several months at the Center devoting his attention to contemporary problems in the application of pharmacokinetics to experimental and clinical pharmacology. As one of the founders of pharmacokinetics, Professor Teorell has made many contributions to the field.

03-00:34:39
Burnett: Great.

03-00:34:38
Benet: And this conference, he sort of was the initiator of the conference. And we're all there, all us young guys and all these old guys. The young guys are Malcolm and me. But here's my graduate student Bob Ronfeld.

03-00:34:44
Burnett: Right. And so that's a real jumping off point, I suppose, for the formation of the identity of pharmacokinetics as an emerging field.

03-00:35:07
Benet: Right, yeah. This was the recognition by the NIH how important it was.

03-00:35:17
Burnett: That's a huge step, right, to have the NIH imprimatur.

03-00:35:19
Benet: Yeah. And Condliffe was the head of the Fogarty Center. That was—

03-00:35:23
Burnett: Right, right. And so this is happening right at the same time and at the end of '72 you submitted this paper to your own journal and this becomes the journal of record. Well, it's the only journal.

03-00:35:37
Benet: Right. [laughter]

03-00:35:40
Burnett: [laughter] So you get to make that claim right off the bat. For pharmacokinetics. Can you talk about reception of the paper? You mentioned that Wilkinson and Shand got some of the glory for—

03-00:35:58
Benet: Well, they got cited a lot more than we did.

03-00:35:59
Burnett: Okay. So '73, '74, '75, did people recognize this?

03-00:36:07
Benet: No, no. Wilkinson and Shand could not get their paper published as a research article. They had to publish it as a—

03-00:36:16
Burnett: As a letter?

03-00:36:17
Benet: —observation or something. Like if you go back and look at their paper, it's not a research paper. The editor said, "No, all you guys are doing is taking this concept and adding this other thing to it." So it's a perspective or something like that. They could not get it published as a research paper—

03-00:36:32
Burnett: Interesting.

03-00:36:32
Benet: —even though it's the highest cited paper in that journal.

03-00:36:35
Burnett: Is that it's more digestible or refined?

03-00:36:39
Benet: The editor didn't view it as being research. It was something there were comments about.

03-00:36:45
Burnett: Theoretical.

03-00:36:46
Benet: Yeah, comments about somebody else's paper and adding to it or something like that. So yeah.

03-00:36:52
Burnett: This is not the entire clearance concept story, right? So there are additional pieces that come later. And you've written about the significance of clearance. It was significant because it was the first non-compartmental parameter. So it didn't depend on these variable systems.

03-00:37:25
Benet: Right. It didn't depend on those pictures Teorell drew. Just here's the human. Here's the body.

03-00:37:31
Burnett: And it did not require the microconstants because it seemed from Teorell's paper that these were constants applied to these different boxes.

03-00:37:39
Benet: Sure. Right, yeah. So Teorell's still back—well, he's early in the days that you get all the rate constants and that's how you solve it and that's what Berman did in all of his huge models, would solve all these rate constants. What Bischoff and Dedrick did, though, is they went further and put blood flows and clearance and everything and put it together at each of the individual organs.

03-00:38:03
Burnett: Okay. You explained that it's for simplicity's sake, right? It's simplicity. Why simplicity? Your answer was that it's a therapeutic tool and it defines—

03-00:38:28
Benet: Drug disposition.

03-00:38:27
Burnett: —drug disposition.

03-00:38:28

Benet: Yeah, it's got two uses. It's a tool in therapeutics, making a decision about drug dosing, which is what really was the big step, but it also allowed you to understand what was happening to the drugs. So it was a tool in defining drug disposition in the body.

03-00:38:43

Burnett: And I guess not every research scientist thinks about the research they're doing as a tool or thinks about its outcome as a tool. Many do but it's not a given. Did your interaction with clinical pharmacology, the fact that you were helping, your unit was helping or your division was helping the [Division of Clinical Pharmacology] assess their lab results, did you think about pharmacokinetics as a kind of service model?

03-00:39:20

Benet: Yes, I definitely did. So the clinical pharmacology fellows were carrying out their research in my lab, in Malcolm's lab, in Sid's lab. That's where they were doing their research, because we had the capability of measuring the drugs and being able to do the analysis and stuff like that. So if they wanted to study what was happening to the drugs, they had to work with us. And so we were really instrumental in the input of clinical pharmacology. We were part of the clinical pharmacology program here and it was to be able to make the decisions of how you're going to dose the drugs in patients responsibly and reasonably. Yeah.

03-00:40:06

Benet: Now, the same thing was happening at Vanderbilt, because that's the other big place where clinical pharmacology was and that's where Wilkinson's having his big impact at Vanderbilt, the same as us here in San Francisco.

03-00:40:20

Burnett: What about Johns Hopkins? Did they have—

03-00:40:22

Benet: No, not in that area.

03-00:40:23

Burnett: They didn't. Interesting.

03-00:40:24

Benet: This was Vanderbilt and UCSF and then Buffalo.

03-00:40:29

Burnett: In the history books—again, I'm going to keep citing the general "history books" —the first fellowships in clinical pharmacology are funded apparently by the American Association of Drug Manufacturers and the first one goes in 1957 to Johns Hopkins and the second one goes in 1959 to Harvard. And they're just fellowships, they're not programs. And they just fell flat? I don't know the history of those institutions. But was there anything similar? Did Merck set up a fellowship at—

03-00:41:05

Benet: Yeah. Yes, they did. Drug companies set up the fellowships. So in the early eighties I was the chairman of the Pharmacological Sciences Review Committee for the NIH, so went and looked at all those programs. We stopped the funding at Harvard. We just felt they weren't doing what the program was supposed to be doing, okay. I don't even recall Johns Hopkins as being a player in those days. But there were people that—because it was pharmacology and clinical medicine and the application of clinical medicine. But the two big players were Vanderbilt and UCSF.

03-00:41:40

Burnett: Vanderbilt and UCSF. Yeah. So there's an understanding that this is a discipline in formation but it is to be of use. It is a kind of applied science in service to clinicians, in service to the medical profession.

03-00:42:00

Benet: Right. So, Paul, here's an interesting tidbit. Clinical Pharmacology and Infectious Disease as disciplines in schools of medicine started at the same time. Young physicians were very excited about it. This was something that they could have an impact on and that they could do something about. The responsibility in schools of medicine, and you've seen this in some of the stuff I've written, was that you're going to bring in money. You're going to treat patients. You're going to have patient beds and you're going to solve problems. Well, that was what clinical pharmacology was supposed to be doing. And so initially with Ken Melmon here and John Oates at Vanderbilt, that's what it did do. And there were also excellent programs at Kansas City in the early clinical pharmacology training programs. Pretty much those were where they were. And it was *successful*. It *was* successful. But if you think about it today, clinical pharmacology doesn't have *any* beds and doesn't treat anything, whereas infectious disease is now one of the biggest specialty disciplines that there is in medicine and they started at the same time as clinical pharmacology. Because clinical pharmacology couldn't sustain the ability of a consult in solving the issues related to patient care and the other problem was that pharmacy came in and solved a lot of those problems. And so the competition was [between] pharmacy and clinical pharmacology in *many* medical centers. Yeah. Yeah.

03-00:43:39

Burnett: And it's right at this moment, right, because in the history of the medical school at UCSF there is this shift at the very same time, because obviously Medicare comes in, Medicare and Medicaid, and you have a switch from researchers getting their funding from fee-based services, which is what clinical pharmacology did, to a kind of NIH-funded, NSF-funded, NIH, all the national institutes, providing money for researchers to do research independently of fees. And this is something that pharmacokinetics is in some ways a child of.

03-00:44:25
Benet: Oh, yeah, it is. For sure it was.

03-00:44:27
Burnett: Completely in a sense, right.

03-00:44:28
Benet: For sure it is. Yeah.

03-00:44:29
Burnett: Yeah.

03-00:44:31
Benet: Because that's how the clinical pharmacologist makes their decisions. It's all pharmacokinetic-based initially. Yeah.

03-00:44:38
Burnett: But pharmacokinetics is immune in a sense to the rivalry from pharmacy because pharmacy was not pleased with pharmacokinetics either.

03-00:44:50
Benet: Right. [laughter]

03-00:44:51
Burnett: Right. Right. But they were unable to get in or cut off pharmacokinetics in any important sense because pharmacokinetics got its source of revenue from the NIH and later from university support, I imagine, because they understood its importance.

03-00:45:12
Benet: Right, yeah. Right.

03-00:45:15
Burnett: That's very interesting. That's very interesting.

03-00:45:16
Benet: So the first two big center grants in pharmacokinetics were here and at Vanderbilt and I led the one here. Started funding in' 79 and Vanderbilt was about the same time, when the NIH said, "Okay, pharmacokinetics is really important." And we were the last two center grants of the NIGMS, when they all phased out eventually over time.

03-00:45:41
Burnett: Right, right. Well, the first center grant period, the beginning of the center grant was I think the Cardiovascular Research Unit at UCSF. So there was a kind of precedent. There was knowledge about center grants, there was knowledge about how to get them. When you brought in the center grant—

03-00:46:08
Benet: People were amazed actually.

03-00:46:12
Burnett: Did you get any advice—

03-00:46:15
Benet: No, I just—

03-00:46:14
Burnett: —from the old hands who knew how to do it?

03-00:46:17
Benet: No, I just wrote it myself. Those days everything I wrote I got funded so I expected it to get funded. [laughter] Those were the good old days. Nah, I didn't have any advice, anything. I just said, "here's a mechanism." NIH is asking for it. Who could do it better than us? We're going to write it. Yeah, yeah.

03-00:46:38
Burnett: So a spirit of a service model to medicine. A spirit but not connected in a fee sense.

03-00:46:46
Benet: Yeah not in a fee sense.

03-00:46:47
Burnett: You're not deriving revenue.

03-00:46:47
Benet: But in the research sense and in what you've read of what I've written, how important that center grant was for many of the both medicine faculty and pharmacy faculty at UCSF in terms of their original grants, original support, to be able to develop the program. Yeah.

03-00:47:06
Burnett: And this is a kind of classic case in discipline formation, right, you have to police the boundaries, but you have to sort of define what it's not, right? That's very, very important in establishing your terrain and your territory and then you defend it. Those are the people that—

03-00:47:28
Benet: Yeah, but I think what we tried to do is to go outside the boundaries. That's what we always tried to do. In other words, yeah, this is what you think it is but in fact this is what we should be doing. Yeah, yeah.

03-00:47:41
Burnett: But it has really important applications. So you were interested in solving an intellectual problem. You and Malcolm and others were interested in solving a problem. At a certain point it occurs to you that this has not only applications for research programs but it has this usefulness, its predictive value as a therapeutic tool. And what's the earliest moment that you can remember thinking of this as this is the tool we needed to say this is what pharmacokinetics is as distinguishable from pharmacology?

03-00:48:27
Benet: Okay, so I didn't do that. I was interested in pharmacokinetics as a tool in defining drug disposition, of finding out what we don't understand and tran—

03-00:48:37
Burnett: A research tool.

03-00:48:38
Benet: Yeah. Of understanding how the body handles drugs. So Malcolm more than me did it as a tool in therapeutics and Ken Melmon and the other faculty members here used it more as a tool in therapeutics. I did very little on therapeutics. I was always interested in understanding basic processes.

03-00:49:04
Burnett: And later you assess it as something that is—you described I think at the end of the seventies, and now we're talking about your taking over the chairship [of the Department of Pharmacy at UCSF] and we're getting ahead of ourselves a bit. But you described the importance of clearance concepts as a way to define what was unique and special about pharmacokinetics, what distinguishes it from pharmacology, what distinguishes it from clinical pharmacology, clinical pharmacy.

03-00:49:38
Benet: Yeah, and from clinical medicine.

03-00:49:38
Burnett: From clinical medicine. And it's separate. Now you have that and—

03-00:49:47
Benet: Okay, so I don't have it yet. You need to add the next thing you want to talk about, which is volume of distribution.

03-00:49:54
Burnett: Right, right. Okay, sorry. Thank you for reminding me. [laughter] So that was a question I did have.

03-00:50:09
Meeker: Are you starting another chapter right now?

03-00:50:11
Burnett: I think we could probably talk about volume of distribution, area, versus volume-of-distribution steady-state, in ten minutes. Yeah.

03-00:50:22
Benet: Okay, sure.

03-00:50:23
Burnett: So what did clearance-concept research do for the use of volume of distribution as area or beta versus volume of distribution at steady state?

03-00:50:38
Benet: Okay. So we knew, or I knew, and actually that's why Bob Ronfeld was at that meeting, because we published the paper when he was a graduate student, that the right volume of distribution—if you really wanted to know how a drug distributes in the body you had to calculate volume of distribution steady state. That was the parameter that was independent of elimination. All the other parameters were much easier to calculate and which people were using changed when elimination changed. But we already knew that half-life was a function of both clearance and volume. So you didn't want volume changing when clearance changed. And so all the parameters that people were using in terms of volume—in other words, the space available in the body for it to distribute, they would *change* if—for example, in renal failure, for a drug eliminated unchanged, if you knew that the only mechanism was elimination in the kidney and renal failure stopped that clearance, if you went back and calculated volume of distribution, it *changed* even though it had nothing to do with what was going on. So it wasn't the right number. So we knew that volume of distribution steady state, or at least I knew volume of distribution steady state was the right parameter. But it was so hard to calculate. We just had—

03-00:51:56
Burnett: Yeah. How do you calculate it?

03-00:51:58
Benet: You had to use all these microconstants. You had to fit the model, do the microconstants and figure them out, and solve it backwards. And you had to go back and *do* all that math that Mones Berman and John Wagner were doing.

03-00:52:10
Burnett: And punch cards?

03-00:52:12
Benet: Well, yeah.

03-00:52:14
Burnett: Right, right. So computing is part of this.

03-00:52:16
Benet: Yeah, and fit the parameters and get the parameters and solve it and get it.

03-00:52:20
Burnett: And it was important especially for comparing diseased versus healthy bodies because the diseased body is going to change the volume of distribution.

03-00:52:29
Benet: That's right. That's right. And that's what you want to know. What you really want to know in a disease is does the drug go the same place? Not only do you change its elimination process but where does it go? Because you're trying to treat something and have you changed where it goes? If you change where it

goes it's not going to do what it's supposed to do because it's going to be someplace else.

03-00:52:51
Burnett: Right, right. So you need to find a non-compartmental method.

03-00:52:58
Benet: I need an easy way to calculate volume.

03-00:53:00
Burnett: Yeah, easy way.

03-00:53:02
Benet: I need an easy way to calculate volume of distribution—

03-00:53:04
Burnett: Fair enough.

03-00:53:04
Benet: —steady state. Yeah.

03-00:53:06
Burnett: Okay. And so that's what you begin to develop.

03-00:53:12
Benet: Okay. Right. No, I don't begin to develop. You know this story. I'm on sabbatical with Dettli, who's a very famous kidney person.

03-00:53:22
Burnett: I don't know if we have too much time but let's talk about your sabbatical. That was arranged. You'd been working on these achievements and why Basel?

[Audio File 4]

04-00:00:00
Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Technology and Medicine series. This is session two, tape four, September 30, 2014. So we were just embarking on a discussion of your sabbatical in 1976. Can you talk about the occasion for the sabbatical and the kind of research that you hoped to do and why you chose the location you chose?

04-00:00:32
Benet: So I'm at UCSF. It's my seventh year. Time to take a sabbatical. I came in '69, you go on a sabbatical in '76. So I wanted to go to Basel because there are four major drug companies there: Sandoz, Roche, Ciba, and Geigy. While I was doing at Ciba and Geigy combined so there's three major companies. But I don't want to go to one of those because then I'm sort of limited [in my access] to the others. So I said, "Well, okay. So what I'll do is I'll go to the university. So Professor Dettli was very famous for his nomograms of how you dose drugs in patients with kidney disease. And I write Dettli. I don't

know him. I write Dettli and say, “I’m interested in coming,” and he’s delighted that I will come and also he’s the head. There’s Medicine One, there’s Medicine Two, there’s Medicine Three. He’s the head of Medicine Three. But guys that are the heads of Medicine One and Two are also delighted that I’m coming. And when I get there I have to go to grand rounds at 6:30 in the morning and stuff like that that I’d never done here but they said, “Well, you’re in the medical school here and you got to show up, participate just like everybody else.” [laughter] But it was wonderful. I really enjoyed it.

04-00:01:44
Burnett: That’s interesting.

04-00:01:45
Benet: Yeah.

04-00:01:46
Burnett: Speaking of disciplinary boundaries. They didn’t seem to have disciplinary boundaries there, as well. Or you were just considered to be a physician in a sense, in a structural sense?

04-00:01:54
Benet: No, they knew I wasn’t a physician but they thought I was.

04-00:01:58
Burnett: They treated you like one.

04-00:01:59
Benet: They knew enough about pharmacokinetics. Because Dettli was basically a pharmacokineticist who was making decisions about dosing patients. And so as far as they were concerned, I could help them in everything that they did and I should be there, part of it. And I had a work permit because in those days you can’t live in Basel without having a work permit. So I’m allowed to work in Switzerland. I could do anything actually. And that allows me to rent an apartment and so on. And the three companies, they’re all delighted I’m there. And I get to stay in the Ciba-Geigy guesthouse, which is on Unterer Rheinweg, right on the Rhine, and I got this fantastic apartment. So it was a wonderful experience and I taught courses in all three of the companies and interacted. It was just a marvelous experience.

04-00:02:47
Burnett: Did you take any time off to see Europe?

04-00:02:50
Benet: Oh, yeah. We went all around all the time. Yeah, yeah.

04-00:02:53
Burnett: And your wife Carol came with you?

04-00:02:54
Benet: My wife and my two kids. So Reed and Gillian were there. They went to the local schools because I've got a work permit so I can be just like anybody else and go to the local schools and everything. Which, of course, the university had to get for me.

04-00:03:09
Burnett: And so the drug companies knew you were there. Did you let them know you were going to be there?

04-00:03:15
Benet: Oh, no, they knew I was coming, yeah. They all knew that I was coming and they were delighted because they had attended—so this is '76 and Wagner had started his PK courses in the early seventies, so they all knew me. I had been to Basel and given lectures. I had lots of interactions with everybody in all the companies. Yeah.

04-00:03:32
Burnett: Okay, great. And did they setup some kind of structure for you to interact with them or did they just take advantage of the presentations you were giving there?

04-00:03:42
Benet: Well, they paid for my housing. The three of them got together and paid for my housing. But I was just somebody they interacted with all the time. I wasn't there as a consultant but I was in and out of the companies all the time and addressed a lot of problems. Confidentiality was a lot different in 1976 than it is now and so I probably had a lot of confidential information that we shared and I would give my opinions on, so it was really a wonderful experience.

04-00:04:14
Burnett: But it was intellectually stimulating for you as a research opportunity?

04-00:04:21
Benet: Right, yeah. Yeah.

04-00:04:22
Burnett: Did the problems of the drug companies influence you as far as shaping the kind of research you did when you came back to UCSF?

04-00:04:34
Benet: No, because I was already doing that.

04-00:04:36
Burnett: Okay. You were helping them.

04-00:04:37
Benet: I was already doing a lot of consulting here in the US which started when I was at Washington State. Actually, let me tell this story because it's a good one. Okay. My first consulting job was with Merck. I'm an assistant professor

at Washington State University and I've got hair that comes down to here, I've got long hair, and I fly into Philadelphia and the guy standing there with a sign that says Professor Benet. And I walk up to the guy, I say, "I'm Professor Benet." He says, "No, you're not." [laughter] And I had to pull out my ID.

04-00:05:16
Burnett: And this is what year?

04-00:05:19
Benet: This is '70. No, this has to be earlier than that. This is about '67. Sixty-seven. And then I'm driving in this limo, we're going across the Schuylkill Expressway and it's being repaired. The guy has the window down and all these guys that are working on the highway are looking at this long-haired guy sitting in this limo. This was before some of our band guys were out there. So I was pretty unusual walking around with this unbelievably long hair. So that was a great experience. [laughter]

04-00:05:47
Burnett: They didn't think you were a rock star?

04-00:05:49
Benet: That's what they did. They did think I was a rock star.

04-00:05:50
Burnett: That's right. [laughter]

04-00:05:53
Benet: They would go, "Wow, look at that." [laughter]

04-00:05:58
Burnett: So you had done some consulting while you were in Philadelphia and—

04-00:06:01
Benet: Yeah. I didn't really carry away anything, although I had a chance then to work on cyclosporine. Sandoz offered me the opportunity to be the first actually—it wasn't approved yet as an immunosuppressant and they gave me the opportunity to have the drug and to work on it in my lab at UCSF and I didn't take that opportunity, which I always regretted later. I eventually did it but I would have had the earliest studies. Yeah, so—

04-00:06:38
Burnett: You had your own projects that you were interested in.

04-00:06:41
Benet: Yeah, I had my own stuff. Right, yeah. Yeah.

04-00:06:43
Burnett: So you're back in Basel and you're working on—

04-00:06:50
Benet: I'm just sitting. Oh, I'm sitting at the desk. Okay, so here's also a funny story. Okay. So this is 1976. I'm a professor, a young professor at Basel. But in Basel when the professor walks in the room everybody stands up. I thought that was pretty neat. Any time I walked into a room everybody stood up. They put me into an office that was a former office that was the—if you were doing your drug assays, you called that number to get the answer for your patient. But they gave me that number. So all these people would call. And, of course, they're speaking *Schweizer Deutsch*. And so they're asking me the question. I have no idea what they're saying. So I finally learn enough *Schweizer Deutsch* that I can answer them and say, "You've got the wrong number. You should call this." But that never works because then they think you understand them and they ask something else you don't understand. But everybody treated me really with respect.

Basel in 1976, if I wanted to go to a restaurant and said, "This is Professor Benet," or had the secretary call, that Professor Benet wants a reservation in a restaurant, a professor, Kantonsspital in Basel, any restaurant you wanted to go to you were—a professor was still—

04-00:08:15
Burnett: Something.

04-00:08:16
Benet: It was really important in the Swiss system at that time at the medical school.

04-00:08:20
Burnett: Wow. A very different kind of academic culture.

04-00:08:23
Benet: Right, yeah.

04-00:08:23
Burnett: Right. Hierarchical but respectful.

04-00:08:26
Benet: Right, yeah. Very respectful.

04-00:08:29
Burnett: And how did you—

04-00:08:34
Benet: Okay, so here's the story of volume. Okay, unless you had something else you wanted to ask, Paul.

04-00:08:39
Burnett: Well, I did want to ask about how you knew Renato Galeazzi.

04-00:08:42
Benet: Okay. So Renato was my fellow. That's Galeazzi. Okay. So he was my fellow here at UCSF doing the Procainamide work, which was the paper that

Malcolm said was really one of the most important papers and that we should pay more attention to it. And basically it was the first PKPD paper. It was really one of the first PKPD papers with a *model*. It's never been recognized as that except by Malcolm. And it was an important paper. It got some citations. Go ahead.

04-00:09:15
Burnett: Do you want to talk about that? Do you want to save that for later? Just talk about what's significant about that specifically? The two compartment pharmacokinetic model with the—

04-00:09:27
Benet: Yeah. Okay. Okay. So this is Lew Sheiner, Renato Galeazzi and me. Renato is a clinician from Berne and he comes here funded by the Swiss National Fund to be a fellow and he's a fellow with Lew and me because if he's going to do any research work he has to do it in my lab and he was interested in the theory stuff with Lewis. So we're working together as a team, the three of us. And so I'm interested in Procainamide because it's the second-most-used antiarrhythmic drug and it has a pharmacogenomic aspect to it that really hadn't been investigated early in the years that we were working on it. And so we did a pharmacokinetic study and we did a pharmacodynamic study. Were two papers that came out of that work. Okay, so I'm going to tell you another story.

04-00:10:27
Burnett: Okay. Sure, sure.

04-00:10:27
Benet: Okay. So after we first published, or maybe we haven't even published. We published one or two of the papers and in subsequent months I'm invited to lecture in Tel Aviv and in Taipei by—

04-00:10:44
Burnett: Consecutive? Right?

04-00:10:46
Benet: Consecutive months. I come back to UCSF in between but these are meetings I get invited to. These are cardiology meetings because I'm working on Procainamide. And so I give the talks on Procainamide and I go to Israel in Tel Aviv, in Tel Aviv Medical Center, and in the department of cardiology to talk about our studies on Procainamide. I had all the data, so I talked about both the PK and the PD. Nobody was paying any attention to me. It wasn't just because all the Israelis—I said, "You invited me to give this lecture and they're talking to each other and nobody's paying any attention. Why?" They said, "Well, we never use Procainamide." I said, "It's the second-most-used drug in the United States." He said, "Oh, no. If we use Procainamide everybody has an immunologic toxic reaction to it. And so we never use Procainamide at all. We always use lidocaine. And that's why, yeah, it was interesting and your science was interesting but, in fact, there was a whole

bunch of clinicians in the room and so they weren't interested at all in Procainamide." The next month I go to Taiwan, give the same lecture in Yang-Ming Medical Center, I remember, in the cardiology department and the guys are sitting on the edge of their seats and everybody is taking notes and everything I say they're writing down and they're asking questions. And I ask the guy afterwards, "That's really great. People obviously got— He says, 'Oh, they loved it. It was a wonderful lecture.'" I said, "Do you use Procainamide?" "Do we use Procainamide? It's the only antiarrhythmic we use!" "Do you ever see any immunologic toxic reaction?" "Never. We never see any immunologic toxic reaction. We never see any of that stuff."

Okay, so I didn't realize, but I recognized within the next year what was going on. The major route of elimination of Procainamide is a genetic polymorphism related to a particular enzyme. Ashkenazi Jews don't have that enzyme so then the drug stays around and it makes this toxic metabolite. Asians are fast metabolizers of Procainamide. They have that enzyme and so they don't have the Israelis' problem of making the toxicity. They don't see it at all. So I had this perfect example of going to give these lectures in terms of the pharmacogenomics that turned out that it was the difference between this enzyme in the Ashkenazi Jews and the Asians that really was completely explained. But I had no idea at the time what was going on and what the difference was but discovered in the next couple of years in terms of that. But it was one of those kinds of things you say, "Why?"

04-00:13:38
Burnett: Did that inspire you later to do pharmacogenomic studies?

04-00:13:41
Benet: Yeah. I was inspired to do that. But, again, I'm always interested in mechanisms so that was understanding a mechanism that could—

04-00:13:52
Burnett: Right. It's not the primary.

04-00:13:53
Benet: Yeah, yeah. Yeah.

04-00:13:55
Burnett: Yeah. That's what others have said about you. The sort of genomic and genetics revolution in the 1980s, you weren't as interested in that as others.

04-00:14:05
Benet: Right, yeah.

04-00:14:06
Burnett: You didn't go down that path.

04-00:14:07
Benet: Right, right. But that was a really perfect example of where I could explain it based on what was going on and understand the difference.

04-00:14:16
Burnett: Well, the Procainamide was a—

04-00:14:19
Benet: Okay, so go on, Paul. I'm sorry. I'm digressing here.

04-00:14:23
Burnett: No, that's not a digression.

04-00:14:24
Benet: So we did the pharmacokinetics and we understood it completely and published a paper and it was a highly cited paper in terms of understanding the pharmacokinetics of this drug. Sort of like the theophylline and the lidocaine paper but we had clearance in it and all this kind of work. Then we tried to say can we look at a pharmacodynamic response because antiarrhythmic drugs are a pretty good drug for looking at pharmacodynamic response. And so we had a pharmacodynamic response. We could look at the PT interval in the EKG and we could see its lengthening or its shortening and we could look at it as a function of concentration. And we published the first paper, Lewis, Renato, and I, showing the hysteresis. On the way up in the curve you had this relationship between concentration and effect and on the way down you had a different relationship between concentration and effect. And then we collapsed the hysteresis because we took saliva samples versus blood samples. Blood samples gave the hysteresis but when we did saliva samples the line fell right on top of each other. So we published in that paper that says you could find a site in the body that would give you a better way to look at the kinetic-dynamic relationship and here is the kinetic-dynamic relationship. So it was an early paper but not that well recognized as being influential.

04-00:15:52
Burnett: I'll check with him, but perhaps Dr. Rowland—there was no direct influence necessarily but it's an instance where researchers are talking about sampling different—

04-00:16:11
Benet: Sites.

04-00:16:12
Burnett: —fluids. That different fluids can give you a different result. Instead of assuming plasma concentration is the gold standard, you could use something else and get a more accurate—

04-00:16:24
Benet: Right. But I think he's more interested in just the fact that it's the first study showing the hysteresis. It's the first study showing that the up curve and the down curve aren't the same and the relationship between plasma concentrations and effect is not an instantaneous relationship. In other words, you need a higher concentration to get the same effect on the up curve than you do on the down curve and that's because of where the drug is acting and

where it is in different places in the body. That's what I think he thinks is the more important aspect of—

04-00:16:55
Burnett: Okay. Right. I think you're right about that.

04-00:16:56
Benet: —what we were able to demonstrate. It was the first hysteresis paper of PKPD. Yeah, yeah. Right. So, yeah, I really appreciate Malcolm. He should cite it more often. [laughter]

04-00:17:13
Burnett: [laughter] But you are working with Renato Galeazzi at this time. And so you had worked out that you were going to go to Basel and he was going back?

04-00:17:25
Benet: He went back home. He was funded for two years in the Swiss National Fund and he went back to his position in Berne.

04-00:17:30
Burnett: Oh, and he contacted you, didn't he?

04-00:17:33
Benet: Right.

04-00:17:33
Burnett: Right, okay.

04-00:17:34
Benet: So he calls me one day. Because I'm in Basel and he's in Berne. I've seen him a lot. We're only a telephone call away. And he says, "Hey, I just read a paper in endocrinology that I don't understand at all and I want to come over and show it to you." So he takes the train down, an hour. Takes the train down, shows me this paper by these guys at the University of Minnesota that were looking at drugs for thyroid disease. And they're calculating clearance and then they calculate this other parameter that appears to change as a function of time but not as a function of elimination, which is all calculated directly from the data. And Renato says to me, "What are they doing? This isn't anything you taught me. What's going on here?" So he goes home and I spend a couple of days looking at it and I realize these guys are calculating volume of distribution steady state in a non-compartmental manner but I think they don't recognize that's what they're doing. So I write them a letter and say, "I've read your paper, very interesting. I like it very much. Do you realize that what you have published is a way to calculate non-compartmentally volume of distribution steady state?" And they write back. They said, "We had no idea. We were just fooling around with the data. This was a way to look at it and this is how it came out. That's very interesting." I said, "Do you mind if we publish it because we think it's an important finding." And he said, "Nah, we don't mind. You don't even have to reference us." We did reference them. He

says, “Because we have no idea what we’re doing. We’re just playing around with numbers and getting these kinds of things.”

04-00:19:27
Burnett: Are these the Stewart-Hamilton theorems?

04-00:19:28
Benet: No, no.

04-00:19:29
Burnett: No, these are the—

04-00:19:30
Benet: Stewart-Hamilton theorem, though, is referenced in their paper. Well, we reference it because it relates back to Stewart-Hamilton theorem. So it’s something related to the Stewart-Hamilton. I had to go back and read the Stewart-Hamilton papers to figure out what was going on.

04-00:19:44
Burnett: Oh, these are the indicator dilution studies?

04-00:19:46
Benet: These are indicator dilution studies. These are the indicator dilution studies that these guys are—and they’re using the methodology from Stewart-Hamilton but they’re doing a calculation that Stewart-Hamilton didn’t do in their indicator dilution and Renato says, “What is this? What’s this parameter?” It’s volume of distribution steady state. These guys have figured out how to calculate volume of distribution steady state non-compartmentally, even though they don’t know that’s what they’re doing. [laughter] And we say in the paper. It’s just a little paper.

Okay, so here’s the way to calculate it. That’s fairly simple. But then the recognition that how do you relate volume, clearance, and half-life? That’s what comes into the paper. So Vss [volume of distribution steady state] equals clearance times mean residence time, which is the inverse of the relationship of the half-life. That was the important contribution. That’s how you get all the parameters together.

04-00:20:48
Burnett: Together, right.

04-00:20:50
Benet: Yeah. In a non-compartmental way to understand it. So that’s what that paper is really important about and that’s why it’s cited so often. Yeah.

04-00:21:00
Burnett: Is that the – I don’t want to say a trinity, but there’s basically three key contributions. The elaboration of the clearance concept, there’s an understanding of its relationship to volume of distribution steady state and mean residence time.

04-00:21:23
Benet: Right. So it shows the independence of clearance and volume of distribution and that parameter that relates the two of them is the parameter that's related to half-life, called mean residence time. So that's why it's such an important paper, because it is the paper that says here is the relationship. These are why they're independent parameters and mean residence time is the dependent parameter.

04-00:21:46
Burnett: So let's talk then about reception because you've said yourself that initially the 1972-3 paper is not—people aren't that aware of it. Wilkinson and Shand get more traction with those refinements. When is the uptake? You talk about getting an appendix in the Gilman and Goodman—

04-00:22:19
Benet: Goodman and Gilman.

04-00:22:20
Burnett: Goodman and Gilman in 1980. When does this become generally recognized as part of research programs, part of drug therapeutics?

04-00:22:30
Benet: Okay. So it becomes pretty quickly recognized. People have bought in. Not everybody. Like David Greenblatt for many years didn't believe—he argued with me about what was the relevant parameter and so on. But I think the field begins to realize because we actually publish some papers showing that what happens is that these volume terms you're calculating all the time change with clearance and that this one doesn't, with the data. Yeah, okay. And so I think everybody realizes, yeah, they'd really like to get Vss and here's the way to get it. Okay. So they don't see the MRT [mean residence time] part of it. They see, okay, I want to be able to calculate volume of distribution steady state and I don't want to have to have a model and I don't want to fit the data and stuff like that. How do I get it? Okay, here's the non-compartmental way to calculate. So it gets picked up pretty quickly. Yeah.

04-00:23:21
Burnett: Can you talk about what this means in practical terms for drug research? Let's say as a measurement of time. How much faster can you do a certain kind of drug research once you know how to do these things? How much easier? It's not just that it makes things faster, it makes things possible. That's another—

04-00:23:47
Benet: Right. So if you got an antibiotic and you're trying to treat a bug, an infection in the blood, okay, what you really want is the drug to stay in the blood. You look at volume of distribution steady state and it doesn't change as a function of all those things you know it stays where it's supposed to be and you can use those measurements and you can relate it. But if it changes, if this volume term changes, then you don't know where it went to and you don't know how to translate your volume. Because volume of distribution just says what's the

space available. You don't know where it is. You just know it got bigger. So is the drug where you want it to be or is it not where you want it to be when you make your dosing decisions? So it's an important advance in terms of being able to apply pharmacokinetics in a clinical setting. Yeah.

04-00:24:34
Burnett: So, it's relevant in a clinical setting in terms of drug-dosing decisions. Does it go upstream to drug development?

04-00:24:46
Benet: Yeah.

04-00:24:47
Burnett: Does it influence how the drug chemistry is –?

04-00:24:50
Benet: Okay. So the aspect of that—then you bring in the MRT. Okay. And this is still in the development phase. I published these papers and they will be recognized in the future. It allows you to make your predictions very, very early about what's the right way to dose this drug. How should you multiple dose it? Because that MRT value is sort of the squinched up half-life of the drug considering—I don't care how complex it is. If you treated it was like this bathtub, this is how it is and if you're trying to get plasma levels, this is how you do it. Okay. So it has some real nice simple ways for the company's to use it. So it has an impact. And I think it improves how people can define drugs and what it looks like and what they can do with it.

04-00:25:43
Burnett: Well, I was speaking with an historian of science about this interview and he's working on the history of the development of HIV/AIDS medications. And he was interested in particular in pharmacokinetics and the development of multidrug cocktails.

04-00:26:09
Benet: Oh, multidrug cocktails.

04-00:26:09
Burnett: Cocktails. And some of your early papers in the seventies are about tuberculosis, I think, and the interactions of two different drugs. Can you talk about what pharmacokinetic concepts, how they can help or whether they facilitated the development of multidrug cocktails?

04-00:26:32
Benet: So you're actually moving now to the nineties, to the beginning of the nineties. That's where we used pharmacokinetics to understand what goes on. Okay. Because what happens between volume of distribution, which is the '79 paper and what goes on in terms of transporter- enzyme interplay and all that kind of stuff, which is what gets explained, is the immunologic toxicity studies. Acyl glucuronides and all that. That's what I spent a lot of time on in those days, in those intermediate days.

04-00:27:07
Burnett: Yeah, the determinants of diuretic response stuff that you were doing and corticosteroid and immunosuppressant reagents.

04-00:27:14
Benet: Well, yeah. Those. Yeah. So, yeah, now I'm dealing with immunosuppressives. But the business of the TB thing is with immunosuppressives and that's where we realize we don't understand what's going on.

04-00:27:27
Burnett: Well, let's shelve that, put a pin in it for now and we'll pick that up in the next session. There is one more paper that I would like to ask about. It may not be relevant. But the Emi Nakashima and Les—

04-00:27:43
Benet: Emi Nakashima.

04-00:27:44
Burnett: Emi Nakashima and Les Benet paper in 1988, "The General Treatment of MRT, Mean Resonance Time, Clearance, and Volume Parameters." It's an effort to describe the relationship between non-compartmental parameters.

04-00:28:02
Benet: Okay. So basically what Emi worked on, and there were a couple of other people that worked on it, is saying can we just write down how you solve all these things instantaneously? As complex as they can be, can you write them down? How can you calculate MRT? How can you calculate Vss? No matter how complex the situation is, where the compartment models are, is there simple mathematical work that would allow you to do it? That's what Emi's paper is. Okay. It's more of a mathematical thing. In other words, it really doesn't have the same impact as understanding something else. It does. It just says you don't have to do all this terrible math. There's simple ways to do it. Okay. But it doesn't really have a big impact.

04-00:28:52
Burnett: And there was mention in the paper itself about the—I don't know how to pronounce his name but Chanter? There's a controversy. He or she criticized the calculations of mean residence times for the whole body.

04-00:29:17
Benet: Oh, okay.

04-00:29:19
Burnett: I don't know if that's familiar to you or if it's reaching too far into a—

04-00:29:23
Benet: How do you spell his name again?

04-00:29:23
Burnett: C-H-A-N-T-E-R.

04-00:29:26
Benet: God, I don't even know who that is.

04-00:29:28
Burnett: Yeah. It couldn't have been that much of a controversy then. We can—

04-00:29:32
Benet: There's still people that say they don't understand this. There's a website called PharmPK and there was just the question the other day that we completely answered in a paper maybe eight years ago. But it comes back. People in industry want to solve something. So they say, "Well, can you do this? Can you do this? Can you do this? And yeah, you can do it and here's exactly how you do it." And it's in that paper. But they don't read those papers.

04-00:30:05
Burnett: Well, there is a paper from 2007, Yang et. al., "The Misuse of the well-stirred model of hepatic drug clearance." It's not a criticism of clearance but it argues that—

04-00:30:19
Benet: Yeah, but it's not that relevant.

04-00:30:21
Burnett: It's not that relevant? That was a letter—

04-00:30:23
Benet: Because, as I said, from a clinical situation, because of the variability that are inherent—sorry. I'm sorry.

04-00:30:28
Burnett: Oh, your mic has—

04-00:30:31
Benet: In a clinical situation, because the natural variability that occurs in patients overcomes those differences that you see with the different models. Yeah. So you just don't get enough additional power by going to the more complicated models. Unless you're trying to really understand the really simple very important little microbes and explain it.

04-00:31:00
Burnet: Right. So the body is radically idiosyncratic. Right. You can take that for granted. On the one hand you have the individual idiosyncratic body; on the other hand you're mass producing a drug. And so your techniques or the techniques that you share with your colleagues and developed with your colleagues are perhaps an important half-way point between the needs of pharmaceutical manufacturers and the individual body that varies incredibly.

04-00:31:35
Benet: Yes, it is. And it's sort of why I'm not interested in pharmacogenomics so much.

04-00:31:42
Burnett: The “personalized medicine” kind of thing?

04-00:31:43
Benet: Yeah. Because the variability that’s not genetic is so great that it’s really hard to prove in terms of drug dosing that you really can improve therapy based on pharmacogenomics. Picking the right drug, yes, for sure. Yes, this drug is going to work or it’s not going to work. So if it’s not going to work you don’t want to dose it. But adjusting the dose. There’s just too much variability that’s not genetics and that’s why I’ve never been really hot on genetics, although I could explain what was happening in Taiwan and Israel.

04-00:32:17
Burnett: Right. Which was fascinating as a scientific problem.

04-00:32:19
Benet: Right, yeah.

04-00:32:22
Burnett: Absolutely. Just to keep a rough chronology, there are a couple of things we could explore in the 1970s, the late 1970s, things that are happening. And you did individual drug research at that time. Are there ones that are particularly interesting to you? For example, the determinants of diuretic response.

04-00:32:50
Benet: Sure. That’s really interesting because the ivory tower developed a drug.

04-00:32:57
Burnett: This is Maxzide?

04-00:32:59
Benet: This is Maxzide, right. Yeah. So on the basis of the work that we did here in terms of understanding what was happening to the different drugs and how they interacted and what the metabolism was we said we can make a better drug. We can make a better drug than is out there. The best, it was at that time, by volume, the highest-selling drug, Dyazide. Wasn’t dollar-wise the biggest selling but in terms of prescriptions it was the drug that was the most prescribed in the United States and it was a very poor formulation and not necessarily the right ratio of Triamterene to Hydrochlorothiazide. And we said, “Well, we can make it better,” and we did. And we translated that and we created then the Drug Studies Unit. We ran the clinical studies and said, “Okay, here’s this new drug,” and were stupid enough to sell it for a million dollars instead of doing it as a license. [laughter]

04-00:33:54
Burnett: A license. That would change in the history of science.

04-00:33:58
Benet: In those days we thought that a million dollars was a lot of money and we didn't know for sure this drug was going to actually do anything. [laughter] So we felt good about it at the time but pretty stupid now. Yeah.

04-00:34:18
Burnett: And that's a drug cocktail.

04-00:34:21
Benet: Right. It was a combination cocktail. Right. What we did was we changed the ratio of the Triamterene to the Hydrochlorothiazide from what was in Dyazide and showed that this was the right ratio, that you'd get the right results. And we improved the absorption and bioavailability of the dosage form so that you would get the blood levels that reflected what was in the pill as opposed to Dyazide, which didn't do that.

04-00:34:46
Burnett: Right. Well, maybe this is a way then to talk about the downstream impact of clearance concepts on drug development and on therapeutics, by talking about these cases a little bit. The mechanisms of intramolecular acyl glucuronides migration—

04-00:35:13
Benet: Acyl glucuronides.

04-00:35:14
Burnett: Acyl, yeah. Acyl glucuronides migration and reactivity.

04-00:35:19
Benet: Glucuronide. Okay. So here's the—

04-00:35:23
Meeker: Can you pronounce that just for the record?

04-00:35:24
Benet: Acyl glucuronides. Glucuronides. So here's what's going on. So I'm a consultant to Johnson & Johnson and they have a drug that is a non-steroidal anti-inflammatory drug that they're selling for relief of menstrual cramps in women. And they do the pharmacokinetics of it and I'm actually a co-author even though the work was all done at Johnson & Johnson. But I'm a co-author because I'm their primary consultant on this drug. And then we start working on it here and we discover that in fact what we published at Johnson & Johnson isn't right, that the analytical method had a flaw in it. Okay. So what we discover is that the major route of elimination—it's a carboxylic acid drug. And the major route of elimination is a glucuronide, adding glucuronide acid interacts and makes this ester with carboxy—so you can make two kinds of glucuronides. You can make an ether glucuronide which reacts with an alcohol and is very stable. You need an enzyme to break it down. Or you can make an acyl glucuronide. Carboxylic acid is an acyl glucuronide that actually can be very labile. Labile. Breaks down real easily. We discover here that

what's going on is that when you take the drug and freeze it and then thaw it to measure the drug and the metabolite, in that thawing process you cleave all that metabolite. And so what we've published with J&J is there's no metabolism but in fact we now recognize yes, there's a lot of metabolism but you have to change the pH. You have to raise the pH of the solution before you freeze it so that when you thaw it what is called acyl migration will not occur and it will not go back to the parent drug.

04-00:37:43
Burnett: How did you catch that? How did you notice this? The study was constructed differently?

04-00:37:50
Benet: How you're sample handling. We actually saw some peaks. Phil Smith, who was the graduate student at that time, Jiro Hasegawa was the post-doc from Japan. Saw these peaks when they took fresh samples that we didn't see when we took frozen samples.

04-00:38:10
Burnett: Frozen samples, okay.

04-00:38:11
Benet: Okay. And that these fresh samples, the peaks changed with time. And so we went back and figured it out and we figured what was going on is that the glucuronide was migrating, okay. It could be in position one when it was formed because there's four groups on the—

04-00:38:35
Burnett: On the chain.

04-00:38:36
Benet: —glucuronide that can interact with the acid molecule. It could be at position one, it could be at position two, it could be at position three, it could be at position four. And these things go back and forth. So we thought we had made this wonderful discovery of what was called acyl migration but we were stupid enough to go look in the library and find out that Emil Fischer had described it in 1916. [laughter] He hadn't described it for drugs but he had described the process. So we reintroduced it to science and said that it's important for carboxylic acid drugs and if you're going to really find out how much metabolite is formed you got to stabilize your samples before you freeze them. Everybody froze the samples but it's not then, it's when you thaw them that the cleavage occurs. And so we actually showed that there was all kinds of data that was wrong in terms of metabolism.

All right. Then we did another really interesting study that really had a big impact. We then showed, because we radiolabeled the drug, we then showed that in fact if we took plasma samples from a radiolabeled drug and you precipitate the proteins and throw it away. What you do if you're measuring plasma is you take the red blood cells and you precipitate the proteins and you

separate it out from the red blood cells. You're measuring the plasma. We looked in what we had precipitated out and there was a whole bunch of drug in there. And what was happening was that the drug was covalently binding to proteins and we were precipitating it out and nobody recognized this. So these non-steroidal anti-inflammatories had a toxic reaction. People were having immunologic toxicities from them. In fact, my daughter has this immunologic toxicity. If she takes a non-steroidal anti-inflammatory she has a reaction and can't breathe and has to go to the hospital and so she never takes them and stuff. So she can take Tylenol, that's it. She can't take any of Advil or Aleve or aspirin or something like that. So we published this paper in, God, a good journal, can't remember now what it is. It's one of my high—

04-00:41:17
Burnett: On this paper—

04-00:41:23
Benet: *Journal of Clinical Investigation*.

04-00:41:24
Burnett: *Journal of Clinical*—okay.

04-00:41:24
Benet: Published the paper in *Journal of Clinical Investigation* and said, "Nobody ever understood this toxicity was idiosyncratic because nobody ever knew what the mechanism was for it and who would have it or who wouldn't have it." And we said, "Well, maybe it's because of this covalent binding that nobody ever saw because every time they cleaved their samples they got rid of these metabolites. So you never saw this stuff. And that made a big impact. That got into headlines, not first page headlines, but got into headlines that maybe we had understood the mechanism for this toxicity of the non-steroidal anti-inflammatories that many people had. And I got a lot of press from that and a lot of grant funding and understanding a lot of mechanisms. Never able to prove that that was the immunologic toxicity. But we made major contributions in that area, at least to understanding how you look at those drugs and how you handle it and how this migration occurs and what are the mechanisms of all this. But when we first did it we thought we had the mechanism. And, in fact, even today when a company makes a carboxylic acid drug, the FDA asks them, "Well, what about your acyl migration and what about your covalent binding?" and then they call me and I come and look at their data and how they ought to look at this and what I think and how they should look at it. So it was a lot of work and many papers but I wouldn't say it really had the kinds of impact we thought when we first published it.

04-00:43:09
Burnett: Right. And neither one of those two examples necessarily is related to the impact of clearance concepts per se. But these are impacts of biochemical research really.

04-00:43:21
Benet: Yeah, this is understanding metabolism and understanding how you analyze for metabolites and what's the correct way to do it and what's the careful way to make sure you get it right. A lot of credibility from that in the metabolism community. I had a lot of graduate students that worked on those projects and many people out there in terms of—my sort of bona fides as a metabolism person really came from that kind of work.

04-00:43:49
Burnett: Right, right.

04-00:43:50
Benet: And we really made some important advances but clinically it turns out not to be that important.

04-00:43:57
Burnett: Because it's quite rare because clearly they would have changed the standards for evaluating clearance because you're using blood plasma.

04-00:44:05
Benet: Oh, no, no. People do change. Everybody changed but it turned out that it's hard to prove that that was—everybody changed because they're worried about it. So they did it right. But it's hard to prove that that really was the answer and that this is the mechanism and that's why you want to avoid it. So everybody does it right today. They do it correctly. Still get a lot of references from it. That paper, "Is acyl migration a toxification mechanism in addition to a detoxification mechanism?" That was where that was.

04-00:44:36
Burnett: In the drug development stage they would know biochemically in advance whether that was likely to happen and the drug would bind to the plasma precipitants?

04-00:44:55
Benet: Right. And they look at that. They know the FDA's going to ask them about it.

04-00:44:58
Burnett: Okay. It's a new best practice that emerges from this research that you did?

04-00:45:02
Benet: That's right. But whether it had any major impact or was clinically relevant probably was not as much as we thought when we first published it. But when we first published it it was hot stuff.

04-00:45:16
Burnett: The other research that was really fascinating, we do have some time. This is the 1980s. I think it's early eighties. The relationship of corticosteroids in immunosuppressive agents. That the prednisone interacts with pred—

04-00:45:29
Benet: -nisolone.

04-00:45:30
Burnett: Prednisolone.

04-00:45:31
Benet: So okay. So, again, I'm having lunch at the faculty club at UCSF and the head of transplant surgery, Oscar Salvatierra says to me, "Les, why don't you do something useful." I says, "Oscar, what would be useful?" He says, "Tell me how to dose immunosuppressant drugs in transplant patients." He says, "I really don't know how." He says, "It's all sort of what somebody thinks and they do it." He says, "Give me some basis for doing that." I said, "Oh, interesting question, Oscar. Let me look into it." So I started. The transplant drugs at the time was really only prednisone, prednisolone. They were really the drugs that were the most effective. We didn't have cyclosporine, Tacrolimus, Sirolimus at that time. And started to carry out their studies and to look and see what the kinetics, what's going on with those drugs, how is the body handling them, is this a reversible mechanism going back and forth between prednisone and prednisolone. What happens? What changes it? What doesn't change it? So we carried out a series of studies where we looked at it. In fact, these are real early liver transplant days where not much liver transplant is taking place and I'm interacting with Nancy Ascher and John Robertson. We're starting to publish some stuff. And I said, "John, when you got a liver that you can't use for transplant, call us and we'll use it." We'd go get it. We were doing rat liver perfusions and we'd take human livers, which are like this, and we'd put them on top of the rat liver perfusion and run these. We were running these human liver perfusion studies because we had the access. Again, today we could never do this kind of stuff.

04-00:47:22
Burnett: In perfusion, like can you describe for the layperson how that works physically? Like technically what do you do when—

04-00:47:33
Benet: Okay. So you talked about the hepatic portal vein coming into the liver. That's what comes in and the hepatic vein goes out and the biliary, the bile comes out of it. So you take the liver and you put a tube into the hepatic portal vein. You put a tube into the hepatic vein and you push fluid through it. You push drugs through it and you look and see what happens to them when they come out and you also collect the bile to see what happens there. So we do studies in rats all the time with that but we did it with humans, too.

04-00:48:00
Burnett: And are you circulating it?

04-00:48:02
Benet: Yes. Sometimes we're circulating it, sometimes we're doing single pass. It depends on how fast the reaction has occurred. So we've got these human

livers sitting in the lab. These big human livers. They're just sitting in the lab. So like sitting on this table. And fluid is coming in, fluid's coming out. And Vicky Hale's sampling them and we're then measuring the prednisone, prednisolone, and what happens to the drug, which way do they go and what kind of metabolism occurs and how much comes out in the bile. And so we start doing these studies. In those days I was still doing a lot of monkey work and we did monkey studies with the compounds and then we started going into other immunosuppressives like azathioprine and **6**-mercaptopurine and stuff and we're starting to look at can we now understand what's going to happen with immunosuppressors and do the pharmacokinetics. So this gets back to the story that I told you before when I was in Basel in '76. Sandoz offered me to look at cyclosporine but I wasn't interested in those days. Took a few more years until Oscar told me to do something useful that I came back. So I would have been way ahead if I could have worked that in.

04-00:49:18
Burnett: And one of the things that you discovered in that research is that, and I may be completely misreading this, that the drugs interact with one another. Is that right? That you—

04-00:49:33
Benet: They go back and forth. They're reversible processes. One gets converted into the other and they go back and forth all the time.

04-00:49:41
Burnett: Oh, biochemically they become one another.

04-00:49:43
Benet: Right, yeah. They become one another.

04-00:49:43
Burnett: In a kind of—okay.

04-00:49:46
Benet: And that's what we were trying to study. Is one a better immunosuppressive than the other because they go back and forth? And what makes them go back and forth? And what happens to them in terms of metabolism? Which one gets metabolized? Does one metabolize and the other doesn't get metabolized? Why do they go back and forth? Now, these were the same kinds of things we were looking with the acyl glucuronides. They were going back and forth, too. So it was a very similar process but now applied to transplant drugs, to what we were looking at with the non-steroidal anti-inflammatory.

04-00:50:21
Burnett: When they started doing this, they would put in equal amounts?

04-00:50:25
Benet: Well, they would dose prednisone.

04-00:50:28
Burnett: Right. Yeah. They would become prednisolone.

04-00:50:28
Benet: Yeah. Become prednisolone but they never looked at that and they didn't know what would happen or where it would go or whether that was good or whether that was bad or whether it was important or not. So that's what we were trying to find out. When you dose this, what really happens to it? Are you changing the immunosuppressive potential or the metabolism and what can affect it? So that's what we were trying to do in those early days.

04-00:50:57
Burnett: Okay. And I guess one of the other families of research, experimental research programs that you had was in nitroglycerin?

04-00:51:05
Benet: Yeah. Okay, yeah. Yeah. Big area for us is nitroglycerin.

04-00:51:09
Burnett: Yeah. And when did that start for you?

04-00:51:11
Benet: Okay. So Sid was working on nitroglycerin and he had a graduate student who was just beginning, Pat Noonan, who came actually from Searle. He had worked at Searle, a drug company that doesn't exist anymore. And he came to work on nitroglycerin because nitroglycerin was a Searle drug. But he died. Sid died when the student maybe had been there four or five months. So the student started working with me and I picked up the project to try to understand what were the pharmacokinetics of nitroglycerin, how did the body handle it, whether metabolites were active or not active and how did you want to dose it and should you dose it orally? If you give it transdermally, we ran some transdermal studies. If you give it sublingually and how active are the metabolites versus the parent drug and what is the bioavailability of a sublingual dose and how much—none of this was known. There were no good pharmacokinetics on nitroglycerin. So we ran a whole bunch of studies on nitroglycerin and a number of students worked on that, yeah, and defined the kinetics of nitroglycerin and the various metabolites of nitroglycerin. Yeah.

04-00:52:25
Burnett: And you were writing about clearance concepts. You wrote that the other big parameter is bioavailability. And we're going to talk about that next time. But were you thinking of capturing a similar kind of concept for bioavailability in the seventies? Is that something you were actively working on or was it more of a case-by-case, drug-by-drug research program?

04-00:52:58
Benet: No, no. I was very interested. If you go back and look at some of those early pharmacokinetic books, and I don't know what I talked about here, but most likely I talked about bioavailability and what affects bioavailability and is it only the liver, is it absorption, and my big contribution was the gut, that that's

a major thing. But I was always interested in it. Some of my earliest studies when I did monkey work here was I had these monkeys with Thomas cannulas in them to find out about absorption and what happens with drugs.

04-00:53:38
Burnett: That's just a port, right? A cannula?

04-00:53:40
Benet: Yeah, it's a port. It's a port. So you have a monkey with a permanent, surgically implanted—Larry Way, who was the head of GI surgery, worked on my monkeys. I had a lot of guys here did surgery on my monkeys because it's a very collaborative place.

04-00:53:54
Burnett: How many monkeys did you have?

04-00:53:56
Benet: At one time I probably had twelve.

04-00:53:58
Burnett: Twelve, okay.

04-00:53:59
Benet: And would cycle them through because sometimes they would die. These weren't terminal experiments so we would continue using our monkeys all the time.

04-00:54:09
Burnett: Did you have a veterinary expert or technicians to work?

04-00:54:10
Benet: Oh, yeah. Yeah, here. Here. This was big. And probably at one time I was probably the biggest monkey user here. It just became too onerous to do the monkey studies. I had to give it up in terms of the outside world, in terms of how they were reacting to it.

04-00:54:29
Burnett: How activists had reacted to vivisection.

04-00:54:30
Benet: Yeah, and the type of money that it cost. My first monkey probably cost me about a hundred bucks and the last monkey I bought probably cost me somewhere around sixteen, seventeen hundred dollars. And this is in the eighties. So it just became—

04-00:54:44
Burnett: Prohibitive.

04-00:54:55
Benet: And I had NIH grants to fund this stuff, too. And so we were discovering what would happen with absorption. So absorption was always something. Because

when I went from physical to biological, I was [looking at] pH and it was the pH in the intestine that I was interested in and how this affected absorption. So I was always interested in going across the gut membrane and what affects going across the gut membrane.

04-00:55:10
Burnett: At the time, I remember in the eighties and nineties the sort of animal-rights claims and the scientists who were really committed to removing animals from the—the argument was that there's no value added from doing animal research. How do you feel about that?

04-00:55:31
Benet: Oh, I don't agree with that at all. We've made major advances in terms of how the body handles drugs and what things happen by our animal research. And not necessarily the pharmacokinetic point of view. Monkey studies are important because they're going to be the closest to man when you're trying to say, "is this going to be safe in man?" And won't always reflect what those are in man and many times it doesn't but it's a model that you want. Because I value the life of humans more than I value the life of animals. Although my latest company has won an award from PETA and there's quotes from PETA saying I'm a good guy because I'm interested in these microfluidic devices that don't use animals.

04-00:56:22
Burnett: So you have done research and made contributions in that domain of—

04-00:56:27
Benet: Right, right. Yeah.

04-00:56:27
Burnett: —non-animal but it's out of necessity probably, as well. Is that—

04-00:56:33
Benet: Yeah. No, no. These are better ways to do it.

04-00:56:35
Burnett: These are?

04-00:56:35
Benet: These are better ways to do it now, yeah.

04-00:56:35
Burnett: Okay. So there are—

04-00:56:38
Benet: But there's certain things you need to do. But when animals were freely available, there's a lot of work that probably didn't need to be done in animals that was easily done in animals. Things like that. Do we have time? What do you got?

04-00:56:56
Meeker: About four minutes here.

04-00:56:58
Benet: So let me tell you my best monkey study. Okay. I got called by the NIH, National Institute of Drug Abuse. No, NINDS, National Institute of Neurological Disease and Stroke called me up one day and said, "We know you have monkeys with Thomas cannulas in them. We are investigating the drug Carbamazepine, anti-epileptic drug, Tegretol, and we're running studies up in University of Washington in their primate center and we can't get any blood levels when we give the drug Carbamazepine to these monkeys. And so it's not working for us and we figured—"And I said, "Well, how do you give it?" "We give it with a banana. We put it in a banana because it's lousy tasting. Would you actually put the drug with a banana into the Thomas cannula and see if you get blood levels? Because we think maybe there's an interaction between the banana and the Carbamazepine." So we did that. We ran the study and showed them, "Nah, you easily get blood levels. There's no interactions between bananas and Carbamazepine." Now, this is the same time *Yellow Submarine* is out. So actually everybody in the community thinks there's something magic about bananas because the Beatles are doing *Yellow Submarine*. We're sort of in the middle of the whole thing. So we said to the NIH, once we told him this, "Well, tell us how you did the studies up in Washington so maybe we can reproduce them here." They said, "Okay, so what we do is we know the monkey, it's bad tasting, so we put it in a banana and we give it to the monkey. The monkey immediately puts it into his mouth and holds it in his pouches." "And we sit there and look and see when the monkey swallows the banana and then we start the clock and then we take the blood level samples and we never see anything we're doing." I said, "Oh, okay." So I said, "I'm going to repeat the study." So what I do is I take my monkey, he's sitting in a chair, but I put him in a box that has three sides in it so all he can see is forward. Okay. And I've got somebody sitting just like they did at the University of Washington, sitting in front of him looking to see if the monkey swallows and starts the stopwatch. But I have somebody else sitting on the other side of the room that the monkey can't see, okay. And so we did the same thing. We gave the Carbamazepine, which is really bitter tasting, in the banana. The monkey immediately grabs it, put it—and the monkey's not going anyplace so he doesn't have to swallow it. He sits there and he's moving it around from one cheek to the other cheek and stuff like that and we're sitting there. And the guy is sitting there watching him to try to start the stopwatch. But you can't watch the monkey 100 percent of the time. You look at your shoe or something like that. When you look at your shoe, the monkey goes, [spitting sound]. Spits out the Carbamazepine in these little balls that are over in the side of the room but my other guy here sees it. [laughter] And so we tell the people. I said, "Go into your room in the University of Washington. Look in the corners of the room. You'll find these little white balls of Carbamazepine that the monkey has spit out because he's separated it out from the bananas." That's exactly what happened. [laughter]

04-01:01:17
Burnett: Brilliant. Brilliant. Well, on that note we'll pick up next time in the 1980s and we'll talk about the next phase of your research career.

04-01:00:29
Benet: Okay, great.

04-01:00:29
Burnett: Thank you.

04-01:00:30
Benet: This has been fun, as always.

[End of Interview]

Interview #3 November 14, 2014
[Audio File 5]

05-00:00:06
Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Technology, and Medicine series. It is November 14, 2014 and we're here at Parnassus Avenue, UCSF. So last session you remarked that you have always been active in researching drug absorption, going back to your work on pH in the sixties and seventies and your work with monkeys in the 1970s. And there's a quotation from one of your papers, actually leaping ahead to 2005, that you're more excited by exceptions to rules than the principles themselves. You're looking for principles but you write, "As in science as a whole, exceptions are clues to new discoveries and new hypotheses." So I'd like to focus on new frameworks for bioavailability in the 1980s. Could you talk a little bit about the conventional wisdom surrounding bioavailability in the 1980s? What did people think it was?

05-00:01:18
Benet: Sure, okay. So the development of clearance in the seventies allowed us to make a prediction and a recognition that when a drug was absorbed it had to go through the liver first before it got into the systemic circulation. And once we had clearance concepts we were able then to predict what kind of first pass loss would occur in the liver. And so a drug like Labetalol, for example, a beta blocker, is completely absorbed, has 17 percent bioavailability, but it's completely absorbed. It all gets metabolized in the liver, or 83 percent, gets metabolized in the liver as it is absorbed. And you could predict that. We could predict that. We could take the clearance in the liver and predict what the bioavailability would be. So that's where we are in the 1980s. We recognize that two things are related to bioavailability. One is absorption. Is the drug going to be absorbed? And the other, it's going to be lost in the liver, okay, first pass in the liver. And so that's the general field at that time.

05-00:02:31
Burnett: Okay. So speaking of exceptions, then, when was the first inkling that you felt that things were more complicated than that?

05-00:02:42
Benet: Okay. So one of my fellows, Mary Hebert, who's a professor at University of Washington now, came to me. And we were doing transplant drugs. We'd been doing transplant drugs for a number of years. Did we talk about how I got into trans—

05-00:02:57
Burnett: We talked a little bit about—

05-00:02:58
Benet: Yeah. That Oscar Salvatierra said, "Do something useful."

05-00:03:00
Burnett: Yeah, that's right. "Do something useful." Exactly. Last session.

05-00:03:01
Benet: Yeah, right. Right. So she said to me, "You know, we've got a problem because all these transplant patients who are immunosuppressed get all kinds of diseases. One of the diseases that they get now is tuberculosis and we're seeing a big increase in tuberculosis of our transplant patients. And the transplant drugs don't seem to work in those tuberculosis patients." And I said, "I know why. Because the drugs that they take, they take a triple cocktail that was Isoniazid, Rifampin, and Ethambutol were the three drugs that they took. And Rifampin is an inducer. So they're going to get induction of their enzymes and that's why they have poor bioavailability. So we know we just need to give higher doses but let's run a study and prove it, show exactly what happens. And so we did. We ran a clinical study where we gave oral and IV cyclosporine with and without induction of the enzymes with Rifampin. And we got all the data and we looked at it and we couldn't explain it. We saw a change in what went on in the liver but it didn't explain this decrease in bioavailability at all. So we said, "Something else has to be going on."

At the same time a colleague of mine at the University of Michigan had also suspected that there were some problems and he asked the transplant surgeons if he could give somebody going in for a liver transplant, if he could give them a dose of cyclosporine prior to their surgery and then take a blood sample. Okay. And he got blood samples from two patients. They didn't have livers. He took the blood sample in between the time that their old liver was out and their new liver wasn't in. They slipped him a dose of cyclosporine and he could get one blood sample from each of those two patients. And one of them he found 50 percent of the cyclosporine in the blood was metabolized and the other he found 25 percent of the blood and he published a little anecdotal article. But we knew about it.

05-00:05:35
Burnett: What was the state of the informed consent letter?

05-00:05:39
Benet: That's a good question. I don't think you could do it today. Yeah, I don't think you could do that today. This is early 1990s. And he published a little note. *Lancet*. He published a note in *Lancet* that said he gave this drug. They didn't have livers and yet half of the blood sample was metabolized and the other one 25 percent. And we were doing our study at the same time and we said, "Well, it has to be the gut." Okay. And so what he did was actually take a gut sample and look at where the enzyme was in the intestine. Now, nobody at that time, and I think we've talked about this before because this is my patents leading to AvMax. Yeah.

05-00:06:25
Burnett: A little bit. Not so much. We've kind of black-boxed that for now.

05-00:06:29
Benet: Okay, all right. So no one at that time thought intestinal metabolism was important. Certainly intestinal metabolism by cytochrome P450 3A. The reason they thought that it wasn't important, and all the textbooks actually said it wasn't important, was because only 5 percent of the enzyme that was in the liver could you find in the intestine. And so they thought that was just too little. And basically there was only one enzyme. There was really cytochrome P450 3A. There was a whole bunch of cytochrome P450s and that was the only one. But that turns out to be the enzyme that's the biggest in terms of human metabolism. So most drugs that are going to be metabolized by cytochrome P450, about half of them are metabolized by CYP 3A. So if you're going to have one there, that's the right one. And Paul did a photomicrograph of the intestine.

05-00:07:18
Burnett: And this is Paul? Oh, sorry.

05-00:07:19
Benet: God, you know—

05-00:07:20
Burnett: Well, we'll fill it in later.

05-00:07:22
Benet: Yeah, yeah, yeah.

05-00:07:40
Benet: This is old age. This is definitely old age. Good colleague, a friend of mine.

05-00:07:45
Benet: I just wrote a letter for him to get some award. Okay.

05-00:07:49
Burnett: It'll come back.

05-00:07:50
Benet: Paul Watkins. So he took this photomicrograph that showed that, yeah, there was very little cytochrome P450 3A there but it was right at the tip of the villi. So every drug molecule that went through the intestine had to go through the cytochrome P450. And so there was very little there but it was a gauntlet that drug molecules had to go through. And then he also showed there was a transporter there and this is what happened in this work.

Our data said there had to be metabolism in the intestine to explain what was going on with cyclosporine because we had a bioavailability that was only about 18 percent when we induced and we're predicting you should have had very little change just based on the liver. A very small change. And yet we were cutting the thing in half. And so we did the calculation and we said, "Okay, so F-absorption times F-gut," so bioavailability is going to be a function of three things. Before, in the eighties, we said it's just absorption

and how much gets through the liver. So if you calculate how much gets through the liver, you can calculate how much was absorbed.

So everybody at that time thought that the poor bioavailability from the immunosuppressants was due to the fact that they were very lipophilic, very poorly water soluble, and everybody thought they weren't absorbed. And, in fact, I was a consultant to Sandoz at that time in terms of their development of better formulations to try to increase the absorption. Because they thought it was an absorption problem.

05-00:09:28
Burnett: Was that the cyclosporine days or this is—

05-00:09:30
Benet: Cyclosporine.

05-00:09:31
Burnett: Okay, yeah.

05-00:09:32
Benet: Yeah, this is cyclosporine before my studies. Okay. Before my studies. So we said, "Well, then, there's got to be a gut portion of this. So it's not just 'bioavailability is liver-absorption' but it's got to be 'liver-gut-absorption'." So there has to be what is called Fg: the bioavailability going through the gut. And we calculated out that absorption times F-gut had to be 86 percent. So that meant that certainly the drug got absorbed.

05-00:10:04
Burnett: It's going somewhere.

05-00:10:06
Benet: Had to be absorbed. And we said it's probably the gut. And that was the paper that we published in 1995, and basically the title was you can't explain the bioavailability of the immunosuppressants based on our previous hypothesis in terms of bioavailability was only a function of the liver and absorption. And this was a completely new finding, so I wrote patents on it. And so I said, "Well, if you can inhibit in the intestine, not only—" We also recognized now it was P-glycoprotein that was sort of cycling the drug. So giving the enzyme multiple opportunities. And so we wrote the patents that said you can inhibit the intestinal enzyme and transporter to increase bioavailability.

05-00:10:50
Burnett: You patented the technique surrounding or the concept?

05-00:10:53
Benet: We patented the method.

05-00:10:54
Burnett: Okay, the method.

05-00:10:55

Benet: It was a method patent. So you can get three kinds of patient. You can get a composition of matter, which is the best, then a method patent, and then sort of a formulation patent. Those are the three types of patents. And the Patent Office, of course, always turns you down but they agreed. Nobody had ever said that if you could inhibit in the intestine, enzymes and transporters in the intestine, you could increase bioavailability. And we formed a company based on that, AvMax.

05-00:11:23

Burnett: Yeah. Could we back up a bit and talk about what's going on in neighboring sciences and molecular biology? In other words, how new is the research on what transporters are, for example?

05-00:11:44

Benet: Okay. It's still very early. Really the only transporter that people paid a lot of attention to for drugs were P-glycoprotein. And that was discovered maybe just four or five years before this, in the eighties, basically because they would be giving drugs to cancer patients and the drug cocktail seemed to work and then all of a sudden the patients became resistant. And a couple of very well-known scientists discovered that what was happening was the tumor had constitutive composition of P-glycoprotein as transporter and as a protective mechanism for the tumor it up-regulated the transporter. And what that transporter did, it was an efflux transporter, so it pumped the drug out of the tumor. It was a protective mechanism for the tumor. But then people said, "Well, where is this thing? Where is this transporter?" And it's all over the body. It's in the brain, it's in the gut and so on. But we were the first people to say, "Well, this transporter and this enzyme are probably working together." This was a pretty famous paper for us where we said enzymes and transporters work together.

05-00:12:53

Burnett: The interplay.

05-00:12:54

Benet: That's a 1995 paper in *Molecular Carcinogenesis* that said an enzyme and a transporter can work together. And the reason we published it in *Molecular Carcinogenesis* was because all the people that knew about the transporter were oncologists. But what we said is, "Wait a minute. If you're going to pay attention to the transporter you better pay attention to this enzyme because it looks like they worked together." And that's what that paper said. You should pay attention both to an enzyme and a transporter.

05-00:13:22

Burnett: And the basic understanding of the cell and these proteins that run across the membrane, like adenosine triphosphate, and all of that kind of stuff, the ACT2—

05-00:13:33
Benet: That's all known.

05-00:13:33
Burnett: —that's all known.

05-00:13:34
Benet: That's all known.

05-00:13:35
Burnett: And how long had been discussed and worked on? That's way back?

05-00:13:37
Benet: That's way back. And these transporters are ATPase transporters. That's their mechanism of how they operate.

05-00:13:48
Burnett: Right. So they work as pumps basically to—

05-00:13:51
Benet: Right. That's their energy source, is ATPase. For those efflux transporters. So that was known about these transporters. And, in fact, people were using the assays of ATPase as a measure of how much the transporters were there. But that turned out not to work too well.

05-00:14:09
Burnett: But it seems like there are earlier instances in your research where you're looking at complicated exceptions. So I'm thinking about the work you do with SK Gupta in the late eighties on the kinetics of cyclosporine.

05-00:14:29
Benet: Right, and food effects.

05-00:14:29
Burnett: And food effects. Did a light bulb start to go on there? Is that a completely different thing?

05-00:14:35
Benet: No, it's not. Suneel had carried out his PhD studies with Malcolm Rowland and actually worked on cyclosporine and then came to work for me as a post-doc. It was well-known there were food effects. It was well-known there were food effects on cyclosporine and it increased—

05-00:14:59
Burnett: And on a lot of drugs, I suppose, right?

05-00:15:02
Benet: Yeah, and a lot of drugs. And it increased the bioavailability. So we were trying to understand why. What are food effects doing? And we published a paper in *Biochemical Pharmacology* in terms of looking at lipids and various things that didn't really give the right answer. Didn't give the right answer. So

we knew there was a food effect and we said, “Well, if this turns out to be a transporter-enzyme thing, we ought to be able to see it in the liver, too.” And we had already sort of recognized that what was happening in the liver was the opposite of what was happening in the gut because the efflux transporter on the liver was on the apical side going into the bile. It was after the drug got into the cell. But in the gut it was right on the apical border next to the intestine. So the interaction between the enzyme and the transporter were different, okay, because when you come into the intestine, you hit the transporter first and then you hit the enzyme. So if the drug gets by the transporter and then has access to the enzyme, if you induce the transporter, what it’s going to do is take that drug and pump it back out again. If you inhibit the transporter it’s only going to give the enzyme one chance to metabolize it. So inhibiting the transporter in the intestine—this is what we showed in these studies. Inhibiting the transporter in the intestine will increase bioavailability. You’ll stop the cycling. The transporter won’t cycle the drug. So the drug would come into the cell, go back out again, and because it’s very lipophilic it would come into the cell again. So the enzyme has multiple chances to do it – and this is what we hypothesized in the *Molecular Carcinogenesis* paper – that what the transporter is doing is giving the enzyme multiple chances to metabolize the drug.

05-00:16:55
Burnett: It’s chewing it, in a sense.

05-00:16:56
Benet: Right. But in the liver it’s the opposite because the transporter is on the other side of the enzyme. So you hit the *enzyme* first. You come in on the basal lateral side. You hit the enzyme in the hepatocyte, *then* you hit the transporter. So now if you inhibit the transporter, you’re keeping the drug inside the cell instead of making it go through faster and you’re going to get more metabolism. And those were the studies that we carried out. So we then said, “Well, let’s take a look at this cyclosporine, get rid of the gut effect, can we see this transporter-enzyme interplay in the liver?” Because if we’re inhibiting the transporter, we’re going to get more metabolism; if we induce the transporter, we’re going to get less metabolism, and that’s what we showed. Nobody had ever tested the high-fat meal effect on a drug given IV. So that was the first study. And we got this data that just says, “Oh, this fits right in with our hypothesis on how the enzyme and transporter are working.”

05-00:18:03
Burnett: And when you’re talking about induction and inhibition of the transporters, does that mean you’re introducing sort of sympathetic chemicals that increase the production of that protein?

05-00:18:16
Benet: Right, exactly.

05-00:18:16
Burnett: The numbers of the proteins will—

05-00:18:19
Benet: In other words, the amount of the protein is getting more. We're not really inducing the transporter. Well, we actually were. But we're making more of it. So that was the major effect. We knew that you made more enzymes with these inducers and therefore you should get more metabolism.

05-00:18:38
Burnett: Right, right. This is explained in detail in your papers. And it was expressed as a hypothesis at the time but this is a really complex process. Once you explain it it's so clear. But, how did you *prove* conclusively that—

05-00:19:02
Benet: Okay, so it *is* a hypothesis and Carolyn Cummins, who was the graduate student at that time, who is now a professor in Toronto, in the faculty, that was her thesis. Can she prove that this hypothesis is correct using isolated cellular systems?

05-00:19:17
Burnett: Cellulars, okay. Right.

05-00:19:18
Benet: So we at that time had availability of a transfected Caco-2 system that had the transporter and had the enzyme and that's what we did in our cellular system.

05-00:19:28
Burnett: That's a cell line? It's a cancer cell line, right?

05-00:19:31
Benet: Right, yeah. Right. Yeah. And, in fact, that cell line's not available. We still have some of it. We don't share it with anybody. But we're the only people that have that cell line still. Yeah.

05-00:19:43
Burnett: That is a whole fascinating story in itself. So that's working with a different set of techniques because historically you and everybody else, it seems, had been working with animal and human studies.

05-00:20:03
Benet: Right. Okay. So now we're taking—

05-00:20:04
Burnett: Right? And in vivo—

05-00:20:04
Benet: —a cellular system and we're running—because our hypothesis is you go this direction you're getting a different effect than you go this direction. So we want like a nice little cell system that we can put the drug on the apical side

and find out what happens on the basolateral side. But we can also put the drug on the basolateral side and find out what happens on the apical side.

05-00:20:25
Burnett: So when did you first become aware of using cellular techniques to work with this stuff? I don't know if you remember but—

05-00:20:35
Benet: No, no, I do remember. I do remember because I used to look at these guys who would show these photomicrographs and I'd say, "Say, that kind of looks kind of neat," but I don't know anything about that. And they would show these ladders and what kind of protein levels were at each molecular weight and stuff like that. And so we said, "Well, we need to do this." We needed a test system and this test system at that time was available to us. We could get it. Because the molecular carcinogenesis papers had an enzyme and a transporter work together, so you got to try to prove it. Yeah. Okay.

05-00:21:18
Burnett: And is this native to UCSF or were you looking—was it an international—

05-00:21:20
Benet: No, there was nobody else. There was nobody else at UCSF doing this at that time.

05-00:21:24
Burnett: Okay. And so where was the center for cellular analysis of molecular—

05-00:21:29
Benet: Okay. There's a lot of guys doing cellular studies here. There was all kinds of expertise doing cellular studies but nobody was working with a gut transporter system with an enzyme transfected into it. So that was the unique part. So at this time cellular systems were being used in molecular biology and for all kinds of things. Liver cells and gut cells and brain cells.

05-00:21:53
Burnett: And the Cummins papers are early 2000s? Is that right? Or earlier than that?

05-00:21:59
Benet: Yeah.

05-00:22:01
Burnett: Late nineties?

05-00:22:02
Benet: Yeah, yeah, late nineties. Yeah, late nineties. Yeah.

05-00:22:06
Burnett: And so those techniques had been around for a while. But she worked with you?

05-00:22:10
Benet: Yeah. She didn't know anything about it, I didn't know anything about it. So we learned how to do it. If I had to say another thing, I like to do stuff that I don't know. So I like to try to use new techniques and to go into—but we needed this. If we're going to prove it we have to have this cellular system. Now, after we did the cellular systems, then we did an isolated perfused intestine to show that it works, that what we predict would work. But initially all the proof of the hypothesis was done in the cellular systems.

05-00:22:45
Burnett: And the isolated – oh, I'm thinking of the rat liver perfusions.

05-00:22:49
Benet: No, this is a rat intestine.

05-00:22:50
Burnett: Rat intestine.

05-00:22:50
Benet: And Caroline's the first author of that paper also. Yeah. And it was in *JPET, Journal of Pharmacology and Experimental Therapeutics.* So she did the cellular systems and the isolated perfused intestine. That was all her thesis and she did a really wonderful job. So I'm blessed being here at UCSF because you don't really need to know anything, you just have all these wonderful students and you say, "Why don't you do this?"

05-00:23:19
Burnett: And they go and find out how to do it.

05-00:23:19
Benet: And they figure out how to do it. Yeah, yeah. Right.

05-00:23:21
Burnett: Yeah, yeah. That's incredible. So you learned that there's a transporter, a protein, and an enzyme that are working together as a kind of protective mechanism to—

05-00:23:36
Benet: That was our hypothesis.

05-00:23:37
Burnett: —for the activity of the gut, for cyclosporine.

05-00:23:48
Benet: Well, then we went on and did the other immunosuppressors and showed they did the same thing. Yeah.

05-00:23:50
Burnett: Right. So there's other—

05-00:23:51
Benet: Yeah, yeah. Sirolimus and Tacrolimus, yeah.

05-00:23:55
Burnett: And it's not just cyclosporine, as well? These are—

05-00:23:59
Benet: Oh, it turns out to be a huge number of compounds.

05-00:24:04
Burnett: Can you talk about, I mean, this is the age of the gigantic blockbuster drugs, as well, and this is really important stuff.

05-00:24:12
Benet: Yeah, okay. So this was really important because at the end of the 1990s a number of drugs came onto the market that were CYP3A substrates. Mibefradil, terfenadine, cisapride, astemizole. They all came onto the market. And in their label it said these are CYP3A substrates. So if you inhibit CYP3A you got to worry about the interactions. Okay. This is in the label. But when the drugs got out in the market the interactions were so much bigger than had ever been predicted from just the enzyme and we were able to explain that. So we were able to explain the reason you didn't figure it out was because when you inhibit the enzyme you also inhibit the transporter and those things are *additive*. And so you're going to see a much bigger interaction than you predicted before. And you won't get it in microsomes because there's no transporters in microsomes. You would have got it in hepatocytes but people didn't look, or enterocytes, but nobody looked at enterocytes in those days. Okay. And basically it was this interplay that was going on. And if you gave the drug IV you wouldn't see it because the liver works opposite than the—

05-00:25:30
Burnett: Right. This is oral dosing?

05-00:25:31
Benet: Yeah. This is oral dosing where it's additive. In the liver it actually goes the opposite way. They cancel each other out. All of a sudden, at the end of the 1990s we were able to explain why these drugs had this problem and it was because of the interplay of the enzyme and the transporter. And so a number of drugs got taken off the market because they had significant toxicity, where basically we could have explained it if we knew this theory in the mid-1990s, before these drugs came on the market. But nobody knew this. But now everybody recognizes it and so you know if you're going to inhibit the enzyme you're going to inhibit the transporter, too, and there's a big overlap, which we were the first to show. There's this huge overlap between substrates of CYP3A and substrates of P-glycoprotein. And so if you inhibit one you're going to inhibit the other and you'll probably have those double effects. So everybody now recognizes this. But this is the end of the 1990s. Completely

new thought and understanding and able to explain why these toxicities occurred.

05-00:26:31
Burnett: And when those drugs were pulled off the market, once this was well-understood, were they able to adjust dosing regimes to—

05-00:26:39
Benet: Those drugs never came back but the industry recognized, "No, I got to pay attention to both of these now. And if I'm going to have a drug, I got to make sure if I inhibit one, I got to look and see what's going to happen if I inhibit the other at the same time." And so now it's recognized. So today we know if we have a CYP3A and a P-glycoprotein substrate we pay attention to it and we look and see is this going to possibly happen.

05-00:27:04
Burnett: Okay, okay. And so just to back up a little bit to the initial experiments that you did with CYP3A and P-glycoprotein. You did some experiments with vitamin E? Is that right?

05-00:27:26
Benet: No, we didn't do the vitamin E.

05-00:27:26
Burnett: Oh, okay.

05-00:27:27
Benet: Vitamin D. Is it vitamin E? I never did any experiments with vitamin E, yeah, that I know of.

05-00:27:35
Burnett: So vitamin E, it would not affect CYP3A but it did affect P-glycoprotein.

05-00:27:41
Benet: No, no, this is vitamin D.

05-00:27:42
Burnett: Oh, yeah? It said vitamin E. I must have misread it.

05-00:27:44
Benet: In where?

05-00:27:46
Burnett: In the paper describing the history of [transporter-enzyme] interplay.

05-00:27:47
Benet: Okay. Okay. So what we're doing is Paul [Watkins] is trying to do the same studies.

05-00:27:58
Benet: But he doesn't have the transfected cell line. So what he's doing is taking the cell line and treating it with vitamin D and that up-regulates the enzyme. So in the paper where we described the methodology we compare it to Watkins' study and show that we think our system is better, more controlled, and we're able to control it. But vitamin D will take and up-regulate the enzyme.

05-00:28:38
Benet: Yeah. Paul's a GI guy and he was at the University of Michigan when he did those studies. Then he moved to North Carolina. Actually is a big liver expert. The Hamner Institute is what he runs.

05-00:28:51
Meeker: So his name again?

05-00:28:52
Benet: Watkins. Paul Watkins.

05-00:28:58
Benet: And, actually, I don't know if you want to get into Avmax because Paul was the chair of the scientific advisory board for Avmax because there was so much overlap in terms of what he was doing and what we were doing.

05-00:29:13
Burnett: We may get into that. It depends. But I try to keep some of this stuff segregated because there's a lot of different things going on. And you did talk about Cummins. And you did talk about why this work is important. So just for the layperson, most often, drugs are interpreted by the body as strangers.

05-00:29:48
Benet: Foreign substances. Xenobiotics. Yeah.

05-00:29:49
Burnett: Right. And so that's part of what you're dealing with. And this has long been known that it's absorbed, it's broken down, or it's treated as a poison and it needs to be processed and eliminated from the body and the key is you want to know what proportion of the drug gets through to the site of action, right. That its disposition is correct for what you dose. And what you're discovering—

05-00:30:19
Benet: Let me stop a minute, Paul because –

05-00:30:19
Burnett: Sure, sure.

05-00:30:20
Benet: Looking at the references here, it's important to say that Erin Schuetz, who was at St. Jude's, at the same time that we published the *Molecular Carcinogenesis* paper, a month later she had a different cell line and she published. We beat her by a month in terms of that there's an enzyme and a

transporter possibly working together. And so we weren't the only people doing it. Erin also saw it. We just were lucky enough to beat her by one month in terms of the publication.

05-00:30:56

Burnett: Well, there's a convergence, and this often happens, right, that it's in the air. Everyone's talking about this kind of stuff. We understand that there are complex exceptions, as you say. That's what science is, is dwelling on these exceptions. So, could you talk about how the way that the body treats xenobiotics is essential to understanding multidrug resistance, for example? Like why this is so important, because now that the cocktails are becoming more important, especially in the nineties when we're talking about HIV cocktails—could you talk a little bit about why that's important or interplay is important?

05-00:31:42

Benet: Sure. All drugs are viewed by the body as bad. The inherent thing is the body should be protected from foreign substances. And so there's all kinds of things in the body to do this. So we discovered really the enzyme systems in the eighties. We discovered the transporters in the nineties and now we're discovering lots more transporters. So as scientists we don't recognize those things. For example, all of the early work on the brain and drug getting into the brain was all thought to be just lipophilicity. But big transporter effects in the brain. But none of that was recognized in the eighties or the nineties. It took the science moving forward for us to recognize how different organs in different parts of the body are protecting themselves. So drugs, to work, have to overcome those barriers. Okay. So a lot of drugs aren't absorbed because the body said, "Oh, I don't want you getting in here!" And so the way the intestine is organized sort of stops those things coming in. But then it says, "Well, there are still some things that are going to get in, so I have to have some backup mechanisms if they get in, so I have some enzymes that are going to break it down so it gets in. And if the enzymes aren't good enough, I'm going to have some transporters there, too, that help it. I'm going to keep pushing it back and I'm going to give the enzyme multiple opportunities." And so in the cancer field, the tumor says, "Okay, I'm going to protect myself." It does stuff to protect itself from these foreign substances. This is a terrible thing. The cancer is a terrible thing but it's inherent in your body. And it's still trying to protect itself from foreign substances because it's part of your body now and so all our work in developing drugs and other therapies is actually to overcome the body's natural mechanisms to stop these drugs and other systems from getting into it.

05-00:33:47

Burnett: Is that what, and forgive me for not knowing this definition, but the excipients? That's an additive?

05-00:33:53
Benet: No, no. Yeah, excipients are the other things that you add to a drug formulation to improve the manufacturing and to make the tablet so you can do it really well. But our patents were that nobody had ever looked at the excipients as potential inhibitors of the transporters and so we were actually proposing that the excipients are doing much more than anybody thinks they are. There's a really perfect example in the history. So when we first developed tetracyclines as antibiotics—the drug company was Lederle. I was a consultant to Lederle in developing those things. And they were orally active. And there's a series of papers, probably in the sixties, from Lederle where they're making formulations of tetracycline to improve the bioavailability of tetracycline. They don't know what's going on. But basically, if you go back and look at those formulations later on, what you realize is that they were using calcium carbonate as the inert ingredient, the excipient to make the tablet. All their new formulations did was decrease the amount of calcium carbonate and put something else in. So the formulations got better and they thought it was because of what they put in but we later discovered it was just because they made calcium carbonate less because calcium was chelating with the tetracyclines and making them unavailable. So all these formulations that Lederle made, and maybe seven or eight publications about how we can make a better formulation—had nothing to do with the new stuff they put in. It's just that they took out the old stuff. So we didn't know that. We didn't know that tetracycline chelates with calcium. Chelate just means—it's like a crab. It just—

05-00:35:51
Burnett: Binds to it.

05-00:35:51
Benet: —binds to it and so on. So that's sort of the kinds of things that happen in science all the time. So they're experimentally making these new formulations. They work better and better. We've overcome the body's problems of getting tetracycline. Tetracycline has no trouble being absorbed. They just made a lousy formulation initially that actually made it so it didn't get absorbed. And as they changed that formulation it got better and better.

05-00:36:17
Burnett: So when you're talking about inducing or inhibiting the production of an enzyme or a transporter, you're going to use a drug like Rifampin, right, and you make a formulation that has a certain ratio of X-drug that was de—

05-00:36:33
Benet: No, you don't want Rifampin in there because that's an inducer. We discovered the reason these transplant patients with TB, the drug wasn't working was because Rifampin was messing everything up by inducing the enzyme and the transporter.

05-00:36:47
Burnett: So that was the example of understanding multi-drug resistance?

05-00:36:52
Benet: Resistance.

05-00:36:52
Burnett: Resistance, okay.

05-00:36:53
Benet: But the reason I got into this was we then recognized that excipients could be inhibiting transporters. And since nobody knew anything about transporters, nobody had ever looked at transporters, and so we took what are called GRAS substances: generally recognized as safe. In other words, these are substances that the FDA says, "You can put these in formulations. They don't have any effect whatsoever." Okay. And they don't. They don't have any biological effect like that. But we said, "Ah, maybe these things are inhibiting transporters and nobody's ever looked at it." And we actually ran a bunch of those excipients and we put those in our patents. That says, "Oh, no, these actually do have some activity. You just didn't know how to look for their activity." And their activity is something that would enhance absorption and that's what those patents were.

05-00:37:40
Burnett: And that's a method patent? Is that what it—

05-00:37:45
Benet: Yeah, it was a method patent. Yeah. Using these things to inhibit.

05-00:37:50
Burnett: So the drug companies could then test, in future, test their excipients for effects on drug transporters and this is how you do it.

05-00:37:57
Benet: Right. And so the FDA actually, when it made its first regulations on good bioavailability and they were going to waive in vivo studies for a certain class of drugs, what they required was that the company show that all their excipients didn't have any effect on the transporters. So that was a result of sort of that early work. Yeah.

05-00:38:25
Burnett: So it's pretty incredible work to take assumptions that people had about absorption of drugs and argue based on these anomalies, explain these anomalies, right, and then you embark on a kind of research program where you move beyond cyclosporine to other drugs and other transporters, right?

05-00:38:58
Benet: Right, right.

05-00:38:59
Burnett: Were there any outstanding differences when you moved to these other—was it kind of the same process of now we understand how this works?

05-00:39:09
Benet: No.

05-00:39:09
Burnett: No.

05-00:39:10
Benet: P-glycoprotein was an efflux transporter. Okay. So we did all the work on efflux transporters and so when Yvonne Lau was a graduate student we said, "Well, let's take a look at the uptake transporters. Has anybody ever looked at the interplay between uptake transporters?" And so we published some studies in the mid-2000s saying, "Look, uptake transporters also. You got to pay attention to it, too. You can have these interactions that can go on." So that's a natural progression. It just hadn't been done. But to us it was the next obvious thing you're going to do. If an efflux transporter has these interactions, wouldn't you expect an uptake transporter to have some different kind of interaction?

05-00:39:56
Burnett: And the research on transporters and enzymes has continued?

05-00:40:02
Benet: Yeah. Yeah. Because it led to BDDCS. But it's continued. Yes. Okay. So as opposed to my colleague Dr. Giacomini and many of my other colleagues who actually are interested in the protein structure of these transporters and cloning them and understanding, that's not my interest. My interest is what are the basic principles. No matter how well you understand the transporter you're not going to get it right if you don't understand the basic things that are going on in terms of transporters in the body. So what I've tried to do in my research, and what I'm most interested in, is understanding the basic principles as opposed to actually discovering a new transporter or discovering the variance of that. Yeah. Because I'm not a molecular biologist. I'm not a geneticist and stuff like that. But I am interested in when that stuff can't explain what's going on. When that stuff can't explain what's going on, those are the kinds of questions I'm interested in because I then feel we're missing a basic concept of what's going on in the body. And that's sort of what I've been doing my entire career. That's what drives me to try to understand stuff that we can't explain. And so that's why I like to see data that I can't explain.

05-00:41:30
Burnett: And the service model of your approach comes in, too, because you're thinking about the utility presumably, as well. Like why—

05-00:41:41
Benet: I'm not so much basic. I am application to dosing of drugs. I'm always thinking about how am I going to improve therapy with drugs by understanding something we haven't understood in the past.

05-00:41:55
Burnett: Right, right.

05-00:41:59
Benet: What do you want to do?

05-00:42:00
Burnett: How much—

05-00:42:00
Meeker: We've got about fifteen minutes.

05-00:42:02
Burnett: About fifteen minutes?

05-00:42:02
Meeker: Yeah, on this tape.

05-00:42:03
Burnett: Okay. Because I do want to go into moving from these exceptions and these anomalies to explaining how they work and then the beginnings of an elaboration of a principle. Did that work start prior to the elaboration of the BCS, the Biopharmaceutics Classification System?

05-00:42:28
Benet: No, no, no. No, no. BCS was there and was having an effect and was a regulatory process that was really important and made it easier for companies and for regulatory agencies to improve certain drugs. My contribution there was that I have a lot of experience with drugs, so if people show me data, stuff like that, I see stuff that people haven't seen before. And sometimes it can be really simple. And what I saw in BCS was that all the drugs that were class one and class two, I knew that in humans they were metabolized. And all the drugs that were class three and class four, they weren't metabolized in humans. Today it's so obvious.

05-00:43:20
Burnett: If you have your experience. And not just your experience but your particular kind of experience.

05-00:43:26
Benet: Right, yeah, yeah. I know about drugs.

05-00:43:28
Burnett: Yeah, and metabolism in particular because you talked about, in one of your papers, the ways in which the research that you did was really important for the metabolism community.

05-00:43:39
Benet: Right. Yeah, it is.

05-00:43:41
Burnett: So that you talked about your *bona fides* in the metabolism community. So you were ready to see metabolism as an important—

05-00:43:56
Benet: Right. So Paul, I haven't thought about this before until you asked the question. But probably it's putting together these compilations, like Goodman and Gilman. So I never felt that the compilation on pharmacokinetics of drugs was good enough and I couldn't trust it and so that's why I started doing the Goodman and Gilman compilation, of the table in the back of Goodman and Gilman that says all that. So since I've done all those drugs I know them. When I think back on it, I would spend months going into the library and just looking up the drugs. I started that thing in 1980.

05-00:43:37
Burnett: Let's explore this a little bit. So can you talk about the work of compilation and what was going on in terms of the actual concrete work of putting together the appendix in—

05-00:44:49
Benet: In Goodman and Gilman.

05-00:44:50
Burnett: —in Goodman and Gilman, starting in 1980. And then you did updates.

05-00:44:55
Benet: Every five years.

05-00:44:55
Burnett: Every five years. And so it was almost like doing scales as a pianist. You're developing a kind of organic knowledge of all of these drugs. Can you talk about how that works?

05-00:45:17
Benet: I feel that if I'm going to understand what's going on a particular area I need to have good data that I can trust. And most of the data you can't trust that's out there. Or the compilations you can't trust. And the reason is because most compilations prior to that, somebody would say to their graduate students or post-docs, "Okay, you go out and look at this drug, you look at this drug, you look at this drug. Here's the information I want and we'll put it together." And there were compilations. But I'd look at those compilations. "I don't believe that. I know this drug does that and that." And it's because the graduate students and post-docs don't have the experience of being able to look at it. So my belief in doing the appendix was I had to look at every drug or my academic colleagues had to look at every drug. No graduate students, no post-docs.

05-00:46:07
Burnett: Right. So you divided up the work?

05-00:46:09
Benet: Yeah. We divided up the work but in essence I looked at every one.

05-00:46:13
Burnett: How many drugs are we talking about?

05-00:46:16
Benet: Well, the original compilation was like 150 or something. But it's now close to a thousand.

05-00:46:23
Burnett: And how many different parameters for each drug are you examining?

05-00:46:25
Benet: Okay. In that time the original one had ten. It had ten. If I can not break the—

[Ed. note: pause to show on camera an example of Goodman and Gilman table of drug characteristics]

05-00:46:51
Benet: Set up the table initially.

05-00:46:53
Burnett: You know what we should do? I would like to get some figures in your oral history and make a note that this should be one of them. Like just a sample page of the table. Okay. Oh, it's on Carbamazepine.

05-00:47:13
Benet: Yeah, anti-epileptic drug.

05-00:47:14
Burnett: Yeah. And it's got clearance, volume of distribution, half-life, effective concen—

05-00:47:22
Benet: Right, right. Yeah.

05-00:47:26
Burnett: Great. Okay.

05-00:47:27
Benet: Eight. There were eight parameters. And when I first did it, in the first compilation, I was allowed to reference it. But after that, Goodman and Gilman has page limitations and I wanted to include more drugs. So I'd have to cut some drugs out. After the first compilation I was not allowed to put the references in anymore.

05-00:48:16
Benet: So this is Goodman and Gilman, [*The Pharmacological Basis of* Therapeutics], which is thought to be the bible of pharmacology. This is the seventh edition. This is the second edition that I worked on. Okay. So I worked on the sixth edition when I first did the appendix. And there's a good story about this. Okay. Well, he's not there anymore. I guess the senior Gilman has passed away. So Goodman and Gilman. Gilman was the professor

of pharmacology at Yale. Goodman was the professor of pharmacology at Utah. And they put together the first edition of Goodman and Gilman back in—it'll say here. Preface to the seventh edition. Preference to the first edition. Nineteen forty. Okay. There was very little pharmacokinetics in there. Al Gilman's son, Alfred Goodman Gilman—Goodman had no children. Alfred Goodman, who is a Nobel prizewinner—and I joined the pharmacology study section together in 1979. He was a professor of pharmacology at Virginia at that time and I was at UCSF. In those days you always had two to a room. Now they don't do that. And since Al and I came in together, we roomed together for four years. Okay. Al didn't know anything about pharmacokinetics but he was interacting with me for four years, three times a year for three days or two days and he became convinced that Goodman and Gilman ought to have more pharmacokinetic information in it. And his father was against it. The professor—yeah.

05-00:50:09
Burnett: I think you told us about this. Yeah.

05-00:50:10
Benet: Yeah. The father was against it but Goodman was for it. And so they allowed me to put the appendix in in the sixth edition. And then in the seventh edition I started writing the first chapters. Yeah. And so I felt this was a big impact. But it was really important to me to have a database, and this is how this all started. Was to have a database that I could trust, that I knew I'm going to look across drugs and I want to know I believe this number. And, actually, since they stopped us doing references after the first edition, it actually was good because then what I would do was look at all the information there and pick out what I thought was the best answer. It was just me or my colleagues and my co-authors making those decisions. We would look at like five different papers that had different numbers and we'd say what we thought was the best number and we'd say what we thought was the standard deviation based on all of the data. It was a critical compilation. That was what I felt didn't exist. There were no critical compilations.

05-00:51:20
Burnett: It was, in a sense, peer-reviewed.

05-00:51:22
Benet: Right, yeah. Right. Critical compilation of pharmacokinetics. So because I had done that, when I looked at the BCS compounds I knew what drugs were metabolized and what drugs were not metabolized. I knew because if we wanted to go back here and—

05-00:51:41
Burnett: It's got clearance.

05-00:51:42
Benet: Percent excreted unchanged.

05-00:51:44
Burnett: It's got volume of distribution, clearance, half-life.

05-00:51:50
Benet: Percent protein binding. Bioavailability. Percent excreted unchanged. Volume of distribution. Clearance. Half-life. Effective concentrations and toxic concentrations, when we could find it.

05-00:52:04
Burnett: Not only are you preparing this appendix but you're supervising graduate students who are working on various drugs, you are consulting for drug companies on various drugs. So you're working with these different popular drugs, important drugs all the time.

05-00:52:18
Benet: Right. But we never did studies to put data in Goodman and Gilman.

05-00:52:21
Burnett: No. No, no, no. No. I'm trying to get a sense of how you developed your experience and skill that enabled you to see in a different way.

05-00:52:35
Benet: Okay. So that's a good point, Paul. So let me follow-up on that. I'm a pharmacokineticist. I'm interested in basic principles. I'm not really a cancer doc that's interested in tyrosine-kinase inhibitors, which a lot of guys, their research is in this particular area and their discoveries are in this area and so they're pretty limited in terms of what they do.

05-00:52:58
Burnett: They're specialized. Highly specialized.

05-00:53:00
Benet: Yeah. The clinicians actually know more about the general drugs. So I'm just interested in drugs, not in any particular category, although I do all the immunosuppressants. I have categories where I do a lot of work in but I'm generally interested in all drugs. Yeah. And so that gives me an advantage. That gives me the advantage to be able to see that that nobody else saw before.

05-00:53:22
Burnett: A kind of synthetic knowledge, right? So that you're obviously a general specialist [laughter] in the nature of all of the major compounds that are available. And you're able to see almost at a glance the patterns that fit. And what jogged your critical reaction, I suppose, is the encounter with BCS which struck you as right in many ways and then in some ways there were, again, some anomalies and exceptions. So with that perhaps we should stop tape and we'll—

[Audio File 6]

06-00:00:10

Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Technology, and Medicine series. This is tape six of session three. We're at UCSF Parnassus Avenue and this is November 14, 2014. So we've just finished talking about transporter-enzyme interplay and a little bit about what makes Dr. Benet see things the way he sees them. And so part of that story is developing a kind of encyclopedic detailed critical knowledge of most, if not all, of the available drugs on the market which start in 1980 at 500 and are now over 1,000 compounds that are routinely prescribed. So one of the things that struck you around the same time that you started publishing the definitive papers on transporter-enzyme interplay and what that meant—it is 1995, 1996. And around that time, if I'm not mistaken, is when Dr. Amidon and his team write a paper about a biopharmaceutical classification system. Can you talk a little bit about the background of that system and what that means. It's called the BCS. What did they do? What was their signature accomplishment?

06-00:01:54

Benet: Okay. So the really interesting thing is that Gordon Amidon took a sabbatical. He spent half of it in San Francisco, theoretically with me, and the other half at the FDA. I say I never saw Gordon while he was here. What Gordon says was he was here, I wasn't.

06-00:02:16

Burnett: That's an interesting gap in the record.

06-00:02:18

Benet: Right. So after he was here he went to the FDA. Gordon is a person that believes that *in vitro* measures of how a drug is handled in the intestine are the primary characteristics of what's going to happen to a drug in terms of its eventual absorption. And not metabolism or anything like that, just absorption. And so he felt strongly in terms of interacting with his colleagues at the FDA, in this same year where he did the second half at the FDA, that we should look at dissolution, solubility, permeability, as criteria for do we need to carry out *in vivo* studies. He felt we were carrying out too many studies that we didn't need to do. Yeah.

06-00:03:11

Burnett: Can you just for the record define dissolution? Solubility's pretty clear. But permeability is—

06-00:03:16

Benet: Okay. So dissolution is we have a drug in a solid form and dissolution is how long does it take to get into liquid? Solubilized. Okay. So you have it in a solid form and it's going to become a solution. Dissolution is the process that makes it happen. Okay. And drugs that dissolve really fast, they go into solution quickly. But drugs that do not dissolve fast, it's going to take a long time and it'll affect drug absorption because the drug has to dissolve in the

intestine before it's absorbed. Permeability is ability to get across the intestinal membrane. And he was specifically interested in the intestinal membrane because he's interested in drug absorption. And he used as his model the jejunum, a portion of the intestine. It is probably the major source of where drugs are absorbed. And he and colleagues in Sweden were carrying out studies where they were intubating patients, putting the drug in a blocked-off portion of their intestine. They would put a balloon so it would not go below this and they'd put the drug in a balloon above it so it would stay right in the jejunum. And then they'd measure drugs that came into the blood. They'd measure it as a function of time. They did about thirty drugs like this over a period—

06-00:04:36
Burnett: And this is a volunteer?

06-00:04:39
Benet: These are volunteers. Yeah, yeah. They did about thirty drugs like this. And they had permeability measurements. The drug was in solution. They put it in solution in this portion of the intestine. How fast did it go across the intestine? Permeability rate. How fast. That's what they were measuring. Because they all were absorbed but some were absorbed very slowly and some were absorbed very fast. What he found was that he could sort of break down the drugs in terms of they were high permeability and he picked sort of a standard. He said, "I'm going to use a beta-blocker called Metoprolol as my standard because he believed at that time Metoprolol was 90 percent absorbed. And so if its permeability rate was greater than Metoprolol he said this is a drug that's going to be absorbed really easily. And then he had to worry about solubility. He said if a drug is highly soluble the rate-limiting step is going to be permeability and permeability is very fast. That drug's going to get absorbed very quickly. And he and the agency working together said, "Well, if we have a drug that's highly permeable and highly soluble, there shouldn't be any problems unless you make a bad dosage form. The drug ought to be absorbed unless you make a poor dosage form." So what's the characteristic of a dosage form getting drug in solution? It's dissolution. So he would say that if the drug is very rapidly dissolved, if the dosage form is very rapidly dissolved, there's never going to be any problems with absorption and you don't need to run studies on these formulations. All you need to do is show that it's rapidly dissolved and that's what BCS was. BCS says if you can show a drug is highly soluble and highly permeable and it dissolves from its dosage form very rapidly, you don't need to run clinical studies. That drug's going to be completely absorbed. Not bio-available, because bio-available includes metabolism. Because he's only interested in absorption, which he can control. That's something that the pharmaceutical manufacturer can control, the absorption of process. They can't control the metabolism.

06-00:06:43
Burnett: Right, right. And just for context, this conversation or this work with the FDA is happening at a time when the cost of clinical trials and verification of the efficacity of drugs is enormous, right?

06-00:07:01
Benet: Right, right.

06-00:07:03
Burnett: And I don't know what the clinical trial sizes are like then, but you could probably tell me.

06-00:07:09
Benet: There's a guy named Jack Cook, you could look up his papers, working for Pfizer. He estimated what the cost would be and how much you would save not doing it. His name is—

06-00:07:20
Burnett: Jack Fisher?

06-00:07:21
Benet: Cook, Jack Cook.

06-00:07:22
Burnett: Jack Cook.

06-00:07:22
Benet: Jack Cook, who works for Pfizer. And he has a paper where he does the financial stuff, and I probably have the slides someplace. But you can look it up. And this was to save money. And there was an ethical issue. We shouldn't be running human studies that we don't need to run. Yeah, yeah. Yeah, yeah.

06-00:07:40
Burnett: Right. There's an argument about the increase in the cost of drugs, is because they're factoring in how much money they have to spend on these clinical trials. And sometimes there's a million people in the study. There's a study in India going on, largest clinical trial.

06-00:07:58
Benet: Sure, there can be.

06-00:07:58
Burnett: One million people.

06-00:07:59
Benet: Can be, right.

06-00:08:01
Burnett: So there are massive outlays involved in getting drug to market. So Dr. Amidon and his colleagues were working with the FDA trying to find a way to give a waiver potentially for certain—you get a pass. You don't have to go

through the step and you can go straight to the next step of clinical evaluation. So he had this technique for identifying permeability. At what point did you encounter this research?

06-00:08:43
Benet: Okay, so I encountered it all the time because I am one of the experts on bioequivalence in the world and the US regulations in bioequivalence, I even wrote some of the regulations. When we formed AAPS, American Association of Pharmaceutical Scientists, one of the things that we did is start working with the FDA in developing regulations that would improve the ability to do things right, correctly. And so I had been very involved and written a number of papers in the bioequivalence area, even though I don't do research in that area. And so I get invited all over the world all the time, and so does Gordon. So we're in all these meetings all the time, where he's presenting BCS and I'm usually talking about healthy volunteers and why you run these kinds of studies and these kinds of things. So I'm listening to this BCS talk over and over and over again.

06-00:09:36
Burnett: And just to back up for the viewers, bioequivalence is important and can you explain a bit—

06-00:09:47
Benet: For generics.

06-00:09:47
Burnett: For generics.

06-00:09:48
Benet: Okay. So bioequivalence is the criteria for generic drugs. It takes a huge amount of money to get a drug approved and you just already gave the example of the study in India where there's a thousand subjects.

06-00:09:59
Burnett: A million.

06-00:10:00
Benet: A million subjects, yeah, yeah. Okay. So bioequivalence says can we guarantee that the same drug made by another company when the patent expires will be equivalent in terms of efficacy and safety to the drug that got approved that you ran the clinical studies on? And so those are the bioequivalence regulations in the US and the world now. That says if you're going to have cheaper drugs you can't have all these drugs run clinical studies. This is an unbelievable amount. You have to show that the drug you already know is safe and effective, what would be the criteria that would allow you to say, "Okay, you can sell this drug and your product should be bioequivalent to the drug that the clinical studies were run on that is on the market."

06-00:10:56
Burnett: Which, given all of the stuff you've just explained over the last three sessions, is an enormous claim to make.

06-00:11:01
Benet: Right, right, right.

06-00:11:02
Burnett: Because of all these different variables. And so that's what's at stake around this time. And we will talk later about your work with the FDA. But tell as much of that story as you think you need to in order for this to be illustrative. You had lots of experience.

06-00:11:22
Benet: Yeah. And I still do today. I gave a talk in Budapest last month. I wasn't there but I did a video of it. In March I'm giving a talk in Argentina. I'm not going to that because I'm speaking at the same time at ASCPT and so I'm doing a video. But next September I will be in Amman, Jordan talking just about this topic. Because especially for Third-World countries, this is really critical because this is a cost-saving issue. And I go to India and talk about this. I go to China and talk about this. So it's an area that I talk about because I'm probably the leading academic expert in generic equivalence. Okay. Gordon does BCS but I sort of do the whole thing, all the regulations and that stuff. And I'm always fighting with the FDA. And we'll get to this. A number of the FDA regulations changed because I say I don't believe this and this is not right and stuff like that. But it's always in that area. It's always in the area of bioequivalence. So I'm a recognized expert in that area.

06-00:12:30
Burnett: Yeah. And so you were encountering the talk that Dr. Amidon was giving and it becomes a paper in 1995, I think?

06-00:12:39
Benet: Nineteen ninety-five, yeah.

06-00:12:40
Burnett: And at what point did you start to look at it and say this is right, but?

06-00:12:49
Benet: No, there's no "but." It's right. There's no but. There's no but. Basically it's Chi-Yuan Wu, who's the graduate student, who is really important in all of this work, the enzyme-transporter interplays on the Rifampin paper and separating these things out. So he's involved in this. Chi-Yuan sees it first and Chi-Yuan says, "Look, the drugs that are the high permeability drugs are being metabolized and the drugs that are the low permeability drugs are not being metabolized." So then we start looking at it and we look and look and say, "Wow, boy, this really, really works. Really surprisingly works." But it's my hearing Gordon talk about this stuff all the time and hearing other people say, "Okay, this should be this, that," and I say, "Oh, that drug's metabolized." And then this drug is poorly permeable and I say, "Yeah, that's

not metabolized." So it's sort of a combination of Chi-Yuan's observing it, me listening to Gordon, and just having the experience of all these drugs, that I know all these drugs.

06-00:14:00
Burnett: Right. Right. Again anomalies. There's some kind of overarching principle and you start to find chinks in the armor, I suppose.

06-00:14:08
Benet: Right. I can tell you, Paul, one of the first times was a symposium at the University of Utah where Gordon is presenting the permeability stuff and he has cyclosporine way down here because he thinks cyclosporine's not absorbed. And we have just done these studies that said, "No, cyclosporine has to be at least 86% absorbed." And so at that same meeting I'm presenting that data and Gordon's presenting this data. This is very early. And Gordon says, "Wow, that's terrific," he says, "because in my theory cyclosporine should be up there but when I looked at the data it's down here. But now you have shown me that it's where it should be." Our expertise, putting it together. To him cyclosporine's an anomaly and then I give him the data that says no it's not an anomaly. It actually fits exactly. It's just that the whole of science is misinterpreting what's going on with cyclosporine. Yeah, yeah, yeah.

06-00:15:08
Burnett: So to talk about BCS a little bit. What is that? It's a quadrant diagram basically. And it's—

06-00:15:21
Benet: And it's just solubility and permeability.

06-00:15:23
Burnett: High solubility, high permeability and then high permeability, low solubility.

06-00:15:30
Benet: Low solubility. Those are class two drugs. Right. So Class One is high solubility, high permeability. Class Two is high permeability, low solubility.

06-00:15:35
Burnett: Solubility.

06-00:15:36
Benet: Class Three is low permeability, high solubility. Class Four is low, low. Okay. Out of those types of things. And so what the FDA and EMA first do is to say Class One drugs, high solubility, high permeability. That's what the regulations says. If you can prove to the FDA that these are high solubility, high permeability, and you've got fast dissolution, you don't need to run these clinical studies for your formulation.

06-00:16:04
Burnett: And that's in the year 2000?

06-00:16:07
Benet: The regulation comes out in the year 2000, right. Yeah.

06-00:16:09
Burnett: I imagine they publish subsequent papers, that's Amidon's group, and they consolidate the model and it takes a while for the FDA to come—so it's a five-year gap, right?

06-00:16:26
Benet: Right, yeah. It's a five-year gap. They can't run these human studies on everything. As I said, they only ran about thirty drugs like this. So they have to have some substitute for how you're going to get the permeability. Solubility, no problem. And so they start using cellular systems to do the permeability. So we're going to now look at these drugs doing permeability and so the FDA regulations say, okay, well, you can get it by actually running the clinical study but nobody's going to do that. Those cost a million dollars, those studies. Yeah. Anymore, you're not going to do that. And so they're running these permeability studies, these permeability-rate studies. Now, what we say is we recognize the anomaly. What Gordon had the data for was for permeability rate, how *fast* something goes across the membrane. But all the data that he had initially, the drugs that had good permeability rate had good permeability extent. In other words it's kinetics and thermodynamics. How much gets across and how fast—

06-00:17:36
Burnett: And how fast.

06-00:17:36
Benet: —it gets across. So Gordon's limited data set, he's got a pretty good correlation with kinetics and dynamics. But we start to see, "No, that doesn't always happen because kinetics and thermodynamics don't always go." There can be drugs that go across slowly and yet all of it gets in. So what the FDA is interested in, they're not interested in how fast it gets, they're interested in how much gets there. And so the original BCS is based on permeability rate. And what we say is, "No, that's wrong because really what the FDA is interested in—

06-00:18:13
Burnett: Extent.

06-00:18:13
Benet: Extent. And that's where we start to see the differences. So that's where we say BDDCS. BDDCS is based on permeability rate because what we observed when we looked at Gordon's data is the high permeability rate compounds, because that's the data he had. Those are the ones that are metabolized. And the low permeability rate compounds are not metabolized. But then we find drugs that are low permeability rate that are not metabolized but they're completely absorbed. And so that's where the difference between BCS and BDDCS comes in.

06-00:18:48
Burnett: So BCS is the Biopharmaceutical Classification System.

06-00:18:52
Benet: Classification system.

06-00:18:53
Burnett: And this is the not replacement but your alternative—

06-00:18:57
Benet: Is the Biopharmaceutical Drug Disposition Classification System.

06-00:19:05
Benet: And in that 2005 paper that Chi-Yuan and I wrote we say, "There's more to BCS than has been recognized. It's not just absorption. There's other things in there that predict how the body's handling the drug disposition."

06-00:19:22
Burnett: Right, right. Could you talk about Chi-Yuan Wu a little bit in terms of your understanding of his work? You worked with him for a while.

06-00:19:33
Benet: Oh, a long time. Okay. So Chi-Yuan initially was a major in the army in Taiwan and he was at the National Defense Medical Center and they sent him to UCSF to get his PhD. And in those days we really didn't accept foreign students and he was an exception. He was sent by the government and he came with full funding. We accepted him. And he chose to work with me. But at the end of three years the army said, "Okay, you got to come back to Taiwan." He wasn't done. But he had done the cyclosporine studies but he hadn't finished his thesis and stuff. So he went back to Taiwan to be in the army and stuff like that. And they said, "Okay, you can go back to UCSF and finish but then you got to sign-up for another six years." Okay. And he said, "No, not going to do that. I'm going to finish my obligation and then on my own I'm going to go back." And so he has a break of four years that he's not here. So then he comes back. And that's after Carolyn Cummins now. So we've taken his stuff that was the cyclosporine and understanding the difference between the liver and the gut, because that was his PhD thesis, understanding, and Carolyn's now proven with cellular systems that this is what happens. And so now Chi-Yuan comes back and now is going to take Carolyn's understanding of his data. Carolyn explains his data, why it goes on, and now Chi-Yuan comes back and says, "Okay, now I've got to go further." And so Chi-Yuan starts looking at the potential of can we predict transporter effects. And that's where BDDCS comes from. So we take the BCS, we modify it just slightly. They're not antagonistic systems because they have different purposes. BCS is absorption. BBDCS is drug disposition, metabolism and transporters and stuff like that. So he starts the work and can we see this difference and can we make these observations. And that 2005 paper, again, it's twenty-three, I can't remember the exact number, we make twenty-two, twenty-three predictions, none of which we had the data for,

based on understanding what Carolyn's data said, what his clinical studies at the beginning said, and our recognition of the difference of metabolism and non-metabolism. And we start making predictions about transporters. And then the lab spends the rest of the time proving those hypotheses are correct.

06-00:22:18
Burnett: It's an astonishing paper. Because I've been going through these papers, right, and other scientific papers for other projects. Your typical scientific paper, the claim is extremely narrow, extremely limited. And this paper, it reads more like you're defining the transporter-enzyme interplay, which is actually a review of work that your lab had done for about ten years. And so it lays out the difference very clearly, the difference of the BDDCS from the BCS, why it needs to be different, and then all of these exceptions and how they would work. So it is, "We propose" or "we suggest that this might be the case."

06-00:23:16
Benet: Let's talk a little bit about that. I have the advantage, like this paper I told you about, the PKPD stuff. I'll be able to get that published because of who I am. I have the reputation. So not everybody could have published that paper that we published in two—because I don't have any data. We're just making a whole bunch of—

06-00:23:38
Burnett: Claims, yeah.

06-00:23:40
Benet: —claims that this is what's going to happen and stuff. So I think that's an advantage of I'm far enough along in my career with enough of a reputation that that paper—now, it got slammed at the NIH. I submitted it as an NIH grant. It got, "You don't know any of this. This is all hypotheses." But the NIH grant said, "Here's the hypothesis. This is what we want to test." Still got slammed. It got terrible reviews from the NIH. "You're just making this up." The NIH grant is basically, you propose something that for sure you're going to get this answer, and that's what an NIH grant is. This wasn't that at all. This was, "I'm going to predict everything, sort of, in this thing and here's my hypothesis and here's how I'm going to test it." I didn't say they were right. I just said I'm going to test all these. Absolutely terrible scores on the NIH grant. [laughter]

06-00:24:38
Burnett: With some of these predictions, you *are* in a sense incorporating some of the previous research that you'd done back to 1990. The Gupta stuff with the high-fat meals.

06-00:24:49
Benet: Right. Oh, no, it's all based on our data. But we can't prove it. It's just like Carolyn's stuff. We proposed in the cyclosporine data this is what happened. Carolyn has to prove that it's going on. That's the same thing as the 2005

paper. Here's what we think all the data means. Here's how the interpretation should be. But we got to go out and prove it now.

06-00:25:13
Burnett: Right, right. So just to review, you're taking that same quadrant system for the four classes of drugs that are predicted, whose activity is classified by the BCS. In the BDDCS, in Class One, transporter effects are considered to be minimal. In Class Two, efflux transporter effects predominate.

06-00:25:38
Benet: In the gut.

06-00:25:39
Burnett: In the gut. That's the transporter enzyme interplay. So that's what's important in that kind of sector and those types of drugs are important. Class Three, absorptive transporter.

06-00:25:50
Benet: Okay. But also the liver's in Class Two, also. But uptake and efflux transporters and enzymes are going to be important because class two drugs are metabolized.

06-00:25:58
Burnett: And the liver would have the reverse—

06-00:26:01
Benet: Right. It would have the efflux transporter.

06-00:26:02
Burnett: —relationship. Right. But—

06-00:26:04
Benet: But we say, again because of my knowledge, we say, "I don't know of any uptake transporter that's important clinically for a Class Two drug." That's just my knowledge. I don't know of any data there. And I don't have the information there.

06-00:26:24
Burnett: Right, proof. Yeah.

06-00:26:25
Benet: And, in fact, that's still what we're doing now. Why that's true. That's what Hideaki Okochi, who's a research scientist in my lab, that's what his recent stuff is. Can we show why the intestine and the liver are different? So it's all based on observation again. I know all this stuff about these drugs, I just don't know of any drugs. And why?

06-00:26:49
Burnett: But why is that the case?

06-00:26:50
Benet: If you've read the recent stuff, in fact, I didn't know why the metabolism occurred for Class One and Class Two and didn't occur for Class Three. I know now. But I didn't know then. And so it's the pathway to say how do you run your research to explain this stuff so that you can understand it?

06-00:27:12
Burnett: Well, the basic explanation at the beginning of the paper, you agree with the BCS except that Class One and Class Two drugs are eliminated via metabolism but Class Three and Four pass pretty much unchanged out of the body.

06-00:27:28
Benet: In the urine or bile.

06-00:27:29
Burnett: Right. And so that's kind of the point of departure for explaining how there's—there's tremendous overlap between your system or your lab's system and Dr. Amidon's system. And then you go on to explain where these important distinctions matter. And there's the least amount of certainty around the class four. So some of the practical policy, c ould you talk about how this would be practical for the FDA, for example?

06-00:28:05
Benet: Okay. Why would any class four drug ever get on the market? I think we say in the paper, though, "But the FDA definition is solubility in water and the gut has surfactants in it." So really those Class Four drugs that become drugs have enough solubility in the intestine that they get absorbed. So they're really acting like class three. So we are trying to understand how could this even happen? Right? So go back to the question, Paul. You remember? [laughter]

06-00:28:47
Burnett: Essentially what you're doing is replacing permeability on the BCS with metabolism.

06-00:28:54
Benet: Metabolism, yeah.

06-00:28:57
Burnett: And you're saying that's what's important and there are consequences to understanding that. And now how does this then become operationalized for the FDA?

06-00:29:07
Benet: Okay. So it's not as much for the FDA as it is for the industry because they've got new molecular entities, chemicals that they've never given to an animal or a human or anything. And BDDCS says, "Boy, you just run a permeability assay and you run a solubility assay and here's all the things that are going to happen to it in the body." And it works. It's amazing. It's such a simple system and it works. Really am gratified when I go to companies and find

out—they don't necessarily publish it, although some do—how much they use it to make their initial guesses of what they think's going to happen to this molecule, stuff like that. So from an FDA perspective, though, it gives them some assurance of what do they have to ask the companies. Had a wonderful example. Let's go back to Class One drugs. We say transporters aren't important. We, BDDCS, says, transporters are clinically irrelevant for Class One drugs. Drugs can be substrates for transporters but it's not going to have any clinical issue related to it. So I was told by one of the companies I consult for, and I'm not going to say who it is, that they had a new molecular entity, they went to the FDA. It's a foreign company. On your new drugs you have to say what's going to happen in terms of is it a substrate for these transporters, is it a substrate for these enzymes and stuff like this. They proposed to the FDA, "This is a Class One drug. Transporters aren't going to be important. And we are asking do we not need to run those studies?" And the FDA said yes. So the FDA accepted that this hypothesis that the company—there's sort of a thing that you run your molecule through — you still had to run does it affect other molecules. BDDCS is what happens to your drug as a substrate. It's not what it does to something else. And so normally you have to ask is it a substrate for this transporter? If they ran *in vitro* studies they would find it's a substrate for some transporters. But if it's a Class One drug, what BDDCS says is clinically it's not important and therefore you really don't need to do this. And so this company told me, and I was really proud, that the FDA agreed with them. They didn't need to run those studies because it was a class one drug. So from my perspective that was a good use and good use of the agency—

06-00:31:47
Burnett: Good impact.

06-00:31:49
Benet: —of saying that.

06-00:31:52
Burnett: There have been celebratory articles about your work and one of the things that was said is that you had, in doing this kind of work, had begun to elaborate a concept of molecular ADME. That there's a way to understand how the drugs pass through the body based on an understanding of the molecules.

06-00:32:18
Benet: That's Dr. Amidon. Amidon says that.

06-00:32:120
Burnett: Yeah, yeah. So there's a kind of mutual admiration society between you two. You're both pretty giant in the fields that you're working in. So one of the things that you argued is that new molecular entities, this is interesting, are frequently Class Two.

06-00:32:39
Benet: Right. Today more than half of them are class two.

06-00:32:43
Burnett: And they're lipophilic. They love fat. They're poorly water-soluble and they're large. They have a large molecular weight. And that's consequential in other words. Is that consequential in a way that wouldn't appear in the BCS?

06-00:33:00
Benet: Yeah, that wouldn't appear in the BCS. Okay. So what happens today, in my view, is it's part of the patent space. So you can't make small molecules and get patents on them today because that space is all taken. So if a company's developing drugs it isn't that a small molecule might not do this. And this is why there's a whole bunch of people looking at repurposing. Because they're probably molecules that were developed for something else that could have done this but people haven't looked at it in the past. But today it's hard to get a small molecule that isn't covered by somebody's patent. And so you make it bigger. And we know more about structural activity relationships and receptors and the grooves and all that kind of stuff. So molecules are made to fit that. But you don't see any small molecules coming out anymore. They're all covered. So by definition you make a big molecule and it's going to be lipophilic. And that means it's going to be poorly soluble. So that's why you get more and more drugs that are Class Two drugs.

06-00:34:06
Burnett: That's really, really interesting. So the revised BDDCS—it's not a revision, it's a different classification system, but it follows the model of the four quadrants. So Class One would be highly-soluble with extensive metabolism. Class Two would be low solubility and extensive metabolism. Class Three is high solubility, poor metabolism. And Class Four is low solubility and poor metabolism. And there's another interesting feature of the 2005 paper. It's almost like a manifesto, right, a declaration of a kind. I love the phrase, "We welcome the opportunity to work with the FDA." [laughter] So we have something here. And that's the context. The FDA at that time—well, you can tell me—they're looking for ways to expand the bio-waivers. They've been using this system for five years and it has saved [the pharmaceutical industry] money because there are these Class One drugs that don't have to be subject to clinical trials.

06-00:35:27
Benet: They're subject to clinical trials.

06-00:35:29
Burnett: Well, the first step.

06-00:35:29
Benet: In terms of their dosage form.

06-00:35:31
Burnett: Right, the first—

06-00:35:32
Benet: Yeah. The change in the dosage form doesn't have to—

06-00:35:34
Burnett: Right, right. So it does save money in part of their regulation. But the FDA is looking for ways to expand the bio-waivers to other drug classes or drugs within classes. How did you feel about that?

06-00:35:51
Benet: Okay, so we're not really for bio-waivers. Bio-waivers are BCS. And so the FDA says, "Okay," and now EMA says, too, "Well, Class Three drugs, because they're highly soluble – doesn't really make any difference with permeability because you can't control that – but if you have highly soluble you shouldn't have any problems." Okay, so we agree. "But," we say, "but, Class Three drugs could be substrates for transporters." So you got to look and see if other things you put in your tablet or your capsule affect transporters because it isn't that they're completely inert in terms of clinical interactions. Transporters could affect them because they don't get metabolized, so you don't have to worry about metabolism. And so basically what the regulations say, and they follow what we wanted them to say, is you got to show us that if you're going to have a Class Three drug, you either have exactly the same things in your tablet that the innovator has, or you show us that the stuff that you have in there doesn't affect your drug, okay, because that comes from BDDCS. BDDCS says there are going to be transporter effects for Class Three drugs.

06-00:36:58
Burnett: So it's not counseling against doing that. It is, "not so fast!"

06-00:37:03
Benet: Right, right. Yeah.

06-00:37:04
Burnett: Right? So you need to consider the effect of transformer—

06-00:37:07
Benet: Transporter.

06-00:37:07
Burnett —transporters, rather, and the effects of the drug additives, the excipients, as well. And, God, diet, as well. And this is something that we didn't talk about, which is complicated and interesting. I'm wondering if you could unpack it a little bit. In this paper you're *also* talking about the effects of other drugs in addition to the drug that you're studying, on transporters of different kinds.

06-00:37:35
Benet: Right. It allows you to predict the drug/drug interactions. Okay. BDDCS allows you to predict the drug/drug interactions, both from an enzyme and the transporter. Because BDDCS says, "Here's what you need to pay attention to. Class Two drugs, you've got to pay attention to an uptake transporter, you got

to pay attention to an efflux transporter and you got to pay attention to enzyme. You've got to do everything." But Class One drugs you don't need to do that. You only need to pay attention to enzymes in terms of the drug interactions. Class Three and Four drugs you don't really need to pay much attention to the enzymes but you got to pay attention to the transporters, both the uptake and the efflux transporter. So that's what BDDCS says. These are the drug interactions that are going to happen. They may be clinically relevant or not clinically relevant but these are what you have to investigate. That's what BDDCS does, tells the company very early you need to look at this, and the FDA.

06-00:38:29
Burnett: I had a conversation with Lawrence Yu at the FDA and we talked about your career. We'll talk about this later in terms of influence and mentorship and all of that. And a great admirer of yours. I was talking about clearance and I asked, "The elaboration of the principles that the Benet lab produced, how does that have a concrete impact on FDA regulation, for example, in terms of the cost of drug development for the industry?" And he said it was enormous. If you're talking about doing a study that involves clearance and the effect of transporters, it may be a couple of hundred thousand dollars. And what that replaces is a trial that could cost twenty to fifty million dollars. So that's the concreate kind of consequence of being able to do this kind of research. But you're also cautioning. You're always trying to make the model a little bit more sensitive to the complexity of the body, it seems.

06-00:39:50
Benet: And we wrote a whole section of that 2005 paper that says caution.

06-00:39:53
Burnett: Right, right. Cautions. Cautions with an S. It was a plural cautions, yeah. So with the remaining time can we talk a little bit about the legacy of BDDCS? Not just in terms of how it's affected policy but also drug development in the industry, but also how your lab has continued that work.

06-00:40:18
Benet: But it's ongoing. BDDCS, it's sort of like the data sets. It allows you to have a context that you can look at different things. So one of the big areas of our lab now is, okay, so if you got a Class Three and a Class Four drug and it's not going to be eliminated by metabolism, how can you tell if it's going to be eliminated in the bile? Because urine, easy. You can collect the urine. But in bile you can't. So we're publishing a whole bunch of papers right now in terms of how you're going to do this and we think we have developed methodology that will allow the industry to make this prediction. And it's really interesting because the drugs that are excreted in the bile, just from physical chemical properties, you can't tell them from drugs that are metabolized. So all the *in silico* work that people do—

06-00:41:10
Burnett: Can you talk about *in silico*?

06-00:41:13
Benet: Okay. *In silico* just means I'm doing computer stuff to make a guess, okay, of what happens. So it's real easy *in silico* to predict if a drug's going to be renal excreted. But when you go look at drugs that are biliary excreted, you just can't tell. They have the same characteristics as drugs that are metabolized. That was what we've been trying to do in the last few years. And Chelsea Hosey, this is what her PhD thesis is on and she's published one paper that just came out and I have a second one in my briefcase that's very close to coming out. It's really an important characteristic because what everybody thinks in terms of these physical-chemical parameters do really nice except when you look at biliary excretion. But not that many drugs get biliary excreted. But if you don't get it right you get it wrong. You're doing all the wrong studies. You're doing all the wrong studies. And so you need to know that. And it's real hard to find out about biliary excretion because biliary excretion takes the drug, now, I'm talking about the unchanged drug, and gets it into the liver, into the bile duct, and back into the gut and comes out in the feces. So if you gave the drug orally, you don't know if the drug got into the feces because it wasn't absorbed or whether it was biliary excreted unless you give the drug IV. But companies don't give drugs IV. That's a lot of expensive material. They don't do that. They don't want to run those kinds of studies. So this is, we think, a really big next step.

And we have three or four other things that we're still working on that we think we're going to explain stuff that people haven't thought about before that come from BDDCS. And I'll give you an example. I know you've studied, Paul, you've studied pharmacokinetics really well now.

06-00:43:01
Burnett: Oh, no. Are you putting me on the spot?

06-00:43:03
Benet: Okay. But if you just look at an equation for pharmacokinetics, for fitting data, you give the drug orally, you get a bunch of exponentials. You gave the drug orally so you know one of those exponentials has to relate to absorption but you don't know which one it is because the mathematics just says the slowest step is the last one, the second slowest step is the second one, and the fastest step is the first. So BDDCS tells us that there is something called a flip-flop model where absorption is slower than elimination. And what we've recognized, this only happens for Class Three and Class Four drugs, the only time where the rate-limiting step is some uptake transporter. So we haven't published that yet. Again, where the drug's absorption—and let me give you a concrete example. The drug Furosemide, Lasix, a diuretic, very potent diuretic. If I give you Lasix IV and look at your half-life, it'll be one-hour. But if I give you Lasix orally, the half-life will be four hours because absorption is slower than elimination. Okay. So how do you predict that ahead of time?

And BDDCS will help you do that. So we think there's still stuff in BDDCS that can lead to further things. These papers that we had on the brain that we published last year and the year before, we think that's another step forward. So I think there's still a lot more in BDDCS in terms of being able to make predictions of different things that we didn't recognize in the 2005 paper. There's more predictions than we had then. Yeah.

06-00:44:45
Burnett: But it's the same research program? It's to look at the complexity of ADME at all points and see what anomalies need to be addressed.

06-00:44:56
Benet: Right.

06-00:44:59
Burnett: Now, is BCS still used by the FDA?

06-00:45:02
Benet: Oh, yeah. Oh, no, BCS is definitely—

06-00:45:03
Burnett: So it's an extremely efficient and effective kind of short-cut and your classification system is a kind of caveat that they also have to take into consideration.

06-00:45:16
Benet: Right. Well, BCS is for you've got your drug approved and you're doing a formulation. Can I get this formulation approved without running clinical studies? That's what BCS does. What BDDCS is, before you even dose anything, here's what's going to happen. Here's what we predict is going to happen to it in terms of enzymes and transporters. So it's way back early. So that's why it's going to be much more important for the industry, BDDCS. BCS is a money saver after your drug's approved. Yeah.

06-00:45:49
Burnett: Right, right, right. Well, I think what we'll do is stop for now and we'll pick up and talk about the institutional story and your entrepreneurship and your work with outside institutions outside UCSF next time.

06-00:46:10
Benet: Okay, great. Thank you.

06-00:46:11
Burnett: Thanks.

[End of Interview]

Interview #4 November 18, 2014
[Audio File 7]

07-00:00:00
Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Medicine and Technology series. This is session four, tape seven and it's November 18, 2014. So, Dr. Benet, last time we were talking about the development of the BDDCS and in 2005 was the paper. But since that time there was an elaboration of your research on this problem and in 2011 you published a remarkable paper on this classification system applied to quite a number of drugs. Can you tell me about why that was important to do?

07-00:01:07
Benet: Okay. So it's in the context that I presented on the Goodman and Gilman compilation. I wanted a dataset in Goodman and Gilman that I could trust, that I'd looked at the data and I felt that it was correct and that I could utilize it and then I could go back and forth between the data. So I wanted a similar thing with BDDCS. So Dr. Oprea and I started in 2007. He was a faculty member at University of New Mexico. Most of the time we met here in this office and we would just do drugs and fill it in. And in this table there's 938 drugs or something like that with eighteen columns of information about each drug related to its BDDCS classification. It took them four years before we finally stopped them. And you could have gone on forever. But we finally felt that we had enough drugs that we could test that we could then use as the basis to see how we could use BDDCS in a number of different areas. So it was really important for me. The first compilation with Chi-Yuan Wu really only had 153 drugs in it and it didn't have all the details that were in the present compilation. So it was really just setting up a dataset that would allow us to say, "Okay, now let's go back and look at this, look at this, look at this." Yeah.

07-00:02:31
Burnett: And there was a question of trust, right?

07-00:02:33
Benet: Right.

07-00:02:34
Burnett: Because you couldn't be 100 percent certain that the data that you had been given for these drugs was either reliable or perhaps standardized.

07-00:02:47
Benet: Right. Well, it wasn't. It was much easier to get metabolism versus non-metabolism, although we had a lot of problems with biliary excretion because, as I think I've mentioned before, it just overlaps with metabolism. But what we didn't have was good data on solubility. And each drug took us probably a half an hour. Looking at the literature, pulling papers out, going on the web, and data that we could believe, that would be correct. So it just wasn't there. And since BDDCS was new it wasn't like the appendix in Goodman and

Gilman where we actually could go find trustable data. A lot of this just didn't exist. And part of the problem was we couldn't trust all the BCS numbers. And so we felt we had to go back and take a look at some of the BCS. When we looked at certain drugs in terms of their BCS class we just said, "Nah, that can't be right." So their BCS class is wrong. And the problem was that most of the data in the literature, the great majority of data in the literature was in silico calculations of solubility. And what we showed in this paper, those are very, very poor because the scientific community does not understand solubility. We really don't know the basic processes. I don't know any better than anyone else. So if you don't know the basic processes you can't do in silico modeling and get it right.

07-00:04:25
Burnett: So some of it is that in silico modeling was poorly done because of a poor understanding of solubility. And was it also that in silico modeling period is a problem?

07-00:04:40
Benet: Some in silico modeling, period. But other is that we just don't understand the physics of solubility. As a scientific community we still don't understand that. As basic as it is, we don't know what governs solubility. And that became very clear to us when we put the compilation together. The in silico predictions were just terrible. And most of the data in the literature was in silico.

07-00:05:05
Burnett: Why do you think that is?

07-00:05:06
Benet: Well, because we don't understand solubility. We don't understand the physics. It's physics. It's not pharmacology and it's not chemistry. It's physics. We don't understand the physics of solubility. It's an area that is tough. I remember going, maybe about five years ago, maybe even longer, six or seven years ago, to visit Roche in Basel and I was telling him I was very concerned about solubility measurements. I didn't think the literature was right. And they said, "We agree with you 100 percent. We don't believe any numbers in the literature. We go do it ourselves. Any drug we're interested in we actually go measure it." And I said, "Oh, that's probably correct." And yet that isn't what's in the literature. Most of what's in the literature are these in silico compilations. And the trouble with a lot of this is that the guys that publish it first, they say it's in silico. But then someone else quotes it and then someone else quotes it and somebody puts a big compilation and you don't know what's in silico. So we found one of the biggest compilations maybe had about 130 drugs, that only fourteen of them were real measurements. The other 116 were in silico measurements. But you didn't know that from looking at the table. Table didn't say that at all. This is—

07-00:06:22
Burnett: So you went back. You were sleuthing. You were going back to original studies and seeing what was done.

07-00:06:26
Benet: Right, yes. So that's what we had to do. And they're not easy to find because it's usually sort of a peripheral thing. They're studying the drug and they need to know some solubilities. And so it isn't even in the title a lot of times, to find those solubilities, where somebody's actually done it. And the BDDCS and BCS solubility is the lowest solubility over the entire gut pH range. So that's also hard to find because somebody had to actually go and look at a bunch of different pHs to see it.

07-00:07:00
Burnett: This is a big question in the history of science. That because the edifice of science is so gigantic and complicated, there's so much, we like to think that scientists are constantly verifying and they're cross-checking and we take it for granted and that's what makes scientific truth so powerful. But in so many instances scientists are required to trust other experiments. They have to take it on faith, which is a terrible word to use when you're talking about science.

07-00:07:40
Benet: Right. So what I say in my talks often, when I talk about this, is the trouble with in silico guys is they want to do everything in silico. But some of the things are so easy to do. Just do the measurements. The things you can't measure do in silico. But the things you can measure, go back and get it right to make sure you get it right. And so that's what we were trying to do here. We found the same thing with LogP, oil-water partition coefficients. It wasn't as bad as solubility but we found if you had less than zero you were probably okay. If you had more than two you were probably okay. But if you were between zero and two, where lots of compounds are, you couldn't trust those numbers at all is what we found in terms of putting this data together.

07-00:08:28
Burnett: And so it was you and Dr. Oprea and others? Or just you two?

07-00:08:33
Benet: Just the two of us. Because just like the pharmacokinetics, each of us looked at every drug that's in this table. The two of us looked at it together and debated it. Do we believe this? Do we believe that? What do we think is the right thing to do? And then the post-doc, Fabio Broccatelli, he wasn't involved in the actual selecting the data. He was involved in putting it together and doing the analysis once we put it together. So all the numbers were Dr. Oprea and me. Yeah, yeah.

07-00:09:09
Burnett: And in this paper you talk about the kind of misclassifications that can result and so you talked about Dr. Amidon's arbitrary cutoff for the definition of solubility, which is this—

07-00:09:25
Benet: But we accepted that evidence.

07-00:09:28
Burnett: Right. You can—

07-00:09:27
Benet: Because it seemed to be useful. Yeah.

07-00:09:30
Burnett: Right. But it has to do with a pH range of one to seven point five. But you can get into trouble when you're talking about drugs that are salts, for example.

07-00:09:45
Benet: Right, sure. Because they go both ways. So if it's a base that is a salt it's going to be at low pH. It will be ionized and in solution. In a high pH it won't and the acids will be exactly the opposite. And so you don't know which one you're going to look at.

07-00:10:04
Burnett: Right. So you're going through getting as much measureable data or data that was dependent on measurement and then looking at, again, cautions. So there are these cautions in the paper that are important.

07-00:10:26
Benet: And we have some wrong. We're going to publish a paper now. The nice thing about BCS and BDDCS, it's self-correcting. Because you sort of have all these characteristics and if you look at a molecule and you've got it in the wrong class you say, "Wait a minute, it's doing all the wrong things. Maybe I've got it wrong." And so you go back and study it. We maybe find seven to ten different of those 930 that we've just got completely wrong and we go back and we figure out, "Oh, now we know why we got it wrong." But the clues are the characteristics. Yeah, yeah.

07-00:10:59
Burnett: And presumably others are working on—or is this kind of your baby?

07-00:11:02
Benet: No, I don't think so. Well, Dr. Varma at Pfizer does a lot of work also and he publishes things like that. But mostly people accept our numbers. A lot of people use our numbers but people generating numbers, there are not a lot.

07-00:11:18
Burnett: And in this same year there was another paper, this is 2011, it's almost like a little précis, on BCS, BDDCS, and regulatory guidance. I was fascinated by this paper because you're referring throughout to FDA guidance on these issues. Can you talk a little bit about the history of FDA guidance?

07-00:11:50
Benet: Sure. That paper was generated by FDA scientists who had also published some things about BDDCS and sort of initially some negative things, thinking

we had stuff wrong. And they organized a symposium that all of us came to, that the FDA people organized, and they were the first and senior author of that paper. “What do we all agree on? What does the scientific community, what does the FDA agree on? Where do we agree? Where do we have it wrong? Where do we have it right?” It’s not referenced that much. There’s only about forty, fifty references of it. But it was a really important meeting to get the regulatory people to agree this is what we all agree are the definitions and this is the difference between BCS and BDDCS and this is where they’re similar. And they’re not competing. Many people view them as competing because their purposes are so different. But you use sort of the same numbers in assigning it and so that was the kinds of things you wanted to make sure you agreed upon. Can I stop? [phone ringing]

07-00:12:55

Burnett: Sure. Okay. So in that paper there’s a discussion, I think you talked about this in the last session, the problem of local versus average permeability. Because in Dr. Amidon’s standards you’re using the jejunum as the kind of sample and then that stands for or comes to represent permeability, period, and that can be a problem. And so you talk about how there could be different ways of measuring that. And also variance in results between the cell studies, the Caco-2 cell studies and in vivo clinical studies for certain drugs. So, again, it’s talking about preparing the reader for the exceptions that are particularly important when you’re talking about drug development and dosing, which is what the BDDCS is for. Right?

07-00:14:01

Benet: Right, right. But progress from that time on, Paul, for the BDDCS part of it, it doesn’t really make a difference where it is. You can use a non-biological membrane and get it right. Okay. Yeah. But that took some time to figure out.

07-00:14:25

Burnett: Okay. And if we pan out a little bit and think about how this fits into regulatory requirements, there’s an international context for this, as well, to which the paper alludes, I think. The European Medicines Agency has a different standard for some of these kinds of things.

07-00:14:49

Benet: Right. So that was how you used BDDCS for BCS. Okay. In other words, a part of BDDCS can allow you to make BCS predictions. Okay. And so what we point out is that BCS is how much gets across the membrane and BDDCS is how fast it gets across the membrane. So in the paper, because of the metabolism, we said, “Well, actually what we recognize is that if a drug is highly metabolized it had to get across fast. It had to be high permeability. And so we published a paper and I was the first author and Dr. Amidon joined in. Everybody joined in. The whole group joined in and said, “You can use metabolism for BCS,” and immediately the Europeans put that in their guidance. We wrote the paper in early 2009 or 2010 and like three months later it was in the guidance of the Europeans that you can use metabolism for

how much. Because if it's metabolized it had to be absorbed. Okay. So that was the argument. And European selected. And in the paper that you referred to, the regulatory paper, the FDA people at that meeting said, "We accept that also," but they've never written that they accepted it. Things don't happen really quickly with the FDA. But they say they did. Yeah. And as I told you last time, one of the things I'm really proud of was this company telling me that they went to the FDA and didn't do certain studies because the drug was a Class One and the FDA said fine. That to me was really—

07-00:16:42
Burnett: Tells you the impact of this.

07-00:16:43
Benet: Yeah, that it was really good. Felt good about it.

07-00:16:46
Burnett: Yeah. And have you brought us up to date as to the status of the research on BDDCS?

07-00:16:54
Benet: Well, we're still doing it. I think I talked about one of the biggest problems was the biliary excreted drugs because they look like metabolized drugs. From all the physical chemical characteristics, they look like metabolized drugs and so it's really hard to separate them and that's what we've been working on recently. But I have all kinds of things that I'm trying to do with BDDCS. I'm trying to predict which drugs will cause Steven-Johnson syndrome from anti-epileptic with HLA interactions with certain HLA alleles and stuff like that. Once I got the dataset—

07-00:17:26
Burnett: So you're bringing genetics into this now? Yeah.

07-00:17:27
Benet: Yeah. Yeah, I am. In other words, certain drugs do it and certain drugs don't. It's sort of BDDCS predictability. Yeah. But we haven't published that yet.

07-00:17:38
Burnett: Okay. No, that's interesting. So in our plan for these sessions I want to leap back again now from the mid-2000s or early 2010s back to the 1970s to talk a little bit about your administrative career at UCSF and the beginnings of your intellectual and perhaps public-intellectual work and your advisory work on the nature of industry/university collaboration. So in the 1970s, and especially from the oil shocks in '73 and all the way to the early eighties, a lot changed in the United States. And a lot changed for the pharmaceutical industry, a lot changed for scientific researchers in universities and especially in public universities. Can you set the context a little bit for taking on the chairship of the department of pharmacy in 1978. Can you talk about what the concerns were, what the fears were, what the hopes were for your institution?

07-00:19:12

Benet: Okay. So we had a lot of very smart young people in the department and some good senior leadership. But we had no NIH funding in this department. I think at one time I had the only NIH grant in the department in the mid-seventies. And we had no entrepreneurial way to generate other funds. And a lot of the work that was being done was pharmacokinetics and maybe you would work with a company on it or maybe not or maybe even just intellectual theory and things like this of how you should approach drugs, taking other people's data. So when Dr. Riegelman decided to step down, he became associate dean for research in the school—he had actually taken a sabbatical the year before and the three of us, Dr. Tom Tozer, Dr. Malcolm Rowland and I, took each four months as being interim chair while Dr. Riegelman was on sabbatical. And when he then did step down the dean asked me to be chair. I was anxious to do it because I thought the department really needed to grow in terms of its funding, in terms of its entrepreneurial activities, in terms of generating new ideas. And it was just a really good opportunity for me. It was a time when you could generate quite a bit of money and you could have a good staff. I've always felt I knew how to use staff but you had to have the funds to do it. If you could become department chair I would have the opportunity to do that and I felt I could make a contribution.

07-00:20:59

Burnett: So you said that you yourself had an NIH grant to support your work and your lab, but in general there was no center grant for—

07-00:21:10

Benet: Yeah, there was no center grant. So I wrote the history and I don't know the exact number. Somewhere around $272,000 is all we had per year in the department when I became chairman.

07-00:21:24

Burnett: How many people in the department?

07-00:21:25

Benet: Oh, maybe about fifteen people. Yeah, yeah.

07-00:21:27

Burnett: All right. Well, you talk about entrepreneurship and historians have talked about scientists as being entrepreneurial, as [being] research entrepreneurs. But that may not have been apparent to a health sciences researcher in the sixties or seventies with the largesse of the federal government. There's the Cold War, there's that support. Was it because pharmacokinetics was a bit orphaned that it had not gotten the traction with the NIH or with the—

07-00:22:07

Benet: No, it had gotten the traction. Well, a real advantage was I went on the pharmacology study section in 1977 and I became the chairman in 1979. So actually pharmacokinetics did really well. I was only the second

pharmaceutical scientist to go on, what we call pharmaceutical scientist, to go onto the Pharmacology Study Section.

07-00:22:31
Burnett: Well, can you talk a little bit about that?

07-00:22:33
Benet: Okay. So pharmacologist versus a pharmaceutical scientist. Pharmacologist is interested in drugs and understanding the basic actions and receptors and how they interact. Pharmaceutical scientist is interested in drugs, but how do you make product that treats people and actually transfers over to be a drug product? Where pharmacologist isn't necessarily interested in a drug product, you know. And pharmacokinetics was really about how you dose products in people. How do you dose it correctly? But it has to be a product. You don't dose drugs. You dose drug products. Yeah.

07-00:23:10
Burnett: So by definition it is intertwined with commercial activity. It's always already part of that, right?

07-00:23:25
Benet: Right.

07-00:23:27
Burnett: We're going to talk later about the literature on the commercialization of science. But the case of pharmacokinetics is a case of a science that's already integrated with commercial practices. It's an arm of that endeavor, right?

07-00:23:51
Benet: Right. So when you're carrying out a study to study human pharmacokinetics you've got to dose an approved drug or you have to write an IND and get approval from the FDA to do it. You can dose a rat anything but if you're going to dose a human and find it out, it's got to be an approved product that somebody says is going to be safe and potentially efficacious, or at least be safe. It has to be safe.

07-00:24:16
Burnett: Right. And so prediction is absolutely a central part of that. So you were concerned as you embarked on the chairship about where the money was going to come from to continue this and to grow the department. And you are on record as having a number of goals that you had set out. And they weren't just about growth, although that was an important part of it. You wanted to innovate and entrepreneurship was going to be a part of it. And you wanted to establish pharmaceutical sciences more as a discipline, to expand its influence.

07-00:25:06
Benet: Right. As a scientific discipline. At that time it was viewed as part of the profession of pharmacy. This was something that a pharmacist might do and sort of a science part of pharmacy as opposed to an independent group of scientists that aren't necessarily pharmacists.

07-00:25:24
Burnett: Right, right. And so what was your first plan of attack on fundraising?

07-00:25:30
Benet: Okay. So the first plan of attack was really while Dr. Riegelman was still chair, to set up this contract research organization within the organization. It was the first academic contract research organization to do pharmacokinetics of drug products.

07-00:25:46
Burnett: Did you call it a contract research organization? What was it—

07-00:25:49
Benet: No, because that terminology didn't exist then. We set it up as an organization, the Drug Studies Unit, that would provide quality data and information to the pharmaceutical industry and to others in terms of how drugs were disposed or how people reacted to drugs in terms of the absorption and the elimination in the metabolism and excretion, which is pharmacokinetics.

07-00:26:16
Burnett: And what was the plan in terms of getting funding from, say, pharmaceutical companies? How would that work and be ideal and how did it end up working in practice?

07-00:26:31
Benet: Okay. So we had this good interaction with clinical pharmacology and so we had all these MD clinical pharmacology fellows working in our laboratory. Because if they were going to do basic science the clinical pharmacology fellows worked for us. And so we had the MDs, we had the expertise, and they were learning the pharmacokinetics. And we knew how to give the information that the FDA needed for approval of a drug. And, in fact, we were defining the information that the FDA needed for approval of a drug. And so we said, "Well, let us do those studies." There weren't any really contract research organizations when we started this. There were a few but they were not very big and there certainly was no academic. So we were going to take the academic imprimatur, our respect and everything, and say, "Okay, we're going to give you quality data and then you can submit it to the FDA and they will like it." And that's exactly what happened. And it was immediately successful. There was a big need for it. And companies really came to us right away.

07-00:27:35
Burnett: Okay. So in the design of this was there any input from pharmaceutical companies? You just understood that this is what they needed and you provided that as a service?

07-00:27:49
Benet: No, not really a lot of input from pharmaceutical companies. This is the kind of information that the FDA wants and you need and we're the best people to

provide it for you. And we can help you design your studies and we'll meet the criteria that the FDA wants and our fellows were in the FDA. People who trained here were at the FDA setting these criteria.

07-00:28:15
Burnett: And so were the pharmaceutical companies, prior to this were they in the dark? Was there a—

07-00:28:20
Benet: No, they were doing it themselves.

07-00:28:22
Burnett: They were doing it themselves. But doing it—

07-00:28:23
Benet: No, no, they could still do it themselves but we just said, "Okay, so if you want an academic institution because doing it yourself always is questioning is the data accurate," or something. So we were the unbiased group of people providing the data. And so a lot of times the companies don't want to do it themselves. They want to have somebody outside and those people write the papers and it's generally better accepted. I'm not saying that the pharmaceutical industry doesn't do quality work. They do. But there's always a perception out there that you're compromised by the fact that it's your drug and you're studying it and stuff.

07-00:29:01
Burnett: Right. And was that a perception at the time that might have led into the perception of the Drug Studies Unit? Did anyone say you shouldn't be doing this because—

07-00:29:20
Benet: Oh, yeah, there were people that definitely said we shouldn't be doing it because this was still at the time when academic research was not industry research. There were definitely people on this campus that think this was wrong. We should not be doing this kind of work that would serve the pharmaceutical industry and the FDA. But our position was this is not just routine stuff. We're making advances in understanding drugs and how the drugs are there and it's important to get quality drugs and to do the studies correct. But we had wonderful support from the administration. The administration just thought this was a wonderful idea because the administration viewed we were going to generate a lot of money and we did. [laughter]

07-00:30:06
Burnett: And who were the people in the administration who were so supportive?

07-00:30:11
Benet: Oh, Senior Vice President and the Business Vice President. We had to do new things that people hadn't done before because we had to meet certain criteria that were federal government criteria in terms of how much of the overhead

are you going to pay, what kind of research is this. And just all the university and the state regulations that we had to meet and the university just helped us do that. And they wanted us to be successful and they were very supportive and they provided us the infrastructure. It was right here. This is where the Drug Studies Unit was.

07-00:30:48
Burnett: In this building?

07-00:30:49
Benet: Down here, yeah. And they provided us the space for it. We paid for it. We paid rent for it but it was still a very good deal.

07-00:30:59
Burnett: And for the record this building is called—

07-00:31:02
Benet: University Hall.

07-00:31:02
Burnett: Is called University Hall.

07-00:31:04
Benet: Which was the original University Hospital for UCSF.

07-00:31:06
Burnett: Right, right. And this is around the time when the university is beginning to recruit Bill Rutter and these other folks. So the bio—

07-00:31:19
Benet: Yeah. Rutter comes in ’68 and we start the drug studies unit in ’77. Wait a minute, no. Yeah, it has to be the year before I’m chairman. Seventy-seven or seventy-six, yeah.

07-00:31:33
Burnett: Oh, so I’m mistaken. But there is the building up –

07-00:31:40
Benet: But Rutter is still here. Rutter is still here when we start the Drug Studies Unit. He has not gone out and started Chiron yet. Yeah. And Herb Boyer is still here. Yeah. Even though they’re setting up Genentech and stuff, he’s still here at that time.

07-00:31:57
Burnett: Right. But there is an enthusiasm around new frontiers and its potential for commercial applications, right?

07-00:32:06
Benet: Right.

07-00:32:07
Burnett: So could you talk about why UCSF is particularly well-suited to that? It's clear that pharmacokinetics is a natural for that integration. But do you have your—

07-00:32:22
Benet: We have this terrific relationship with clinical pharmacology that other places didn't have. Clinical pharmacology was very strong at Vanderbilt and they had some good pharmacokinetic people but not the kinds that you had here. Pharmacokinetics was very good at Buffalo but they didn't have any clinical pharmacology people. It was really one of the powerhouse clinical pharmacology. So we had the physicians who were interested in drugs and how the body handled drugs, both ways, pharmacokinetics and pharmacodynamics, and the scientific expertise that really allowed us to do this. And it was our former fellows who actually ran the unit. That's who we hired, our former MD fellows and our PhD fellows who came in and ran the various aspects of the clinical part, the analysis part, analytical analysis in terms of drug measurements and the data analysis part. Those were all our former graduates that we hired to run these things. And so we had it built in. Yeah, yeah.

07-00:33:28
Burnett: And it fairly quickly resulted in some unique successes. Can you talk a little bit about some of those?

07-00:33:35
Benet: Yeah, yeah. So we made a new drug. It was called Maxzide. It came directly out of my NIH grant and research to understand how diuretics work and the combination of Triamterene and Hydrochlorothiazide. I had an NIH grant on and understanding the metabolism and why there were problems with the big drug that was out on the market. And so we just said, "Oh, we can make a better drug than the one out on the market." And we went and did it.

07-00:34:03
Burnett: And so it was a different combination of doses, of a ratio—

07-00:34:08
Benet: It was a different ratio and a better delivery system. Yeah, so it was a combination changing the delivery system and changing the dose ratio to maximize the right way to give this drug to get the right response.

07-00:34:19
Burnett: Thus the name.

07-00:34:19
Benet: Okay. Yeah. Right, yeah. Right.

07-00:34:22
Burnett: And how long did that take to translate into a drug that was patented and all of that?

07-00:34:30
Benet: Okay. We patented the new combination. I was a consultant to Lederle Laboratories at the time and I said to Lederle, "I'm developing this thing. This would be a really good drug for you." And they turned it down. They just didn't think it was going to make a—the biggest selling drug on the market at that time was Dyazide, made by SmithKline and French. Wasn't the biggest dollar volume but it was the biggest prescription volume. So it was obvious to us it was going to be very successful. So what we did is we formed an alliance with Mylan Pharmaceuticals. Big generic firm but a real little firm at that time. But we went and formed this alliance with them to do this, to make the product. And they would provide some of the money to it but we owned it.

07-00:35:27
Burnett: And when you say we, what's the legal entity?

07-00:35:29
Benet: UCSF.

07-00:35:29
Burnett: UCSF is the legal entity.

07-00:35:31
Benet: UCSF owned the product. And so as we got ready to say, "Okay, now we can go commercial with this thing, we're going to go to the FDA and get approval," Mylan said to us, "We'd like to buy it." And we weren't very sophisticated in those days and we sold it. Instead of licensing it to them—

07-00:35:55
Burnett: Licensing it to—

07-00:35:56
Benet: —and getting a royalty from it we sold it to them for a million dollars and we thought we had really made out. We thought we had really made out. Hey, it was a million dollars. That was a lot of money in the early eighties. Yeah.

07-00:36:12
Burnett: It was if you had a quarter-million-dollar operating budget for your whole operation.

07-00:36:16
Benet: Right. Yeah. So we sold it to them and they licensed it to Lederle. Lederle bought it from Mylan. So Lederle ended up being the manufacturer. When I was trying to sell it to them they didn't buy it but Mylan, when they had developed—and we were further along obviously when Mylan had it. And so I always thought, "Oh, God, Lederle could have made so much more money if they had done it with me. We probably would have made more money, too."

07-00:36:46
Burnett: Well, in the days, I suppose, before technology transfer officers that were savvy and had armies of lawyers.

07-00:36:52
Benet: Right. Oh, yeah. Technology transfer didn't do anything. We did it all ourselves.

07-00:36:59
Burnett: Right, right. Well, I think at the time the University of California had two people for the entire UC system to process technology transfers.

07-00:37:08
Benet: Right. And this wasn't really a good patent. It was just a reformulation. So what would happen is you'd get either three or five years, depending on what was the change. So you had a period of exclusivity that you would get but it wasn't the patent. So the university definitely didn't know what to do with this at that time.

07-00:37:28
Burnett: Right. It didn't fit the model of what they knew. I'm not entirely sure about the exact data but it's in the late seventies where you're on a panel, an advisory committee in the 1970s on industry/university relations. Did that follow from this experience or was it prior to this experience?

07-00:37:57
Benet: Okay. So each campus had a faculty member who was on the patent board of the university and that patent board made the decisions for the university of what it was going to do in terms of regulations. I became the UCSF member of the patent board.

07-00:38:16
Burnett: And when was that? Nineteen seventy-eight?

07-00:38:18
Benet: I'd have to go back and look.

07-00:38:20
Burnett: I think it's right around—

07-00:38:19
Benet: Because it has to be around then.

07-00:38:22
Burnett: —then.

07-00:38:22
Benet: It has to be around then. So all of a sudden I'm the campus expert on intellectual property because, you're right, there was nobody over there. The eight members or the nine members of this committee really set the policy for the university. So I learned a lot in terms of dealing with these guys. But it became very obvious if we were going to do this we had to worry about conflicts of interest. And I always worried about conflicts of interest. But this campus was very farsighted in terms of saying, "We got to get right on this and make sure that we don't kick ourselves in the foot and make sure, because

we are an academic institution and our responsibility is to the state and to the people. We've got to be pure in our science."

07-00:39:11
Burnett: And your credibility, which is absolutely essential. If it seemed that your expertise can be purchased not only in terms of the expertise but in terms of how you'd like the expertise to play out with respect to a certain drug, that's a huge problem that's still dogging these debates about industry/university collaboration. So do you remember some of—this is the problem because I don't know how much—

07-00:39:40
Benet: No, no, no, I do remember.

07-00:39:41
Burnett: —some of the conversations about this.

07-00:39:42
Benet: The committee was called the Bennett Committee. It was chaired by Leslie Benet, but not me. Leslie Bennett who was the head of physiology. He spelled it with two Ns and two Ts. At the same time and then he actually became Vice Chancellor. But at that time he was head of Physiology.

07-00:39:58
Burnett: Take note archivists.

07-00:40:00
Benet: We had a lot of fun. We used to have a faculty club and we often ate lunch together and a new person would come in and he would say, "I'm Les Bennett, hi," and I'd say, "I'm Les Benet, hi." And many people thought I was his son because he was significantly older than I. We didn't look alike but we had the same name.

07-00:40:20
Burnett: Yeah, Les, Jr.

07-00:40:21
Benet: But the spelling was different. And he was the chairman and we brought in really good people from here and we had community members. It was one of the first university committees that had community members, lay people, that were interested in the quality of the university and wanted to make sure we also didn't stub ourselves in the foot. And that committee tried to set the policy that we thought would allow us to still do entrepreneurial work but to really say we weren't compromised, that we would do it the right way.

07-00:41:01
Burnett: Was it a question of establishing mechanisms or guidelines?

07-00:41:06
Benet: Yeah, yeah, we set guidelines. We set guidelines. And I as chairman, because I was already chairman then, I felt I actually did a lot of that because my guidelines in the department were much stricter than the university guidelines, okay. So I would not allow any funding by a faculty member from a company that they had a major position in. And, in fact, this was just contrary to why people were setting up companies in those days. So faculty members were setting up companies so they didn't have to go to the NIH, so they could generate the company, the company would then pay for their research in their laboratory. A lot of people got around it by they weren't the principal investigator of the grant, somebody else was the principal investigator of the grant. I just wouldn't allow it. I would not allow any research to be funded in the department by a company that was—

07-00:42:05
Burnett: That was owned by—

07-00:42:05
Benet: Yeah, a principal was one of the faculty members. And they really weren't owned. They had to be full-time faculty members. So everybody had to be a full-time faculty member. You weren't going to be 20 percent with the company and 80 percent in the faculty. You had to be a full-time faculty member and your responsibility was to your graduate students and your post-docs and under no conditions would they work on anything that had to do with your company or things like that. Even if it wasn't funded, they shouldn't be working on stuff that was related to your company. So I was probably more tough than the committee. But the committee, that's where the rules went at UCSF. And we did a really good job because we really never had a major scandal at UCSF in terms of conflict of interest. And I think we were very farsighted in terms of making sure that we did that. And the committee would have people monitor when it looked like there were potential conflicts of interest. People would monitor the studies and the results and what happens and things like that.

07-00:43:08
Burnett: If a company wanted to support research that was going on in the lab, they could do so but the money could never go directly to the PI, right?

07-00:43:27
Benet: Well, yeah. But that's, again, the UCSF and that's really UC rules genius that we always had—not always, because I was a junior faculty member. When we introduced what was called the full-time compensation plan, I was probably an associate professor when that happened. What the university said is from now on you can't keep any of your consulting money. If you own a company and you have shares in it you can keep that. But any consulting money or any research funds that you receive you cannot personally benefit from that. It must all come into the department. It can be funded of your research but it has to go through the department. None of the money comes to you. None of the

money is salary unless you negotiate that with your chair, which you renegotiate every year. It's not easy to set those rules. But at least we had that barrier that said you cannot get money directly from a company. So you had to make a decision whether you were going to go with the new rules or the old rules. Now, the new rules then said you're going to be on a full-time compensation plan so you're going to get your state salary plus an X-factor that relates to this extra money that you've brought in. Do we need to stop?

07-00:44:49
Burnett: No.

07-00:44:51
Benet: And so as a department chair that was wonderful because nobody had conflict of commitment. They had to be full-time faculty. They were not getting their funds from starting a company. They could start a company and they could make a lot of money from owning the stock and all that kind of stuff but they couldn't get a salary from the company. They couldn't get the company paying them money directly, stuff like that. It was wonderful. I just thought it was the ideal situation and it was really good for UCSF.

07-00:45:22
Burnett: And it brought a certain focus to the research programs because people were really committed to what was happening in the departments. Perhaps while we're on the subject we should talk about Metformin, as well. I don't know if I'm pronouncing that right.

07-00:45:41
Benet: Okay, sure. No, okay.

07-00:45:43
Burnett: It was a Glucophage, is that right?

07-00:45:44
Benet: Yeah, it's Glucophage. A huge selling drug. So it was being developed by a little company called Lipha Pharmaceuticals and their medical director was a woman named Anita Goodman. They had gotten out of—what's in Cleveland? What's the—

07-00:46:03
Burnett: Case?

07-00:46:04
Benet: Case Western, yeah, okay. So they had got her from Case Western. She was the medical director. Even though the company was in France she was the medical director. It was in Lyon, France. And she had no way to run the clinical studies. They had the compound, they thought the compound was good. And we created a relationship with her and she ran all her studies here. And so we designed all the phase one and phase two studies for Metformin and faculty members in the department, if you go look at those papers, we're the senior authors of those papers, the early Metformin papers. And then

Bristol Myers Squibb bought from Lipha and then we were out. Although at that time I was the consultant to Bristol Myers Squibb, so I'd actually told them about it, and they were interested in it. But it wasn't me. I'm not taking credit for that at all. It was obvious that this was potentially a very good drug. But we ran all the phase one and phase two studies and then BMS took it over and did the phase three studies to prove safety and efficacy and get the FDA approval.

07-00:47:10

Burnett: That's interesting. So the science-studies community came really late to analysis of contract research organizations. So it wasn't until 2005 that they started publishing articles about this phenomenon when people have been talking about it for a long time already. And people are talking about it either in a negative or a positive light depending on where you stand on the issue. But their framing of it is that contract research organizations are these private firms that offer—kind of by definition private firms offer targeted services to pharmaceutical clients. And it's because they're fulfilling a service to the pharmaceutical industry and to the FDA in providing these kind of flexible services because of what happens in the eighties and especially the nineties, the enormous increase in the costs of drug development and regulatory procedures. So these trials get huge and no pharmaceutical company can stand to have massive in-house research facilities. It's too costly. And so they emerge to manage the costs. But the argument within the science-studies research community is that this also alters scientific practice. So the way that the research is done changes and the way that the science is done is now responding to cost constraints and is all defined by meeting specific narrow guidelines. And so the research can be so constrained and focused that you cannot really call it basic research in any sense. So it's a story of risk and dipping your toes too far into this private commercialized sector.

07-00:49:18

Benet: Okay. So let's do the time factor. You're talking about 2005. We started the Drug Studies Unit in '77. When we did it, we were designing the studies. So by the time the science community was looking at this the companies were designing the studies and they were going out and getting as cheap as they could to do it well, do the studies right. But they were controlling it and that wasn't what was happening. What we offered was here's all these clinical pharmacology, pharmacokinetic, pharmacodynamics expertise. We'll tell you how to do the studies and then we'll run them for you. So that was what was so unique. Now, we closed the clinical unit in '97. So the clinical unit was only around for about ten or eleven years because we could no longer compete, financially compete because now we have all the university regulations, we're not unique anymore. There are these other organizations out there that see this as a goldmine in terms of making money and they're no longer academic institutions whatsoever. And so we closed the clinical unit. But for that ten-year period or eleven-year period we were unique and we

really set the stage. And we were doing outstanding research leading to outstanding papers.

07-00:50:36
Burnett: There's a commercial dimension to it, absolutely, in the sense that there is this demand for these services. Of course you have the freedom to do what you want with this kind of work.

07-00:51:06
Benet: It's about a twenty-year period.

07-00:51:05
Burnett: Yeah, it says '78.

07-00:51:06
Benet: Yeah, says '77 to about '96, '95 when we closed the clinical unit.

07-00:51:12
Burnett: Yeah, '77 to '87 and then there's a consulting arm of it that lasts for another ten years or so. Is that right?

07-00:52:19
Benet: Yeah, okay. Yeah.

07-00:51:23
Burnett: So I guess the concern with the CROs as they're defined in the science studies papers that I'm alluding to is that these for-profit companies, by requiring scientists that work for them to do things a certain way, to meet certain kinds of cost constraints or deadlines, there's little to no room for the research that could yield, could spur open-ended exploration. And you're saying that since you and your colleagues were in the drivers seat sort of defining what it was you were going to do for the drug companies, that led to a lot of—and you're coming at it from your identity as a research scientist. So you're thinking about it not only as how can we make a cost-effective way to do drug dosing but also what's scientifically interesting. And those are not completely separate in your mind, right? This is just how you understand your work. It's, again, the service model. Like an agricultural extension agent, right? You want to do your science, you want to do interesting scientific research but there is a county of farmers who need help, right, and so you're defining your problems in collaboration with those outside agents.

07-00:53:01
Benet: Yeah. We actually turned studies down, too, because we only had so much capacity. So we couldn't do everything. So we did the stuff that we thought was the most interesting science in those days.

07-00:53:15
Burnett: Right, right. You talked about when you were on the Committee for Industry-University relations, that the public was brought in, the community members were brought in to talk about what this would mean. It's the late seventies.

There's a lot of political ferment about the role of government and the role of corporations in the public sphere. So was there any kind of press about this kind of work or was it kind of below the radar? It wasn't really a public issue?

07-00:53:55
Benet: It was below the radar. Below the radar.

07-00:53:58
Burnett: No one was really—

07-00:53:59
Benet: It gave us so much freedom as a department. We could fund the research; we could fund new faculty members; we could bring in people. None of that money went to us personally. It went back to the department. So it just was very useful in terms of moving the agenda of the department and the school. I think you used to give the school 20 percent of what we brought in and kept the rest for ourselves.

07-00:54:30
Burnett: That's great. Overhead costs have changed in the interim. So I would like to ask before we change tapes one more question about the center grant because that's also in the mix in 1979, right?

07-00:54:51
Benet: Yeah. That's right. That's right.

07-00:54:53
Burnett: Can you talk about how that came about?

07-00:54:55
Benet: Okay. So, again, funding is very low and I've got really a cadre of young really smart people in a new discipline. NIH is out there saying we're looking for new ways to fund different things and center grant was one of the mechanisms. I think we were the third pharmacological sciences center grant from National Institute of General Medical Sciences. And when we closed down twenty years later there were only two left. And it was a different philosophy. The philosophy then was that the center grant should be used as a group of people to really improve a discipline and to be a funding source not just for the senior people who write the grants but for the junior people, too. And the junior people get brought along to that. So the center grant allowed me to give money to all my junior faculty. They would make proposals or projects and it would be their first funding. And, again, it was so good for us as a department to bring this in. Now, that got a lot of publicity because that original funding was for a million dollars and, again, that was a lot of money in those days. So when we got the center grant at UCSF people paid attention to that.

07-00:56:33
Burnett: And was it on a five-year renewable?

07-00:56:35
Benet: It was five-year renewable and we went nineteen years. Yeah.

07-00:56:38
Burnett: Yeah. That's phenomenal. I guess that goes back to the original notion of the National Science Foundation, which was that you need to support for long enough to allow a kind of scientific culture to emerge and to produce results.

07-00:56:55
Benet: And the other thing in those days, there was money for administrative purposes also. So the Center Grant had their own paid administrative staff that actually also was really a wonderful thing in those days. So the department had not only its department resources but it had its administrative staff people coming from the center too that was funded off of this grant. So there was an administrative core of funding that allowed the department to have an editor and to have somebody that arranged meetings and all the things that maybe somebody would do but this was their full-time job and they were part of the department and facilitate the growth of the department.

07-00:57:38
Burnett: It's important to recognize. Former UC President Mark Yudof wrote a kind of public declaration in 2013 arguing that the federal government not only should be funding specific kinds of research but it needs to fund some of the basic infrastructural elements of these universities because state funding has dropped out.

07-00:58:02
Benet: Right. And it did. And it did when it first started. The NIH also ran out of money, too, so they made their choice. "We're going to fund the basic science." But those were the good old days.

07-00:58:18
Burnett: Well, it sounds like the good old days was the decline of one model of support for scientific research and the beginning of another. It's probably not a good idea to ask an open-ended question but how do you feel about the nature of support for scientific research? Do you think it should be state funded or it should be privately funded or it should be a mix of both? What are the effects of one or the other?

07-00:58:57
Benet: Okay. So I would like it to be federally funded as opposed to state funded. Only because we never got any money from the state so I never even had that model.

07-00:59:08
Burnett: Well, I meant the state as in government.

07-00:59:09
Benet: Yeah, yeah, the government. Yeah, federally funded. But it's evolved into not a good situation anymore. Basically I think the wonderful advances that we

still make with NIH money are really the investigators fooling the study section [of the NIH]. Because what the study sections look for today is—because there's so little money and they're so worried about it—what they want is to make sure you're going to get results. So in essence you sort of have to already have the answers before you do your grants. And so you got to have the results. Still, a lot of good stuff comes out of it, but a lot of times it's not what's written in the grant that comes out are the major focuses. Because what's written in the grant is "here's the question, here's the answer, here's how I'm going to do it. And these are the steps I'm going to do and I'm going to follow through." But the brilliance that comes out of it, they're not in those steps; it's what comes out with the funding. So we still get a lot of really good stuff. But I don't think it's what's written in the grant. And, as I said, BDDCS got turned down just flat. [The NIH evaluators must have thought] it couldn't possibly be useful because we were asking questions that we didn't know the answer to. So I think that's not a good thing, the way it works. But it's still important that funding be continued and as people develop and do good work they get funded and it works. So I'm not against it and I do think it is the federal. Because industry has a tough time funding it because they are responsible to the shareholders and they want to have an output and an outcome that is beneficial to the company. So they define their outputs or what they want pretty narrowly also. But you're going to make your breaks not doing narrow stuff. That's where you're going to make it. And we don't really have a mechanism, we just sort of make it work. But there are things like MacArthur Foundation and stuff like that where all of a sudden—

07-01:01:21
Burnett: There are private foundations –

07-01:01:21
Benet: Where do you get money for just unusual ideas and stuff. But it's not the major funding mechanism.

07-01:01:28
Burnett: Right. And so there needs to be stable steady support from the federal government to create a context in which innovation in scientific research can take place to make the mistakes to go down blind alleys.

07-01:01:44
Benet: Yeah. No, you've got to go through the blind alleys. And also Congress and the people who don't appreciate science— and most people today don't appreciate science—they feel, "we're giving you the money, what's the outcome?" And that's unfortunate because it's basic science that sets the groundwork for where all the major discoveries come from and it's why we're so great, the US is so great. We had that structure. I still think we're still great but we're not as great as we used to be because the funding is not as forthcoming.

[Audio File 8]

08-00:00:00

Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Medicine and Technology series and this is session four, tape eight, and it's November 18, 2014. So we were talking about development of an entrepreneurial spirit and a set of entrepreneurial institutions that would allow the department of pharmacy to grow in the 1980s. Now, in addition to the Drug Studies Unit, you also have the center grant for drug kinetics and dynamics. Can you talk a little bit about the scientific talent that was attracted to your department during this time and some of the people that you worked with who were extraordinary?

08-00:01:05

Benet: Okay. So what was different about our department was most of the pharmaceutical science departments in the country, or departments of pharmacy, had a concentration on drug delivery and we didn't. We didn't have a concentration at all on drug delivery. We were pharmacokinetics, pharmacodynamics and some toxicology and metabolism. So I thought it was really important that we compete and have expertise in the drug delivery area. So we chose sort of two areas to focus on. One was putting drugs in liposomes and the other was transdermal delivery. And we were able to recruit two really outstanding young faculty members, Frank Szoka in the liposome area and Richard Guy in transdermal delivery. They came, they setup their programs, they were attractive, they got a lot of research money. They brought in graduate students and post-docs. So we were more like other departments of pharmacy. We now had a drug delivery focus, although we weren't across the board and we weren't technology in terms of manufacturing and these kinds of things. We did have that. So I thought that was really important. We recruited really outstanding young people. Kathy Giacomini who became my successor and really has done an outstanding job in pharmacokinetics but started to move into genetics. Deanna Kroetz, who was a young faculty member. We had a history with Deanna. When Deanna was an undergraduate at Ohio State University she applied to graduate school here and we accepted her and she turned us down and went to Seattle. When she got done at Seattle I offered her a post-doctoral fellowship and she turned me down and went to the NIH. But at the end we got her here on the faculty.

08-00:03:04

Burnett: [laughter] Okay, great.

08-00:03:05

Benet: And she's really blossomed very well also in the genetic aspects of it. Wolfgang Sade came in. Wolfgang had been a post-doc with Dr. Riegelman, Sid. He then was on the faculty at UCSF. But one of the things we tried to do as a department to do the pharmacokinetics was we wanted to have a patient focus. And so we wanted to be able to have a laboratory that would measure the drugs that you needed pharmacokinetics and dosing. And so we brought

Wolfgang back. Actually, Sid did. Brought Wolfgang back and we setup a pharmacokinetic analysis laboratory that we would measure the drug levels and we would give those levels back to the clinicians or we would setup our own consultation service in terms of being able to make recommendations to patients in terms of what they would do. And then we brought in young faculty members like Lew Sheiner and Stu Beal in pharmacodynamics and in the data fitting programs needed to make pharmacodynamics work. And all of those people got funded in the center grant when they first came in. So that was really an important mechanism.

Then I thought that we should have some immunology, that we needed to have an immunology person in our department. Again, one of the things that I've always thought UCSF did so well was we never duplicated scientific disciplines within schools. So there was no physiology department in the school of pharmacy. There was no pharmacology department. There was no immunology department. So we had an immunology department and they taught everybody, all of the four schools. And I think, again, that's been a real strength of UCSF, that you didn't have first-class and second-class faculty. First-class faculty teaching the school of medicine and the second-class faculty teaching the other health professions. So that was a genius of UCSF and it really served us well. But I thought we needed to have an immunologist from a research focus that would interact with the kinds of things we were doing, transplant drugs and still like that. So we recruited Frances Brodsky. But she got in with the immunology department. She got a joint appointment but she was our Frances. This was her department. And I can recall once with Frances, I insisted, "You're in the department of pharmacy. Those papers have to say department of pharmacy. This is where you are and this is where your loyalty has to be because this is where you're funding is." And that worked and everybody bought into that. And so we brought in good people.

We had a lot of pharmacokineticists. Svein Øie who's now the Dean at Georgia and Bob Upton who's now retired in Australia. But all these people come back and teach in our one-week course every year. [laughter]

08-00:06:06
Burnett: Oh, really?

08-00:06:07
Benet: Yeah, yeah. Yeah.

08-00:06:07
Burnett: Okay. So it's kind of a reunion every year.

08-00:06:10
Benet: Yeah. Right. We have a one-week course, Pharmacokinetics for Pharmaceutical Scientists. We're in our twenty-seventh year this year.

08-00:06:17
Burnett: That's right. That's extraordinary.

08-00:06:19
Benet: It's strictly for the industry and unabashedly this is to make money for the department. And so we don't give any discounts to academics. You come in and you pay the full fee. But all of our faculty who have been in the department come back and still teach in this course. The dean at Georgia comes back one-week every year and we teach here. And Bob comes from Australia every year and a lot of our former fellows. Particularly people in industry in the Bay Area come in and lead the workshops. That was another entrepreneurial thing we did now twenty-seven years ago to generate funds for the department. Yeah.

08-00:06:59
Burnett: Right, right. And when you described early on in this description of the people who helped, you talked about creating this relationship with a way to study patients, basically, and drug dosing. You had that relationship before with clinical pharmacy but you were—

08-00:07:28
Benet: Clinical pharmacology.

08-00:07:29
Burnett: Clinical pharmacology. But you were doing their lab results for them.

08-00:07:35
Benet: But we weren't until then.

08-00:07:37
Burnett: Okay. This is when it starts.

08-00:07:39
Benet: Yeah, this is when it starts. Okay. So you need a good analytical method to be able to measure the drugs sufficiently enough that you can make dosage recommendations. And so the department of laboratory medicine had setup a bunch of drugs but they didn't do them all. And we setup a whole bunch more. And so we actually had two labs. Depending on which drug you were on, you either went to laboratory medicine to have your drug assay—and these were patient samples—or you went to us to do it. It just sort of broke even. It just sort of broke even.

08-00:08:14
Burnett: Yeah, but it was important scientifically.

08-00:08:17
Benet: Yeah. But what I did was I traded our assays to the department of laboratory medicine, that they would fully fund Lew Sheiner and Stu Beal. Okay. So they became fully funded in their department and I gave them our assay. So we weren't making any money and I'm an entrepreneurial guy. And the other thing that happened at UCSF, which was really good. When Ken Melmon left to become Dean of Medicine at Stanford, Clinical Pharmacology didn't know where to go or what to do or Department of Medicine didn't know what to do.

So I negotiated with Holly Smith, who was the chairman of the department of medicine, “Why don’t you let clinical pharmacology become a joint division between [the School of] Pharmacy and [the School of] Medicine and stop requiring them to bring in patient dollars and bed dollars and let them act like academic scientists or basic science scientists and bring in all their money through grants and overhead money like that.” And he agreed. And we actually did some joint appointments between pharmacy and medicine and so the division became a joint division and that got rid of any conflict between medicine saying, “Okay, we want to do the consultations,” or pharmacy, “We want to do the consultations.” And I was very proud of that because there was no conflict that our clinical pharmacy, who now was developing and wanted to do the consult service—there was no financial thing that they had to fight against. So the physicians and the pharmacists could work together with nobody worrying about it because nobody had to bring in a certain amount of money to do these consultations. Yeah. And that was something I’m really very proud of.

08-00:10:09

Burnett: Of course, in 1980 Congress establishes the Superfund Act, right, and so there’s all of this concern over environmental remediation and all of those scandals about Love Canal and all of that stuff. So there’s a concern about toxicity. Can you tell a story of how the department was able to—

08-00:10:38

Benet: So Berkeley wanted to put in a superfund grant but they didn’t have any medical people and they didn’t have any people that did assays of contaminants. We didn’t do that either but we knew how to do it. And so Berkeley came over here and said, “Would you like to join us and we’ll put in a joint Berkeley/UCSF superfund application?” I thought, “That is a terrific idea. Sure, we’re interested in doing that. And, in fact, we’ll setup a whole division of toxicology that that will be under.” And so Neal Castagnoli, who was in the Department of Pharmaceutical Chemistry, moved over in our department and became the chief of toxicology and we got this superfund money and we got money from the state and we got money from the federal government and we did a lot of good stuff. It was just an opportunity. Of course, UCSF came out of Berkeley so it was natural to go back and work with Berkeley when you needed two different components in terms of having the superfund grant. So I was the UCSF PI on the superfund grant and there was a Berkeley PI and we worked together and we brought the money in and shared the funds until they disappeared.

08-00:11:54

Burnett: Right. How long did that last?

08-00:11:56

Benet: Oh, it probably lasted about ten years.

08-00:11:56
Burnett: Yeah, yeah. And so this is another example of how shifting priorities in government support of science creates new opportunities for you to develop and build out the work that you're doing. And did the division of toxicology continue?

08-00:12:19
Benet: No. Well, in paper it did. So the state thought this was a terrific idea. The School of Medicine thought this was a terrific idea and everybody agreed that we would setup a division of toxicology within my department. It would be a division in my department. But it would represent the campus. So just like we don't duplicate anything—so toxicology was going to be in the department of pharmacy at that time. And at that time we got the insurance building over on the other side of the city and we were going to have a whole bunch of space, okay, and so toxicology was given a floor of that building, okay. What was the name of the insurance company?

08-00:13:11
Burnett: I don't know.

08-00:13:14
Benet: Big insurance name. We bought the building. The campus bought the building and we were going to expand and have a toxicology. And gosh, and I had a lot of money. And the state said, "We're going to give you two funded FTEs and sixteen graduate students for toxicology because this is an important area." And it would be within the Department of Pharmacy. And so Neal got recruited to Virginia Tech to be the Peters Professor of Chemistry, so he left, and so I needed now to have a toxicology head. But I had all this money, all these FTEs and all these graduate students. There were a lot of people that wanted to work on this. We recruited on an international level. We were looking at people that were really National Academy people who thought coming to UCSF and interacting with this environment would be really good. A whole floor of space with two new state-funded positions and we had the superfund grant in that time, so there were other positions you could bring. Sixteen new graduate students. And then the people in the City [of San Francisco] were opposed to having science in the building over there. They opposed it and so we never could get approval for laboratories over there.

08-00:14:33
Burnett: Oh, because of the fact that you'd be working on toxic materials?

08-00:14:36
Benet: Yeah, that's right. They didn't want any laboratories over there. This was a neighborhood and it would contribute to the detriment of the neighborhood.

08-00:14:49
Burnett: Those rowdy graduate students, right?

08-00:14:51
Benet: Right. And they didn't want students either. They didn't want any students. And we said, "Well, you're not going to have students. Only graduate students." "No, no, we don't want them either. We don't want these laboratories."

08-00:15:01
Burnett: That's too bad.

08-00:15:01
Benet: So it all disappeared. But it's on the books. We really only got one-half of an FTE that actually got funded by the state. They never gave us the money for the graduate students, they never gave us the other one and a half. But it's still on the books. [laughter]

08-00:15:16
Burnett: It's all right. [laughter] Well, there are a couple of things I want to talk about. Just briefly, the Department of Pharmacy becomes the Department of Biopharmaceutical Sciences. Can you talk a little bit about that name change?

08-00:15:34
Benet: Okay. So the faculty, and me, too, thought, "This is not the right name for a basic science department, Department of Pharmacy, because what you think is we're going to be filling prescriptions," and that's what everybody on the outside thinks. But nobody could agree. I was chairman for twenty years and we probably changed the name after about sixteen years. But I would say after the first eight years everybody was agreeing we should change the name but we could never reach an agreement of what the name should be. And we had different factions that wanted this and wanted that. And so finally we agreed I think somewhere around '95, '96, on biopharmaceutical sciences and we became the Department of Biopharmaceutical Sciences. The people that didn't want that name was because biopharmaceutical then started to mean the large molecules, antibodies and peptides and proteins and stuff like that. But with time the name became more general and so it didn't mean that anymore. So it became a more acceptable name and we finally agreed as a department to change the name.

08-00:16:40
Burnett: Oh, that's interesting. So you're saying '96 or '86?

08-00:16:44
Benet: No, no, not '86. It was probably the last six years I was chairman. So probably somewhere around '92, '93.

08-00:16:51
Burnett: Okay, '93. Okay.

08-00:16:52
Benet: It's in the documents for the school.

08-00:16:54
Burnett: Right, right. And another important milestone is the foundation of the AAPS. So this goes outside of the department administration, more in the discipline formation, which was a goal of your department.

08-00:17:13
Benet: Right, it was a goal.

08-00:17:14
Burnett: Something you set out to do. Can you talk a little bit about—setup the problem. What was the problem that led to this?

08-00:17:22
Benet: Okay. So the problem was that the pharmaceutical sciences—and we were the Academy of Pharmaceutical Sciences from 1966. One of the visionary leaders in the pharmaceutical sciences, Takeru Higuchi, who was first at Wisconsin and then at Kansas, created within the American Pharmacists—what was then called the American Pharmaceutical Association, this division that could be scientists. And it was called the Academy of Pharmaceutical Sciences and it was formed in 1966. But it was a subdivision of the professional association. And the professional association was very wary of us because these were the days that generic drugs were starting to come out and the scientists were against generic drugs because the scientists, many of them came from the pharmaceutical industry. There wasn't any small industry. It was all the major pharmaceutical industries. The pharmaceutical industry as a whole was against. So the profession was very afraid that these scientists were going to compromise the pharmacy profession. And the pharmacy profession was very much for generic medicines because it would decrease the price and would allow people with limited means to have access to drugs that they were really having trouble with at the time.

08-00:18:52
Burnett: And that was their perception but they were wrong?

08-00:18:55
Benet: No, it wasn't a threat at all but it was their perception. And so as part of their perception, if you weren't a pharmacist you couldn't vote in the American Pharmaceutical Association, okay. And so it was really hard to attract somebody who wasn't a pharmacist to join the American Pharmaceutical Association so they could become part of the Academy of Pharmaceutical Sciences. So in 1985 I became president of the Academy of Pharmaceutical Sciences within the profession. I am a pharmacist. I'm trained as a pharmacist. And I proposed in my inauguration speech or my first speech that what we ought to do in the next year is to try to change the rules so that science would grow within the APhA and to create an academy that was able to function on its own, that was able to set its own policy, that could attract people who weren't pharmacists and so that we could have an impact. Because we had no impact. We were not allowed to take any positions. We could never do anything that was opposed to what the pharma—

08-00:20:06
Burnett: If you can't vote, you can't vote.

08-00:20:07
Benet: Yeah. What the pharmacy profession wanted or what was viewed as the pharmacy profession. And there was a hard-nosed executive director who felt he could control the money and he could control us and he said no to everything we wanted. We didn't really want some terrible things. We wanted an observer's seat on the board. Because all this stuff was happening and we never knew about it and then all of a sudden we'd find out about—so we wanted an observer's seat. We wanted to be able to set our own policy. We wanted to be able to raise our own money and keep our own dues and we wanted to have a vote. We wanted the scientists to have a vote within the association. They refused any of that. And so they served as a nice vehicle to take the association and move it out. And it was never my objective. It was never my objective to take the scientists out of the American Pharmacists Association. My objective was you will benefit by us having more influence.

08-00:21:06
Burnett: Right, right. And at the moment of the split what proportion were the scientists in the total APhA?

08-00:21:17
Benet: Okay. So the scientists at that time had about 2,300 members. There were about 2,300 scientists and there were probably about 1,200, maybe even more, because you have all these students so it's really hard to count. You don't know how to count students. These professional associations, they don't really tell you what their membership is because they count all their student members and stuff like that. It could have been as much as 40,000. I think it could have been. They said they were 40,000 but I think a lot of them were students. But we were just a little piddly portion of the association.

08-00:21:52
Burnett: One of the things that I read in this story is that it was partly a consequence of the UCSF's hiring of basic scientists to teach pharmacy.

08-00:22:10
Benet: Okay. That's in the UCSF history. So the deans at UCSF, Troy Daniels and Jere Goyan, strongly believed that you don't need to have a pharmacist teach basic science courses within the curriculum. Okay, so this is important. There's no double physiology, there's no pharmacology double, there's no immunology double but there's no chemistry on this campus because we're a medical school and a medical campus. So chemistry is now part of the School of Pharmacy. So your basic science in chemistry and physics is in the school of pharmacy. And so are you going to hire pharmacists to be your chemists or your physicists? Yeah, you could. There's some of them. But the majority of them, if you're going to try to become an outstanding recognized department you want to go out and get outstanding chemists. You don't want to get outstanding chemists who also happen to be pharmacists. If you could find

one, okay. So the Department of Pharmaceutical Chemistry, which had the chemistry in the curriculum, had a lot of strong basic scientists and they never attended the American Pharmacists Association. They would attend the American Chemical Society or whatever discipline they were in. But we were sort of in this weird situation because we taught courses that the pharmacists needed in terms of how to make dosage forms, how to do pharmacokinetics, how to make drug dosing decisions. And so we're all within the [School of] Pharmacy. And most of our faculty at that time are pharmacists because they're the people that know these aspects. So we're starting in this department to recruit a lot of people that aren't pharmacists. So the people that I told you, Frank Szoka to do the liposomes, and Richard Guy to do the transdermal, those were just the nucleus. They brought in other faculty in these areas and none of them were pharmacists. And so we're starting to have really strong scientists in drug delivery who aren't pharmacists. But we don't have any vehicle. We don't have any vehicle to be recognized and no association to be recognized. And so where do these people go? And so we felt we needed to have an association. We needed to have an association that represented the pharmaceutical sciences that weren't the chemists. Right. And so that's why we created it.

08-00:24:38
Burnett: I talked to Dr. Borchardt about some of this story and he seemed to suggest that it was rather dramatic when the eventual split came.

08-00:24:54
Benet: It was dramatic.

08-00:24:55
Burnett: I think you and Tanaka [sic]—

08-00:24:59
Benet Takeru Higuchi.

08-00:25:00
Burnett: —Takeru Higuchi both stood up and said, "We're leaving." Can you tell that—

08-00:25:06
Benet: No, no. It's not so much we're leaving. So if you're going to start a new association you have to have funding. Money. Okay. APS started by me giving them $200 and then $5,000. Lending them. Starting. But we needed to have more money than that. So both Tak and I said each of us will commit, if needed, to put in $50,000. Okay. This is 1986. We never had to do that. In fact, I got back my $5,200 within two months when people joined the association and started making contributions to the association. Because the American Pharmaceutical Association wasn't going to give us any money. It was our money. We had raised it in meetings and all this kind of stuff but we didn't own it and they weren't going to give it to us. And so we had to have

somebody that would say, “Okay, we’re going to fund it if need be.” But we didn’t need to do it.

08-00:26:10
Burnett: Right, right. There’s a couple of dimensions to this because, as with any split, you have to kind of divide up resources, right?

08-00:26:25
Benet: Right. But we didn’t take any resources but the people. We didn’t take anything. We didn’t have a journal. Okay. But that’s another story. I don’t know if we want to talk about that, at that time. [laughter]

08-00:26:37
Burnett: Well, yeah, there’s that. Okay. Well, let’s put a pin in the journal story. But one of the things that Dr. Borchardt talked about was the fact that initially you were the AAPS. You were running it here or wherever your office was.

08-00:27:03
Benet: Right. I did it here. And we started February 5, 1986. We setup an office in—what’s the town next to Arlington? Right across the river from Washington? Oh, so bad when you get old.

08-00:27:20
Burnett: Well, I’m thinking of Arlington, Virginia. Fairfax?

08-00:27:25
Benet: No, no, closer in. Right across the river. You go right across the river and you get to it. Okay.

08-00:27:33
Burnett: I’m blanking, too.

08-00:27:34
Benet: That’s when we hired away some people. Well, yeah, we hired away some people who were the people who did the association at APhA, American Pharmacists Association. We hired a couple of people away to run it because they were interested in being the scientist people. That’s what their job was and there weren’t going to be any scientists in the American Pharmacist Association so they wanted to be where the scientists were. So we setup an office. So it really was never here except I needed to have an executive director and so I took one of my faculty, Ken Lem, called him into the office one day and said, “Ken, how would you like to be the executive director?” I said, “There’s no money in this but there’s a lot of glory. You can be the first executive director of the association.”

08-00:28:24
Burnett: Great. And just to conclude for this session, could you talk a little bit about the consequences of the split, both positive and negative?

08-00:28:37
Benet: Well, it created a lot of bad will, initially. Really bad will. I was anathema to many of the pharmacists and really feeling I had destroyed the American Pharmacists Association, American Pharmaceutical Association by taking the scientists out. No sympathy that we didn't have any rights and if you had given us a few rights we probably would have been there. Because when they reformulated their new association they did everything that I had asked for initially. They had a seat on the board, they could set their own policy, they could control their budgets and so on. But it became sort of a social science part of pharmacy, administration and stuff, which really wasn't—in other words, AAPS became the hard science, laboratory science, and the social sciences part of that sort of did stay with the American Pharmacists Association because they were the people that had to interact with the pharmacists in terms of what would affect their practice and things like that and the economics.

08-00:29:47
Burnett: So kind of the sociology of—

08-00:29:47
Benet: Yeah, sociology and—yeah.

08-00:29:52
Burnett: Okay, okay. Consults and—

08-00:29:53
Benet: And business administration. And the administrative people.

08-00:29:54
Burnett: Right. Health economics, perhaps.

08-00:29:57
Benet: Yeah, right, that kind of stuff. They stayed with the association.

08-00:30:00
Burnett: Okay. We're twenty-eight years since that happened. Most people just don't even pay attention to it anymore. Here are the pharmaceutical scientists and here are the pharmacists. And they work together and there's no competition and negative aspects of it.

08-00:30:27
Benet: Over time did you make overtures or do any bridge building?

08-00:30:34
Burnett: Sure, yeah, a lot of it. I have now won some awards from the American Pharmacists Association so they got over that. [laughter] I won their highest scientific award, which is the Takeru Higuchi Prize, and I know there were guys that said, "Over my dead body would Les Benet ever get anything [laughter] from the American Pharmacists."

08-00:30:59
Benet: Wow. Well, according to Dr. Borchardt, he said that in the recent years you've been really building bridges with APhA and trying to make that work.

08-00:31:07
Burnett: Right, yeah. Because we want to work with the pharmacists. We're the scientists that work with the pharmacists.

08-00:31:12
Benet: Right, right. It would make sense. Yeah. So we'll stop for now and we'll pick up next session.

08-00:31:20
Burnett: Okay. All right. Good.

[End of Interview]

Interview #5 December 9, 2014
[Audio File 9]

09-00:00:00
Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Technology and Medicine series. We're here at UCSF, Parnassus Avenue, in Dr. Benet's office, and it is December 9th, and this is session five tape nine. So I wanted to continue from last session because we were talking about the split, the development of the AAPS that you shepherded. There was a story we didn't quite get to about the status of the journal. Can you talk a little bit about that?

09-00:00:56
Benet: Sure.

09-00:00:56
Burnett: What happened?

09-00:00:57
Benet: So one of my faculty, Dr. Wolfgang Sadée, born in Germany, and studied and raised in Germany, was approached by a German publisher, Thieme, to start a new pharmaceutical journal called *Pharmaceutical Research*, and he did that about 1983, I think. But it was not going well and he came into my office in maybe late 1985 or fall of 1985 and told me that the journal was not successful. It really wasn't doing and Thieme was not interested in it because it didn't seem like it was being a big success. And he was going to stop. He was going to stop being editor and Thieme was going to give it up. And I said, "Wolfgang, don't do that." I said, "I may need a journal in a few months. Just hang on for a few months and I may create a situation where Thieme can sell us the journal and we will have a journal if we start this new society that will then be built in to have it then." So I think in either the third year of the journal or the fourth year of the journal it became the official journal of the American Association of Pharmaceutical Scientists. And it was a good deal because it's hard to start a journal and here we had one built in and we had an editor, a really competent editor, and so we had a lot of credibility right from the beginning.

09-00:02:33
Burnett: And was there some talk prior to that of the *Journal of Pharmaceutical Sciences*, which had its home in the APhA?

09-00:02:43
Benet: Yeah, right. So we actually made an offer to APhA to sell us or to give us the *Journal of Pharmaceutical Sciences* and initially they were going to do this. And we started to do some negotiations with them. But there were members of APHA that were really mad at me and under no conditions wanted to do anything that would support this new science organization and so they eventually backed away from it. Yeah.

09-00:03:14
Burnett: Okay, okay. And is there a different character to the *Journal of Pharmaceutical Research*? Different set of specializations or—

09-00:03:22
Benet: No. No, I don't think so. It really overlapped a lot with the *Journal of Pharmaceutical Sciences*. It turned out to be that it was a more prestigious journal. It's always had a higher impact factor, right from the beginning. It became an AAPS journal, it had a higher impact factor than *Journal of Pharmaceutical Sciences*. But *Journal of Pharmaceutical Sciences* is an important journal for the field of pharmaceutical sciences and some of my early papers—for many years I had the highest cited paper in that journal and now it's the second highest cited paper and the third highest cited paper in the journal. So we've come together and there's no antagonism in terms of that. The editor of the journal is Ron Borchardt, who was one of the presidents of AAPS. Yeah, yeah.

09-00:04:13
Burnett: Yeah. According to Dr. Borchardt, the bridges have been built and it sounds like the community has come together a great deal.

09-00:04:26
Benet: Right. The scientific community was really not split. It was the pharmacists who were mad at us, that we had taken the scientists out of APhA and created our own association. So the pharmaceutical scientists, that didn't bother them. They published in both journals all along.

09-00:04:45
Burnett: Right, right. Right. So the AAPS is born in the mid-eighties and it's carried through to today. A lot is also happening in that period, so I want to segue to a couple of different subjects that we want to cover in the next couple of hours. One is your own personal entrepreneurial turn. I guess I'd like to know how that developed for you personally. You did talk about the Drug Studies Unit, which is a kind of initial baptism in that world. After you worked in the drug studies unit and out of that came Maxzide and Metformin or the new formulations thereof. Can you talk then a little bit about how this developed for you as entrepreneurship?

09-00:05:58
Benet: Okay. So actually I had a few offers at that time, after we studied the drug studies unit, to create my own CRO. My own company that would be a CRO. But I didn't find that very enticing. That I would—

09-00:06:15
Burnett: Why not?

09-00:06:17
Benet: Well, it's service. It's service and doing work for other people and things like that. I was always a very strong consultant to the pharmaceutical industry. So I interacted with the pharmaceutical industry a lot but I didn't have any of my

own inventions. And it wasn't until I had my own inventions and wrote patents that I thought, "Yes, now I can start entrepreneurial and start a company and take advantage of that."

09-00:06:46
Burnett: So then let's follow that. You have an impressive number of these patents. Can you talk about the very first ones that you developed? You talked about them a little bit already. You've already talked about the screening method for identification of bio-enhancers through the inhibition of P-glycoprotein transport in the gut.

09-00:07:22
Benet: Right, yeah.

09-00:07:23
Burnett: Now, is that the first one?

09-00:07:24
Benet: That's the patent, that's the first patent. Yeah. Now, that came out of the work of Chi-Yuan Wu, his PhD thesis came out of that work. In fact, there was data in the literature that said this wouldn't work and so that's always great for patents. When the literature said this wouldn't work and it's not going to be useful, then that's a real invention and you can go to the patent examiner and say, "Look, this is obviously something that people didn't agree on." And so we wrote the patents and Chi-Yuan and I were the authors of the patents and did just as you were supposed to do. Licensed them through UCSF. But at that time we didn't have our own patent group at UCSF. The university had not diversified. Remember I was a member of the patent board. And so at that time the whole University of California patent system ran through Berkeley or in Oakland where the office was, the president's office, and that's where the patents were.

09-00:08:33
Burnett: And this is early nineties that we're talking about?

09-00:08:34
Benet: This is early nineties. Yeah.

09-00:08:36
Burnett: So just as background, Bayh-Dole in 1980 allows universities to license inventions or techniques for the first time, right?

09-00:08:49
Benet: Right, yeah.

09-00:08:50
Burnett: And so that leads to a kind of bonanza in the 1980s. But in the early 1990s still it was not the most efficient or easy—

09-00:09:06

Benet: Well, the patent office in the university was not that wonderful. But I dealt with all those guys and I knew them because of serving on the university patent board and was able to interact well with the people and I thought they did a good job in writing our patents and supporting them and they felt that they were worthy patents. At the same time we thought, "Well, let's form a company to take advantage of these patents." And the University of California has been very good at supporting its faculty in terms of licensing back the patents to entrepreneurial activities in the companies. And I was a strong believer that you separate out what you're doing in the university from your entrepreneurial activities. And so once we wrote the patents and carried them through into the university, then we formed AvMax, maximum availability. This is an interesting story. I went and talked to Alex Zaffaroni, who was the founder of ALZA and many other companies, and he had one piece of advice to me. He said, "Start the name of your company with an A," which he did with all of his companies, because it all comes up at the beginning. And I said, "I think we were going to have MaxAv or something like this." Said, "That's not good. You need to start the name of your company with A. So he said AvMax, availability maximum was the name of the company.

It was one of those things that the idea looked like it was really a good idea, nobody had recognized it before. It looked like something that could have a major impact in terms of drug delivery. And the first venture capitalist that I went to present to made me an offer, which was Venrock, and I was so stupid that I didn't accept it, which I should have. In fact, they made me two offers and I didn't accept either of them. And even later on they made me another offer. I should have. And I knew this. I knew that faculty members don't know what they're doing and that they need to have professionals in terms of this. They always think their ideas are much better than they really are and that they're going to make more money. And I made all those errors, even though I knew it. But it's just built into academics to think that they know better than what goes on. And so I should have accepted the offer from Venrock, which was the Rockefeller Foundation venture firm. But I didn't. But AvMax, you know, it succeeded and we did well and we functioned for a number of years. I did hire one of my post-docs, Vince Wacher, who was one of the principle scientists in AvMax. One of my faculty members, Deanna Kroetz, had a boyfriend that was in Washington. He was at the NIH and we hired him to come out here so I could be a full-service department chairman. Not only did I support their research but I actually brought their spouses out to the—[laughter]

09-00:12:26

Burnett: The spousal hire.

09-00:12:28

Benet: Yeah, Jeff Silverman was his name and he became one of the other principles. And it had a CEO and stuff like that. I was not involved in the running of it. I was the founder and a member of the board and on the scientific advisory

board. But that was trying to follow the university rules and try to separate out to make sure that you didn't run into conflicts in terms of what your graduate students or post-docs were doing. Didn't overlap with the company.

09-00:12:56
Burnett: Okay. One moment.

09-00:12:57
Benet: Okay.

09-00:12:59
Burnett: So I wanted to ask, because you're on advisory boards for industry/university relations, I'm going to find this, from 1981 to the year 2000 according to your bio here. You're on the Advisory Panel on Relationships with Industry, the Chancellor's Committee, and from 1985 to 1990 you're on the UCSF Intellectual Property Advisory Council as a member.

09-00:13:29
Benet: No, not UCSF, the UC.

09-00:13:31
Burnett: UC. UC Intellectual Property Advisory Council and going back to the 1970s you were the chair of a panel on industry/university relations. So long before you ever started a company you had been learning about the tortuous process by which academic scientists start companies, start private companies, and all the pitfalls that you can run into. You've talked a little bit about creating a barrier that protects, that isolated academic research from for-profit motives. Can you talk a little bit about the mistakes that you saw in your time? This was a learning process for everybody. Can you talk about some of the things that went wrong early on that you—how did they come to decide that these kinds of measures would be effective?

09-00:14:40
Benet: Okay. So even though I didn't do my own entrepreneur activities, as chairman of the department in 1978, this is a very entrepreneurial department. And so there were companies being started by faculty members in the department. And so I had to have a set of rules or criteria that I thought were really important. And so I established those rules not because I thought there were any mistakes within our department; I just felt that it is impossible—and I know from my own experience. Even though you think you're unbiased and you're not overlapping and you're not really looking at your data with a rose-colored glass, you do because it's your data and it's really difficult for a student or a post-doc working in an academic environment to be caught in that situation where they want to publish, they want to present their information, and they're also caught in the situation where this is funded by an outside agency and they're writing their patents and I'm not allowed to publish it, I'm not allowed to talk about it, and I've got to follow their directions. And so I just didn't want that to happen. And so I created some strong barriers in the department which were much tougher than most of the UCSF barriers. I

would not allow funding from the company to come back in our department in any manner from an entrepreneurial activity. What other faculty members were doing were saying, “Okay, well, I’m not going to be the person that gets the money but my colleague is going to be the person that gets the money and run this research,” and therefore they sort of got around these barriers by doing that.

09-00:16:22
Burnett: They’re gaming the system.

09-00:16:23
Benet: Yeah. And then this committee on industry/university relations would be faced with how do you monitor and make sure that we’re holding up to the standards that the university wants? And that was really difficult. Really. I can recall a number of situations on the committee where I just felt these guys are really—

09-00:16:45
Burnett: Pushing it?

09-00:16:46
Benet: —yeah, pushing it, and it’s not fair. It’s not fair. And I can recall a couple of my faculty members, one in particular, a very entrepreneurial faculty member, Frank Szoka, coming in and telling me he was doing something. I told him, “Frank, you have to make a choice. You either are going to be an academic and meet the rules of academics or you could go do your companies and be very successful.” In fact, all of my faculty chose to stay and be academics. We had this nice situation. The department benefited because all of the founders gave stock to the department in their companies and, of course, their patients would bring money into the department. The way they used to give patent royalties in those days was more beneficial to the department and the individual faculty member than it is today.

09-00:17:36
Burnett: Why is that?

09-00:17:37
Benet: Well, just because of the administrative responsibilities of the university in terms of the taxes that they take.

09-00:17:44
Burnett: Increasing overhead costs.

09-00:17:46
Benet: Yeah, increasing overhead, costs like that.

09-00:17:46
Burnett: Yeah. We’ve experienced that, as well, at Berkeley. I think it’s like 57 percent. So it is interesting. I was thinking about what you had said last session. Let’s see, the guidelines that were developed. One, the entrepreneur

in the department cannot get the salary from the company, cannot be a principle in the company though they can own stock in the company. And then there's larger University of California rules that consulting dollars come into the department as a whole but not to an individual researcher.

09-00:18:30
Benet: Okay, so that was a UCSF rule.

09-00:18:31
Burnett: Oh, UCSF, okay.

09-00:18:32
Benet: That was a UCSF rule and it was a really good rule and it was created while I was still a junior faculty because you had a choice of either buying into the system or not doing it. So it happened sometime in the seventies—

09-00:18:46
Burnett: In the seventies, yeah.

09-00:18:47
Benet: —that you had to make that decision. Yeah.

09-00:18:49
Burnett: Right, right. And no system is perfect but I do kind of wonder about incentives. Because I don't think the money necessarily drives people in entrepreneurship either, right?

09-00:19:05
Benet: Fame.

09-00:19:06
Burnett: That there's recognition, the challenge. Or yeah. The puzzle-solving enticement of the challenge. And so it does incentivize, right? If you bring in money to your department, not you personally but to the department, that's good for the department but it is also good for you. It's good for everybody. There's a certain kind of potlatch element to this kind of gifting of your entrepreneurship. So there are still questions, I suppose, around it. It's certainly better than someone saying, "I'm going to go out and I'm going to make money from this," and that could distort their activities as a full-time faculty member and that sounds like a good system for guarding [against that]. But it doesn't completely solve the problem of incentives, I guess.

09-00:20:04
Benet: Well, if you start the company and you have stock in the company and it does well, that's going to be more than anything you get that comes in on the royalties or any of that. So that's where you really make a lot of money. And we've had some spectacular successes at UCSF. Herb Boyer and Genentech and lots of others who have done really well. In fact, at one time I felt that if you didn't own a company you really weren't a faculty member at UCSF. [laughter]

09-00:20:37
Burnett: It was that kind of a climate.

09-00:20:39
Benet: Right, yeah.

09-00:20:40
Burnett: Right, right. Well, so Genentech, 1976 it's formed, right, I think?

09-00:20:47
Benet: Yeah.

09-00:20:49
Burnett: So that's right around this time that you're on this committee. And so do you remember anything about that, how that changed the climate?

09-00:20:56
Benet: I remember Dave Martin who became the chief scientist at Genentech and he came to UCSF at the same time I did. He was a faculty member in the Department of Biochemistry. I remember talking to him about what do you want to do, which way do you want to go? How do you want to be successful? There's lots of different ways to be successful. I think Genentech is really a perfect example because Stan Cohen, of Cohen-Boyer fame. Stan Cohen, who I see, just saw last week or two weeks ago, is the other [owner of the] Cohen-Boyer hybridoma patent, okay. But Stan Cohen takes no money from any company and takes no royalties on anything versus Herb who started Genentech. So there's a wonderful dichotomy here of someone who feels, "No, I'm an academic, full-time academic, and I don't want to be involved in any way with any companies." And there were a number of faculty members here, like I said, Keith Yamamoto, when we first started talking about entrepreneurial activities, was very much against it. But he changed. And I think UCSF did a really good job of doing this separation. Herb had to leave. Well, he had so much money it was good for him to leave anyway. But he had to leave because he was going to do these entrepreneurial activities and really be involved and generate a lot of money that direction. Yeah.

09-00:22:36
Burnett: Yeah. And it would just be infeasible. Never mind the question of barriers, it was just infeasible for him to remain in any capacity. Right. So there is this tremendous climate, already in the 1970s, prior to Bayh-Dole, right?

09-00:22:53
Benet: Right.

09-00:22:53
Burnett: And then it just explodes in the 1980s with tremendous entrepreneurial activities. And yet it's early nineties before you're thinking about this. And as you said, you didn't have a method or a product that you wanted to patent.

09-00:23:12
Benet: Right. It wasn't attractive to me. I was bringing in a lot of money through consulting. I've always brought in a huge amount of money in my consulting activities. And I think that's really important because I learned so much from my consulting. I wouldn't say that I would pay the companies to allow me to consult with them but I learned a tremendous amount. It really has an influence on how I progress as a scientist in terms of interacting with the industry and seeing things that you don't have the opportunity to see otherwise.

09-00:23:43
Burnett: It brings you questions as a researcher. Your inquiry is being shaped by the questions that they ask you and then you say, "Oh, there's a need for this and I don't have an answer for them," is your reaction and then, "I need to go find out." That spurs your next research project. Was it ever dizzying for you? Did you have a long laundry list of problems that you wanted to solve that you then had to do triage and figure out which ones to solve first?

09-00:24:19
Benet: Well, I'm an unusual academic because I don't focus. [laughter] What people say is if you're going to be successful in academia you have to focus. And I've never believed in that. I believed in doing anything that I thought was interesting. And so my graduate students all have different projects. They're not all doing anything closely—it can be completely different. And it's exciting to me. And I can study different things and I've created an environment where I can bring in the money and allow me to study anything I want. But I was thinking about that in those days. That's the environment I want to create and that's what I want to do in terms of being able to go in these directions.

09-00:25:06
Burnett: The Benet program is to have no program. No, no, I mean to allow things to flower, right?

09-00:25:13
Benet: Right, yeah.

09-00:25:14
Burnett: Yeah, yeah, yeah. To grow. And there's an explosion of your research that we've already talked about in the 1980s and into the 1990s. And so let's return now to the early nineties and the climate for the development of the method patent, which you've described a little bit already in a previous session. And so you already knew a lot about patenting?

09-00:25:47
Benet: Oh, yeah. It's something I paid a lot of attention to. Well, I've been on the patent board of the university and I was on the university industry-relations and you learn a lot about patents. It was interesting. It was interesting to know how to do stuff and how you generate certain things. For example, when I

started my company I didn't want the university lawyers to write the patent because I didn't think they were of the quality of what I wanted. And so I sort of went against the rules. But the university was fine because they had the patents. Yeah, yeah. But I said, "No, I'm not going to have the university attorneys write the patents. I'm going to have a really first-class firm write the patents," because, to tell you the truth, being on the patent board, I knew the university attorneys, the patent attorneys, weren't at the same level as some of these really fine corporate attorneys and patent attorneys that we have in the Bay Area. So I went to Wilson Sonsini and had them write my patents.

09-00:26:56
Burnett: You could imagine that they could be better but what kind of experience did you have with the private firms prior to that that would lead you to believe—advice that you'd had?

09-00:27:06
Benet: No, I think more just from interacting with our own patent office and the patent guys here. Because if they were really good they got recruited away. [laughter]

09-00:27:18
Burnett: Yeah, there's that, I suppose. Yeah, yeah. And so you found this good company and they went through it. Did you work with them on the process?

09-00:27:29
Benet: Oh, yeah. Oh, yeah. Definitely.

09-00:27:29
Burnett: And they would send you drafts and you would—

09-00:27:31
Benet: Oh, definitely. You'd go back and forth all the time in terms of that. And you originally write your idea on the disclosure form to the university. But at the same time I wrote that I was saying, "Okay, here, you guys, you look at this, too," my outside attorneys, which I was paying in those days. I didn't have a company to pay it. I wanted outside people to look at it and tell me what they thought. And I had the advantage, Paul, I also do a lot of expert-witness consulting. Yeah. So I do a lot of expert witness stuff and a lot of that's on patents. And so that again gives me a lot of training. Now, back in those days I probably didn't have the kind of expertise I have now. Today I really could look at a patent instantly and know whether I'm going to support it or not support it and whether it's an invention or something that I can feel comfortable with. And I get a lot of requests. I think I charge the most of anybody at UCSF and yet I have all kinds of offers all the time. And I turn them down because if I can't agree that I can support this patent then I'm not going to be their expert. I've got to agree that your position is my position. Now, every expert should do that but most don't. I have I guess the good fortune to be able to do that. I've gone to trial nine times and only lost once. So that's a pretty good record.

09-00:29:04
Burnett: Yeah. Because you knew exactly what you were doing in terms of the science and in terms of the legal aspects, as well.

09-00:29:12
Benet: Right, yeah. And I have a big case coming in January in Boston that I've been working on all through the expert reports and the depositions and stuff. Now I'm going to trial. And stuff like that. So I've done a lot of that.

09-00:29:29
Burnett: And a fascinating world, too. And I want to ask you about that in the next session, about the differences, or the tensions, perhaps, between scientific truth and legal truth.

09-00:29:43
Benet: [laughter] Oh. That's interesting. Let me say one thing right now.

09-00:29:46
Burnett: Sure, sure, right.

09-00:29:48
Benet: People say, "How can you charge so much?" I said, "Well, I charge so much because if you want me you've got to pay a lot of money. And if you're not going to pay a lot of money and you don't want me then that's fine." I'm not going to be insulted in the least bit because I've got to believe that you've got the right story and that it goes the right way." I've made people a lot of money and a lot of cases have been settled. I've probably done eighty to ninety depositions.

09-00:30:26
Burnett: Wow.

09-00:30:27
Benet: Somewhere in that range.

09-00:30:31
Burnett: Yeah. As you said, it's an opportunity cost for you. Every minute you spend working on legal matters is a moment you could be spending working on science.

09-00:30:41
Benet: Right. Doing something else. Right, yeah. Okay. And the other reason I charge so much is that otherwise I'd be overwhelmed. I can't do all the stuff I get asked to do. And I actually love it. I love doing litigation. It's a battle of wits. But it gets you nothing, nothing except sort of like doing Sudoku. You have the ability that you've solved it or you've won it but at the end you don't get anything from it as opposed to doing research where you get something from it. You publish a paper or you make an advance and something like that. In a legal case you don't get anything. It's just the fun of doing it. And most people hate it but I happen to like it.

09-00:31:29
Burnett: Well, these are, as you said, cases that you have almost like a—not a personal interest in but they're aligned with your scientific opinion of what's true.

09-00:31:41
Benet: Right, right.

09-00:31:42
Burnett: Right. So you're not a hired gun.

09-00:31:46
Benet: Right. Well, people will call me and say, "Here's the case, what it is." I said, "No, you've got the wrong guy. I'm on the other side of this. But I can tell you who believes in your position and this is the person that you should go talk to." [laughter]

09-00:32:01
Burnett: Great.

09-00:32:02
Benet: "No, that goes against what I believe in."

09-00:32:04
Burnett: So there's scientific expertise, there's management expertise in running a department. There's this legal expertise that you've cultivated over a long time and a familiarity with the administration of a university and a university system. So this is the armature that you have going into the entrepreneurial world. So you are already well-positioned and in a sense come from a long line of entrepreneurs, as well, because in your family, there's Dara Pharmaceuticals. You grew up with that. So it was not something foreign to you.

09-00:32:52
Benet: Right, right.

09-00:32:53
Burnett: And I think that that might be a factor. I don't know how Stanley Cohen feels about the entrepreneurial side but it's something that you grew up with and maybe that was part of it, as well. So early 1990s you're ready to go, in a sense. I suppose in a sense it emerged from the science that you were doing. Is that the right characterization?

09-00:33:20
Benet: Right. Because the kind of science I did doesn't lead to inventions most of the time. The science I did was to sort of explain things. And that doesn't necessarily lead to inventions. You're just explaining something that is already there and that's no patent whatsoever. It doesn't make any difference if nobody knew the reason. It was already there. You didn't discover it. But I sort of discovered, when we discovered the transporter enzymes in the intestine and how important they could be, that was not something that people

recognized. And they didn't think it was important and so that's why it's an invention. It becomes an invention, yeah.

09-00:33:56
Burnett: Well, there's the discovery of it and then there's the development of the method patent. Can you talk a little bit about method patents and how it occurred to you to patent this insight?

09-00:34:14
Benet: Okay. So yeah. Okay. So there's three kinds of patents. The strongest is composition of matter, where you're actually making a new molecule or drug and something like that and it's really the strongest because there's nothing there beforehand. A method patent says: "I take a whole bunch of information that's out there, that everybody knows, but they don't know how to put it together. And here's a unique way to put it together. And if you do this then you can create this situation." So they're not as strong. From a patent's perspective they're not as strong as a composition of matter but they're stronger than the next set of patents, which is a formulation patent. So we actually wrote method and formulation patents. But formulation patents are relatively easy to get around because you just sort of change some of the formulation. You sort of can't cover everything. A method patent says you're going to do this to accomplish this. And it's not something you can get around. You can argue –and this is why they're weak – you can argue that, "Well, this is obvious. Everybody knew this. It was obvious and you put this thing together. You just happened to be the first person to do it but it's obvious." And that's how those patents get challenged.

09-00:35:32
Burnett: And that's a key part of the original patent system in the United States. Has to be novel, non-obvious, right? Is that the phrase used?

09-00:35:38
Benet: Yeah, that's right. Yeah, yeah.

09-00:35:39
Burnett: And what's the third thing? Anyway—

09-00:35:41
Benet: Yeah. I can't think of the right words.

09-00:35:50
Burnett: Non-obvious.

09-00:35:50
Benet: No, you have to be able to bring it to practice.

09-00:35:53
Burnett: Oh, right. Right.

09-00:35:56
Benet: There's a set of words that are the right thing that you have to do.

09-00:36:00
Burnett: We'll consult.

09-00:36:00
Benet: So it's not just that you discovered it; it's that you actually made it happen. Yeah, yeah.

09-00:36:05
Burnett: Right. Proof. You have to prove the concept effectively. So the method patent wasn't as strong or robust in terms that other people could work around it or game it. But you decided that you wanted this to be recognized in a legal sense. Were you concerned, if you did not do it, that other people would patent it?

09-00:36:41
Benet: Well, it was pretty obvious from the literature that I had discovered it, that I was the first person to recognize that it was happening. Okay. So I wasn't worried about that. You can find other papers that sort of say, "Well, you might do this," or something, do this. There were papers like that, yeah.

09-00:37:00
Burnett: And so it led you to establish this patent. And it was accepted. Were you a kind of witness on your own behalf in a sense?

09-00:37:11
Benet: You always get turned down by the Patent Office but we were able to answer all the questions and we got the patent from Europe going through Munich and through the European patent office and we got them here. And they pretty much did okay. I think one time I had to defend against something. It was one of those weird things that happened in Europe. I didn't know actually what I was defending it against but I had to make an appearance in a court in Munich in terms—

09-00:37:47
Burnett: They weren't required to disclose?

09-00:37:50
Benet: Well, it was some kind of weird thing. I didn't know what it was. I was being asked questions about it, answering questions, but I didn't know why, what the challenge was.

09-00:38:00
Burnett: It's like the Kafka division of the European—?

09-00:38:03
Benet: Right. And we had patent attorneys in London. This was after AvMax was already formed. We had patent attorneys in London and in Germany who were writing the response to this stuff. And we ended up winning it but we

don’t actually know what we won. The board said, “Yeah, it’s valid.” Somebody challenged that it wasn’t valid, that the patents weren’t valid. But we didn’t know actually who had challenged it. It was some weird way that this situation worked.

09-00:38:36
Burnett: You didn’t have the right to face your accuser?

09-00:38:38
Benet: No, we didn’t face our accuser.

09-00:38:39
Burnett: That’s fascinating. And your remark, “patents are always turned down?”

09-00:38:45
Benet: Oh, yeah. Well, the guy who reads it says, “Oh, this is obvious and here’s the citations in the literature that I look at and figure that people said this is before and you aren’t the first person to say this.” The guys who work for the patent agencies aren’t the best because when they get really good then they go someplace else and they get hired away from the Patent Office and stuff like that. So sometimes they don’t understand it. The patent reviewers don’t understand what you’re actually doing. They think you’re doing something else. Our guy in the US thought this patent was completely useless. He told us that he thought it was completely useless. All we could patent was what was happening in the gut. Everybody knew that these things happened in the liver. What we discovered was that they happened in the gut and it was really important for compounds like cyclosporine. The reviewer, he said, “I’ll give you this,” he says, “but I don’t really think this is useful at all.”

09-00:39:53
Burnett: The knowledge was so new that there was nothing to really compare it against.

09-00:39:57
Benet: Right. Right. I guess so. Yeah.

09-00:40:00
Burnett: Yeah. Yeah. That’s interesting.

09-00:40:02
Benet: That was you or me?

09-00:40:06
Burnett: So you have a patent out as part of AvMax or you’d founded—

09-00:40:10
Benet: Yeah. There are three patents that get licensed to AvMax by the university.

09-00:40:17
Burnett: So that’s this glycoprotein transport in the gut. That’s the method patent.

09-00:40:21
Benet: Well, they're all sort of the same. All these patents have the same basic structure to them. It's only the claims that are different.

09-00:40:29
Burnett: Okay. So the benzoin gum to inhibit P-glyco—

09-00:40:32
Benet: Oh, no, no, that's different. That comes out of AvMax. Yeah, yeah, yeah.

09-00:40:37
Burnett: Okay. All right. But the two patents on the use of essential oils to increase bioavailability?

09-00:40:43
Benet: Right. Those are the original patents. Yeah.

09-00:40:45
Burnett: Essential oils.

09-00:40:46
Benet: Yeah. Well, in other words, what we discovered is if you didn't know this thing was happening then you didn't know that this was a potential— So what we found were that things like peppermint oil, or stuff like that, could inhibit these transporters or inhibit these enzymes. And nobody had ever thought—they just thought they were sweeteners or flavors or something like that. But we now said, "Well, this thing is going on and we ought to go look at all these substances and see if they're affecting it." And so we patented all these basically GRAS substances, generally recognized-as-safe substances, that people thought were just inherently—

09-00:41:27
Burnett: Inert.

09-00:41:27
Benet: —yeah, inert, yeah.

09-00:41:29
Burnett: Yeah, yeah. That's fascinating. It's almost ayurvedic. It goes back to ancient medicine, that there are small dietary elements that produce balance or imbalance in the body. In a sense you've done a very, very, very precise version of that, right? It's like this oil does this very specific thing in the gut. So that comes out of AvMax. So when is AvMax founded?

09-00:41:58
Benet: Oh. The patents are '94. They're awarded in '94 so they're submitted a few years before that. So AvMax must have been founded in the late eighties, early nineties, and I just don't remember.

09-00:42:13
Burnett: So it says that the transport of the gut glycoprotein patent was issued October ’96.

09-00:42:19
Benet: Ninety-six, okay.

09-00:42:21
Burnett: And then the two patents on use of essential oils to increase bioavailability are ’97 and ’98 respectively.

09-00:42:26
Benet: Okay, maybe.

09-00:42:27
Burnett: So perhaps early nineties, ’93, ’94.

09-00:42:30
Benet: Yeah, early.

09-00:42:33
Burnett: So AvMax is a small company with a few of the folks?

09-00:42:40
Benet: Has about fifteen employees.

09-00:42:41
Burnett: Has about fifteen employees.

09-00:42:44
Benet: Yeah. And it has offices down in South San Francisco and labs in South San Francisco. Yeah.

09-00:42:51
Burnett: And in your *Forbes* magazine description, there’s a little bio, in *Forbes* magazine it says you have founded or co-founded four start-up companies. So AvMax is the first. And is Hurel the next one that you developed?

09-00:43:14
Benet: No, Hurel’s the last. Well, not the last. The next one is actually AvLan, that Elan and AvMax have a joint venture. Elan Pharmaceuticals. And we form a company based in Bermuda that is a joint venture to do formulation and bring things forward. And the third company’s called OxoN Medica. And that’s completely different. I did a lot of work on nitrates, understanding the mechanism of nitrates and OxoN Medica was that you could make nitrates that didn’t create tolerance. Okay. So one of the problems with nitrates is as you continue dosing them, you have tolerance. But I had a whole series of research studies on nitroglycerin and nitrates and cardiovascular areas and stuff and that led to a series of patents. And so that’s OxoN Medica. Then actually there was a company called Limerick BioPharma, okay, with Wendye Robbins, and that was to—

09-00:44:23
Burnett: At Stanford.

09-00:44:24
Benet: —actually activate trans—it started off to activate transporters in the brain to get around toxicity issues with opioids and stuff like that. But then it moved into completely different areas. So there's really five now. AvLan maybe I shouldn't count because it came out of AvMax and stuff. But Hurel would be the fourth. Yeah, yeah.

09-00:44:49
Burnett: So Limerick BioPharma is developing transporter activators. This is 2000s, though. This is much later. Transporter activators. The idea is that you keep drugs out of certain tissues to protect them, those that are not the target. So you sort of focus. So it's kind of—

09-00:45:09
Benet: Right, to get rid of side effects. And I get a call one day from an anesthesiologist at Stanford named Wendye Robbins and she calls me up and says, "Dr. Benet, I've read your papers and I'd like to come and talk to you." And I said, "Anybody that read my papers I'd be happy to talk to." So she comes up here and said, "I read your papers and I got this idea that I could activate transporters in the brain and you have actually published some stuff that would activate transporters." They weren't drugs but they could activate. "And I gave them to patients that were having toxicity from opioids and they had less toxicity." And so she said, "It looks to me like this thing could potentially work. Are you interested in starting a company with me?" I said, "Yeah, sure, it sounds like a good idea that you got from my paper." I said, "Yeah, I'll start a company with you." But it moved in a completely different direction and then it ran out of money.

09-00:46:09
Burnett: Oh, okay. So it's no longer operating?

09-00:46:10
Benet: It was venture funded and it stopped about two years ago or three years ago. And OxoN Medica also was venture funded. The OxoN Medica patents actually went through the Hebrew University because it was a post-doc, Abdullah Haj-Yehia, who worked with me and we did those patents through Hebrew University. He was a faculty member at Hebrew University that came and worked here. Yeah.

09-00:46:39
Burnett: You've written about him as a remarkable figure. He was an accomplished scientist. So AvMax and then AvLan with Elan Pharmaceuticals—

09-00:46:56
Benet: Pharmaceuticals, right.

09-00:46:57
Burnett: —which is a—and they're generics, are they?

09-00:46:59
Benet: No, no.

09-00:56:49
Burnett: No?

09-00:47:00
Benet: They're Alzheimer drugs and stuff like that now but they were doing everything at that time.

09-00:47:07
Burnett: Okay. And OxoN Medica for nitrates, Limerick that was going to be transporter activators. Has that been taken up by anyone else?

09-00:47:17
Benet: No, no. Because actually we ran some clinical studies in Australia and actually sort of had positive results but had trouble getting funding and got some other ideas and it moved in a different direction and then that didn't work. But that's what happens with start-ups.

09-00:47:34
Burnett: Right, right. That's the kind of definition.

09-00:47:35
Benet: That's what happens with start-ups, yeah.

09-00:47:36
Burnett: Yeah, you take a chance and that's why you have venture capital to support these things. And then there's one more. There's Impax. Or did you not found that?

09-00:47:46
Benet: Oh. No, I didn't found Impax. I'm just on the board of Impax. I'm on the board of directors of Impax since 2000. Yeah.

09-00:47:54
Burnett: They make controlled-release versions of central-nervous-system drugs.

09-00:47:59
Benet: Right. Yeah, yeah.

09-00:48:00
Burnett: Right. And so that your expertise is—

09-00:48:06
Benet: Well, it's actually a wonderful experience. Most academics do not get the chance to be on the corporate board of a listed company. And it is an amazing experience in terms of what you learn and all the kinds of things that you do. Deans and people like that occasionally will be on boards but very few

academics get this opportunity. But I actually knew some guys who were starting these companies and they thought I could help them so they asked me to be on the board in terms of delivery. And then I was able to bring Suneel Gupta, who had worked at ALZA.

09-00:48:50
Burnett: Right. He did the high-fat stuff, right?

09-00:48:52
Benet: Yeah, he did the high-fat stuff with me, right. But he's developed Concerta, he developed Ambien. So he developed a lot of these new formulations for ALZA and then when Roche bought ALZA and closed it down, he had a choice of either going to New Jersey or finding a new job and I said, "Well, why don't you come and work for Impax and be the chief scientist at Impax." And so he's done that and he's developed some really good stuff at Impax.

09-00:49:19
Burnett: Yeah, I bet. I didn't know that he was behind Ambien.

09-00:49:22
Benet: Yeah. Not Ambien. Not Ambien. But another one, really blockbuster. He did Concerta, which is the methylphenidate for children, hyperactivity children, things like that.

09-00:49:41
Burnett: Okay. Attention deficit disorder.

09-00:49:43
Benet: Different formula. Attention deficit and the different formulation. And he did some really spectacular stuff and he's done some really good stuff for Impax. So the guy who was one of the founders of Impax, Charlie Hsiao, I knew him when he was a graduate student and I knew his wife when she was a graduate student at University of Illinois because they worked for a guy who sort of followed me here at UCSF and I went there and knew them. And then the other founder was Larry Hsu and he had been a graduate student at Michigan and I was good friends with them. And we were on another board of another company that went broke, Charlie and I, and so Charlie said, "Well, why don't you come on the board. There's a board seat opening at Impax." It was just started. It was a combination of two different formulation companies coming together. "Would you like to join?" I said, "Yeah, that would be really interesting." It's been a really exciting experience.

09-00:50:45
Burnett: Well, that's high praise from someone who works in these other exciting domains, right, court cases and developing new ways of understanding the body.

09-00:50:59
Benet: But all of that's good for Impax. The court cases. These companies have all kinds of court cases, so this is really good for me, too, because I have a lot of

expertise and so I can ask the corporate attorneys and I know exactly what's going on there.

09-00:51:13
Burnett: So what in particular is so exciting?

09-00:51:20
Benet: Well, it's a completely different world. It's a world of business. Though it's a world of science, it's the world of business taking advantage of science. Okay. And the reason scientists aren't on the boards of these companies are because they're scientists and they look at the scientific aspect of it. That could have nothing to do with success or lack of success. The business guys are unique in themselves in terms of what they do. I'm sort of a crossover guy. So I do lots of different stuff. I've learned a lot. I've learned a lot about finance and how things work and all kinds of regulations with the government. And I have all these good FDA contacts, so I sort of understand some of the FDA aspects that the drug companies have to face. And from that perspective I think I do a good job on this board.

09-00:52:15
Burnett: In the histories of famous accomplished scientists, like Charles Darwin, for example, one of the important things to remember about them is that they were accomplished scientists and incredible geniuses, but what was really important is that they were at the center of these massive networks. They knew everybody and they could bring people together and they could bring ideas together. And maybe that's a little bit of what's exciting for you, is that you're crossing from one domain to the next but you can help connect people who would otherwise maybe not run into each other as quickly. And that's maybe part of the excitement, is that you're kind of a knowledge broker. You're bringing different bits of knowledge together in new ways that allow people to realize things.

09-00:53:07
Benet: But most boards are corporate people and finance people. But my board appreciates me because I bring some unique aspects. I know some things that they don't know. [laughter]

09-00:53:20
Burnett: Right, right, right. Their vista is limited in different ways—it's so time-sensitive for them, right, because they need to move things along in a certain way at a certain pace and you can give them advice that can be helpful one way or the other about that.

09-00:53:39
Benet: But one of the real advantages of being on the Impax board is I generate funds to run my lab.

09-00:53:44
Burnett: You're consulting, right.

09-00:53:46
Benet: I take that money and bring it back into the lab, and not only just what I get for the yearly fees, but I bring my stock back and bring it into the lab. So it gives me this unique opportunity that I can fund anything I want to do. Yeah, yeah.

09-00:54:08
Burnett: And so this is what explains kind of the growth of the research projects that surround you. It's where most of your income comes from given that the NIH begins to dry up a little bit?

09-00:54:23
Benet: Well, it is drying up but it's also focused. You're focused in an area that you know you're going to succeed at and you know where you're going and you're not really at the beginning of the project. It's something that's moving along and the NIH money doesn't really fund very early innovative things, people to use their NIH money to do very early innovative things. But usually their grants aren't written like that. Their grants are to solve a recognized problem that I can do the solution, and I can tell you the experiments I'm going to run, and at the end I'll know the answer. And actually innovation doesn't work like that at all. Innovation works, "I don't have a clue, but boy, here's something that I don't understand, and I want to understand it and I'm going to run a whole bunch of things to figure it out."

09-00:55:18
Burnett: So the story in the science-studies analysis of the commercialization of science is that the privatization of aspects of research has narrowed the domain of inquiry for science, right, in all kinds of ways. We could talk about it forever. But what you're saying seems to be the exact opposite. A case can be made for the funding strictures on the NIH beginning to bite and forcing the NIH to produce measurable outcomes. So they're becoming more like a corporation, right? Produce this outcome or tell us what the outcome is and we'll hold you to that. But here you are, you're doing all this consulting for private companies. You're not benefitting personally but you're bringing this money into the lab. And then, as you said, you get to do whatever you want with it because you've already been paid.

09-00:56:16
Benet: Right. Yeah.

09-00:56:18
Burnett: And so are you then saying that the commercialization of scientific research as you've experienced it has resulted in corporations being the sponsor of basic research to some extent, more so perhaps than the NIH?

09-00:56:42
Benet: But not me. No, no. Actually, I'm very unique, Paul, and I like being that aspect. You have to cultivate this environment, that you're able to create what I've created over the years. Industry does sponsor a lot of work in universities

but, again, it's focused. It's focused to answer a specific question or sometimes it is to do blue-sky stuff. But they know they're doing blue-sky stuff and this is where the blue-sky is going to go. But I'm not doing that at all. I'm saying you don't have any rights to any of these ideas. I've got the money and I'm going to do what I want to do. And so I'm in a really unique position in terms of being able to do that. And I love it. [laughter]

09-00:57:35
Burnett: [laughter] Well, one of the people I spoke to whom you've mentored, or continue to mentor, talked about the period before you entered your entrepreneurial phase and during this growth in your entrepreneurial phase and they said that you just lit up. You were always excited by the science but—and I asked, "Well, why? What do you mean by lit up?" And he said, "Well, it's fun for him. It's really fun." And teaching is also fun and mentoring is fun and doing scientific research is fun. But, according to this person, there is an element of play to it. Do you agree with that? Is that something—

09-00:58:30
Benet: Oh, for sure. That's why when people say, "Why don't you retire?" I say, "Too much fun." I don't want to retire. I'm having too much fun.

09-00:58:36
Burnett: As with the consulting, you can take it or leave it. If you don't buy into it, if you're not interested in it, and it doesn't motivate you, then you're not going to do it. You don't have to do it. So you have that freedom to choose your projects that you're interested in. So your message is that we should be careful about generalizing from the Benet model.

09-00:59:00
Benet: It's hard to create. I've been very fortunate. It's really hard to create. But I've thought about doing this for years. This is the situation I want to be in and I knew when I got older it's going to be harder to structure and continue your NIH grants. Because I've seen lots of guys. They have their pathway they go down, but science has moved beyond them. It's moved someplace else and they don't have the opportunity to move someplace else because their grants are in this pathway and this is where their expertise is and they keep moving in that pathway. And maybe they discover some new things but they don't make jumps because they're moving down that pathway. And eventually their funding stops because they're no longer at the cutting edge. What they've done is no longer at the cutting edge. And so it was very obvious to me that this is what happens to the people that have to retire, scientists that have to retire. And if you're not going to retire you can't be following that model. You followed that model when you're young, and I did. My grants were in this way, this way, this way—

09-01:00:08
Burnett: The pathway. Right.

09-01:00:10
Benet: —although they were different. But you can't continue to follow that model. You can't continue to function by that model. You've got to be doing stuff that moves you in different directions. Yeah.

[Audio File 10]

10-00:00:08
Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Technology, and Medicine series. This is session five, tape ten, and it's December 9, 2014. We just finished talking about what's unique about what you developed at UCSF in terms of financing your curiosity and enabling and facilitating graduate students and post-docs to go in unique directions. And so I was talking about science in general and the accusations that science has become commercialized or corrupted, perhaps, and I wanted to suggest that perhaps you have found something that deploys private funds in a way that facilitates basic scientific research. And you were nervous about that because you felt that this was something that's fairly unique. If you were forced to operationalize it, if you had to give advice to—let's say there's a new National Science Foundation that is going to fund research, and it could be any blend of corporate, foundation, state funding, what would be a kind of Benet model that could work?

10-00:01:44
Benet: Well, I had the advantage of being a faculty member at the time that could get a center grant. Center grants in my mind really created new opportunities. And we've discussed this in the past.

10-00:02:01
Burnett: Yeah, that's right.

10-00:02:02
Benet: The NIH decided not to do that. They did R01s. Individual research for individual faculty members, stuff like that. But I thought that a center grant, with the right kind of leadership, really created new aspects and new vistas, that allowed people to go into with a relatively small amount of money.

10-00:02:26
Burnett: But stable money, right?

10-00:02:27
Benet: But stable money, right, yeah.

10-00:02:29
Burnett: Right. That's the key.

10-00:02:30
Benet: But the decision was not being made by a review committee. The center grant was funded by a review committee but that small pot of money that the individual like me had could really take some wonderful new ideas and move

it forward without having to say, “I know exactly the experiments I’m going to run.” No, this is innovative. Try to do this. Now, the model that works really well is DARPA. DARPA in—

10-00:03:03
Burnett: The Defense Advanced Research Projects Agency.

10-00:03:04
Benet: Yeah, in the Department of Defense. And I’ve done a lot of work on bio-warfare agents and interacted with them a lot.

10-00:03:12
Burnett: You have? [laughter]

10-00:03:14
Benet: Yeah. No, I’ve headed all these committees at IOM on countermeasures to bio-warfare agents and stuff like that. So I interacted with DARPA a lot. I love the DARPA model but you’ve got to be tolerant to put up with DARPA because they’re doing all kinds of really crazy things. But I thought that was a really nice model in terms of being able to take young faculty members and give them a start and not have it be something that was so constrictive in terms of how they moved forward. And it was a real mentorship model. This was my responsibility to mentor these young people and to bring them forward in terms of their research and my other senior people on the grant did that, too. So I’d really like to see that return. And that would allow interactions with industry and bringing into these new projects. And I like the SBIR model. I continue to get SBIR grants.

10-00:04:17
Burnett: Can you talk about SBIR? What’s special about it?

10-00:04:19
Benet: Okay. That’s Small Business Industrial—I can’t remember what it—

10-00:04:26
Burnett: [ed. note: Small Business Innovation Research, funded by the 11 largest US federal research agencies]

10-00:04:28
Benet: Something like that. So I worked with small companies and I’m chairman of the Scientific Advisory Board and others and we write SBIR grants to fund the innovation in terms of these companies, in terms of translating into new science, that is, funding people that are able to go out there and work and make a lot of money and create new science. So I do that, too. So basically my NIH money today comes from SBIR grants and grants where people have asked me to be part of this to help them in terms of a group project and things like that. And I’ve sort of stopped writing individual grants.

10-00:05:15
Burnett: And so in the design of institutions, I think we often pay attention to kind of the structure. But what you're talking about seems to be so much more about the human aspect. Like what drives people to do innovative things and what drives people to do excellent things? It's not easy to quantify or structure or institutionalize because you're talking about institutionalizing a human relationship. And that's something that comes up over and over and over again in the background interviews when I talk to people who have worked with you over the years. I think I asked a generic question about what is Dr. Benet like to work with or something like that. And several people said exactly the same thing. "Well, you've met him," is the answer that comes back. And I know what they mean, right, and so I know that they're talking about your dynamism and your concern for others. So if you go back on these tapes you will be able to see that when you talk about your students work you're more excited than when you talk about your own work.

10-00:06:50
Benet: Well, I don't do any of my own work. [laughter]

10-00:06:52
Burnett: Okay, fair enough. That's right. [laughter]

10-00:06:55
Benet: I might have said this on the tape before. But when people say to me, "What's so good about UCSF?" I said, "Well, the great thing about UCSF is the students and post-docs that you get are so wonderful that you don't have to know anything as a faculty member. You just have these people here and you say, 'Go ahead, do something, make me famous,'" and they do.

10-00:07:12
Burnett: Right, right, right. Right. But, again, you're a knowledge broker. You're bringing people together to work on things. If somebody needs, "I need this kind of person," you know who to talk to to get them together. And that's hard to institutionalize, I imagine. So if you're talking about the Benet model, you're talking about replicating something unique about what you do. But you've pointed to those elements. [phone call] The students that you've mentored. There's a theme of the generosity of your mentorship and these are longstanding relationships that last from the time that they're first a student until now. And so you can go in whichever direction you like. You have worked on patents with a number of students. You're on the boards of some of your students' companies. So can you talk about some of the mentoring that you have done with respect to some of your students?

10-00:08:34
Benet: Gosh, okay. So Victoria Hale would be one of the ones. I'm chairman of the board of her company, Medicines360, which is a nonprofit drug company funded by an anonymous donor initially for about $86 million to make sure that there would never be any women in the US that could not afford birth control processes. Yeah.

10-00:09:04
Burnett: Right, right. And she spoke about your mentorship and that it was powerful because you never told her what to do. She would ask you advice and you would say, “Well, here’s the likely outcome if you do this and here’s a possible outcome if you do that.” And you’d be so respectful of her goals and you would try to just give her the best advice that you could give.

10-00:09:40
Benet: That’s interesting. I’m not sure I think that that’s true. [laughter] Because I do tell people what I think they should do. [laughter]

10-00:09:49
Burnett: But there’s not an overbearing sense that they need to follow—yeah, yeah.

10-00:09:53
Benet: No. Okay. So here’s one of the things that I always tell my new students that work with me and the post-docs. I said, “You are living your life, not mine. You have to make your decisions to what you want to do. I’m not going to be upset with you no matter what you do. You’ll go this direction or you’ll go that direction. This is what I’d do. I don’t expect you to do what I do. But you can see how much I enjoy what I do.” Right. “But you’re not going to disappoint me by what you decide to do and where you go because you have to be happy in what you do.”

10-00:10:32
Burnett: And Dr. Hale, just as an example, did not continue in academia. That’s right, right?

10-00:10:38
Benet: Yeah.

10-00:10:39
Burnett: And I think she was at a kind of crossroads and she went in a different direction. Worked at the FDA and then started this company, about which she’s very passionate. There’s a moral and political orientation to her passion that is very important to her. And you’ve supported her in that. Are there other instances of mentoring that you could talk about that are—

10-00:11:16
Benet: Well, I can think of a good example, of a student named Rae Yuan. Rae is Chinese. She came to work for me at a time when Roche had these—they selected two fellows a year that they would support sort of lifetime science and stuff like that. And she was one of those selected and she didn’t do that and she came to work for me. And she has become very successful. She does work for Roche. But she had to make some decisions. She went back to China and she tried to make some decisions. She was first offered to be head of clinical in China, to be Roche’s head of clinical. And I told her to take it, but she didn’t. But then she became head of the whole thing in China and then she did that for a while and then she lost interest in that and she went to work for the biggest antibody company in China. And I told her, “If you’re going to do

this, you've got to be careful and here's what kinds of things you should demand and stuff like that." And she didn't follow any of my directions in terms of what she should do and it turned out that I was right and she left that company after about a year and a half because interacting with the guy who was taking advantage of her and things like that. And now she's sort of a venture-capital person in China. But I tell them, "This is a lifelong relationship. Anytime you want advice and stuff, I'm going to be there." Sometimes they follow my advice and sometimes they don't. It's very interesting to hear that some of them think I don't give them advice, that I give them the choices. [laughter]

10-00:13:13
Burnett: That is advice. That is advice to say, "This is what I think are the likely outcomes if you do this. And these are the likely outcomes if you do that." That is advice and that's shaping but it's not a sense of don't do this, it's a mistake necessarily. But you are direct, right? So that's something that other people have talked about. Is that you are direct. [laughter]

10-00:13:46
Benet: Well, I have no one to fear, Paul. I have no one to fear. I'm an academic. A very good colleague of mine, very successful at GSK just lost his job because GSK decided to close down their entire research in North Carolina. And this guy was top of his field, doing really well, but now he doesn't have a job or he's soon not going to have a job. And I made that decision a long time ago, I was never going to let myself get into that kind of a situation. Being an academic, theoretically you don't make a lot of money but you can make a lot of money. But you get yourself into a situation that I have nobody to fear. Nobody can really take advantage or hurt me.

10-00:14:32
Burnett: Right, right. So there's tremendous freedom in that.

10-00:14:34
Benet: Right, yeah.

10-00:14:36
Burnett: But also the motivations are different. What you seem to be interested in is cultivation. Cultivation of the science, cultivation of the people who do the science. And that requires being stable yourself, right? You have to be a kind of anchor for this other stuff to get torque around you. Then you've got some real action happening. And so that's an interesting feature of your identity. You see yourself as the rock for these other folks who then go on to do great things around you, as well. So I guess we're circling around the cultural—

10-00:15:36
Benet: Let's come back to this.

10-00:15:37
Burnett: Okay, sure.

10-00:15:38
Benet: But I'm in a backwater.

10-00:15:41
Burnett: Really?

10-00:15:41
Benet: I am.

10-00:15:42
Burnett: In what sense?

10-00:15:43
Benet: In science. The pharmaceutical sciences are not where people look and say, "These are the guys getting the Nobel prizes." Or even members of the academy, okay. But what I've been trying to do is to change that environment. But I recognize that I'm not at the cutting edge of where science is going. But I've tried to go around it, and I *will* be there. [laughter] If you really want to make a big impact today you're probably going to be in stem cells or—

10-00:16:20
Burnett: Yeah, genetics. Regenerative medicine.

10-00:16:21
Benet: But I guess my goal has been to change that in terms of making pharmaceutical sciences a well-recognized discipline and I needed to get it away from pharmacy as a profession and that's why we created AAPS. But continually to do work that does have this impact and to try to be the first person that is recognized for doing so. Because you are in that backwater, you've got to be self-sufficient so that you can go in new directions without getting other people to agree. I've been in the Institute of Medicine now for twenty-five years, twenty-seven years. And when I got in it was really hard for a pharmacist or a pharmaceutical scientist to get into the Institute of Medicine. Not so hard anymore. But you try to break those barriers and to realize that you're not really what people consider the first-rate fields that are moving forward at this present time. And I think that's a good picture of what's happening at UCSF. What we've done at UCSF is to really make the School of Pharmacy and the pharmaceutical sciences, really—people view us completely different than they would have twenty-five years ago. I think they now think we are first-rate and making groundbreaking discoveries, whereas previously people would just say, "Okay, well, those guys are doing formulations."

10-00:18:19
Burnett: I want to perhaps suggest an alternative to "backwater" because I suppose the cutting edge of research looks at the body, the functioning of the body by itself: genetics and gene regulatory networks in cells, replication of cells. That's been hot for so long. And your body of work surrounds what happens to these introduced substances to the body. So it concerns a particular set of events, of these 1,000 drugs that can be put into a human body and what

happens to the drug and what happens to the body. So it's considered to be applied knowledge, I suppose, but what you're doing is bringing in the latest research on the nature of the activities of the cell, the transporters, the enzymes. There's a lot of sophisticated biology that goes into the work that you're doing. So it's been, not a backwater, but it's been considered to be an adjunct of the pharmaceutical industry, let's say. Maybe that's part of it. And what you're trying to do is develop techniques for understanding xenobiotics in the body that is as close to basic scientific research as you can probably get. Given that that's what it is, it's always already applied, right? If you're talking about the introduction of drugs into the body, that's applied. And there's no way around that. But once you accept that then you're looking at this phenomenon – If you're looking at the development of tumors, which happens spontaneously; in the case of drugs you're looking at an introduced drug that does X and that's what you're studying in a very basic-scientific way. So that's the contribution perhaps of UCSF and your contribution to UCSF is being in line with that spirit of bringing these different ways of seeing the body, ways of understanding the body, and developing a new way of understanding the body based on them.

I wanted to come back, I think, to circle back to this question of the legal changes that happen around pharmaceuticals that have an impact on the scientific research that you are doing and that others were doing. And I find this really extraordinary. So, in your last session you talked about how over 50 percent of new molecular entities are these lipophilic large molecules. And, in part, or in large part because all of the smaller molecules already have patents out on them so the drug companies want to make big molecules because they're not patented. Are there any consequences to that kind of shaping, the fact that the intellectual property regime then kind of dictates the kind of drug development that's going to take place?

10-00:22:16

Benet: My recognition of this was because I developed BDDCS. I probably wouldn't have thought about it without BDDCS but this is a whole class of drugs, these class two drugs, highly permeable, highly metabolized, poorly soluble compounds that are the majority of new molecular entities. So my reaction to that is okay, now, yes, this is what you're doing but you have to recognize that these are the limitations and you need to study this stuff and you can't just take any molecule. It's not just the activity of the molecule. It's got to be that it can get to its site of action and work and it can get through membranes and it could be soluble enough and it goes the right places and the transporters do the right thing to it and it avoids the enzyme and stuff like that. So my recognition of that allowed me to say, "This is what's going on here," and to get that insight, that that's why you have all these molecules there. For a large company I was on what was called the developmental ability board.

10-00:23:25

Burnett: The developmental ability board.

10-00:23:26
Benet: Right. For a large pharma company. And we didn't look at any specific drug class or something like that. We just sort of looked at molecules. And then I brought to them, I said, "You're making all these Class 2 drugs that have these big solubility problems and they're way over here in BDDCS. Those aren't going to work. You've got to move them this way. You've got to solve the problems. You have to think about this kind of stuff." So it allowed me to be able to see these molecules, first of all, that I had the access to. Not even knowing what they did but just to see these molecules, to have access to them and say, "Well, I can tell you this isn't going to work. This drug will never work. You don't want that. The characteristics of this molecule aren't going to be successful in terms of—" And then to realize, well, why do you have to have those? Well, because the patents sort of restrict you in terms of what you're doing. Patents can be very restricting in the pharmaceutical industry.

10-00:24:30
Burnett: Absolutely, yeah.

10-00:24:31
Benet: Yeah. In terms of where they're willing to go and where they're not willing to go.

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Burnett: We'll pose that as a question for next session, other instances in which the intellectual property regime shapes or influences the actual nature of the drugs, right, the actual size of the molecule, for example, which is a really interesting case. So we can put a pin in that for now. One other thing that I wanted to ask – there's probably a really simple answer to it – but in 1984 the Hatch-Waxman Act facilitated the development of generic drugs. How did that affect the work that you were doing or did it affect the work that you were doing?

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Benet: It had zero effect on the work that I was doing but I became an expert in this area. And I still am an expert in this area.

10-00:25:38
Burnett: On bioequivalence?

10-00:25:39
Benet: On bioequivalence. And it's interesting. A very well-respected pharmaceutical scientist told me that he wasn't going to work in this area because it just was too routine and it was just looking at generics, something that already existed. And my reaction to that, thinking about it, was, "Gosh, there's got to be a leading scientist that looks at this that will be critical in terms of the science." And so I decided this was something I needed to do and so I've really put a big impact. And what I wrote on the plane yesterday was all about that.

10-00:26:20
Burnett: Oh, really? Okay.

10-00:26:22
Benet: Yeah. On the new rules on bioequivalence that I don't like in terms of what the agency's doing and I think they're not paying attention. What's happened is the clinicians and the bioequivalence biopharmaceutical scientists have abdicated their responsibility and allowed these statisticians to make all these rules that are really crazy. So I very much want to see good-quality drugs at affordable prices around the world. At the wedding I interacted with Yusuf Hamied. Yusuf Hamied, who I've known for a number of years, is the president of Cipla. Now, Cipla was the company that brought the AIDS drugs to Africa and the combinations and basically created the situation that sort of undermined what the US was trying to do in terms of the prices. I've always admired him and interacted with him and really had some good discussions with him and really been his supporter in terms of how these kinds of drugs should be available. And I want quality generic drugs. And the financial aspects of the generic industry are so overwhelming. I might have said this before but for a blockbuster drug every day that the innovator company can keep the generics off the market they make a million dollars profit. Profit. Every day. So the incentives to—

10-00:28:09
Burnett: To block.

10-00:28:09
Benet: —stop and block. And it's all science-based but it's not good science-based. And so that's, I think, a very important niche for me in terms of critically evaluating the science and saying this is nonsense and here's the data and you haven't thought this through correctly and this is not the right way to do it and when the agency makes regulations that I think aren't following what I believe is the right kind of science I speak up because I think that's really an important part of my responsibility.

10-00:28:43
Burnett: And you've given talks around the world on highly active antiretroviral therapies and stuff. So in the case of that, in case of HIV/AIDS drugs, I don't know, I think under patent it's something like $20,000 a year to keep someone alive with those drugs. Ten to twenty. Maybe it's down. It's lower now than it was. But twenty initially. And Cipla does it for about $700.

10-00:29:10
Benet: Right. Something like that.

10-00:29:13
Burnett: Something like that. So it's a lot cheaper. But what about the argument that Big Pharma makes about "you're going to hamstring the next drug development, the next blockbuster drug."

10-00:29:30
Benet: Well, it hasn't done that. They've made that argument for years and it hasn't done it. Why? Because I could make a new blockbuster and make billions of

dollars and they try to do it. Or they don't even make blockbusters anymore, they make drugs that are for niche markets, and orphan drugs that make billions of dollars. So there's still a tremendous incentive to go out and develop new molecules. And what Big Pharma has recognized is that they're not the innovators. They're the developers. What they're really good at is developing. And so they let somebody else do the innovating and then they buy it or they license it or something and they develop and still make a lot of money. Yeah. It costs a lot of money to bring a drug to market but they still make a lot of money, too. Yeah. Yeah. They always make the argument that we could do more but it really hasn't hamstringed us.

10-00:30:33
Burnett: Right, right. So you're a bit in line with the kind of Marcia Angell and Arnold Relman approach to—

10-00:30:47
Benet: To some extent.

10-00:30:48
Burnett: To some extent. Do they go a little bit too far?

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Benet: Well, no, but Relman and I were on this IOM drug forum together. So I interacted with Arnold a lot in terms of different aspects of things. I've been on the evaluation committees of the FDA. I'm really the only pharmaceutical scientist that's had this opportunity. And there needs to be more of us. But I'm on those committees. Or I have been on those committees. I'm not anymore.

10-00:31:19
Burnett: Well, it seems to me that you or your body of expertise is particularly relevant to these arguments about drug development. Both Relman and Angell are medical doctors, right, and they've been editors of the *New England Journal of Medicine*. They're very established. But they don't necessarily, based on their expertise, know about drug development the way that you do. You understand the business side, you understand the patent side, you understand the science side.

10-00:31:53
Benet: Yeah. But they might not agree that I know all that stuff. [laughter] Basically they do recognize, though, that I'm somebody that actually knows what happens to drugs in the body. But I was the first pharmaceutical scientist on the FDA Science Board, which is sort of the umbrella science board.

10-00:32:13
Burnett: And what year was that? Do you remember?

10-00:32:15
Benet: Egads. I don't know.

10-00:32:16
Burnett: Roughly? By decade?

10-00:32:19
Benet: Well, Kessler was FDA commissioner. So it probably had to be the nineties. [Ed. note: Member, Science Board, Food and Drug Administration, 1993-98] And the people who followed me, they're really outstanding people. Like Bob Langer. Bob Langer sort of took my job on the science board and actually became chairman of the science board. But he's a MIT development person in terms of new aspects of the delivery and that's sort of what I do, which is understanding drug molecules in the body.

10-00:32:58
Burnett: I'm quoting now from this oral history but the last session, "I'm always fighting with the FDA about drug classification." And so you've been advising the FDA and you've been arguing with the FDA for a couple of decades now.

10-00:33:20
Benet: But friendly.

10-00:33:21
Burnett: Oh, no, of course, of course. I think what I want to ask is in general do you feel that they don't recognize the complexity of what you and your colleagues have discovered or that they move too slowly?

10-00:33:41
Benet: No, no, no. They recognize it. They recognize it. And they pay attention to me. When I was talking about what I don't like about some of the new rules, someone at the wedding who was a former FDA employee said, "You are the only person that can take this position that they'll listen to and you need to say it."

10-00:34:04
Burnett: So your word carries weight. Your opinions are not exclusively about science. The example of the generics, right. The argument is not just based on science but a feeling that people should have access to drugs that are good quality and affordable. Is that a—

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Benet: Yes. Right. Yeah.

10-00:34:32
Burnett: That is part of the—

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Benet: Right. But you have to do the right science to make it happen. Because there has to be an objective measure that the regulatory agencies have to follow and that objective measure has to be a scientific measure. And so the criteria gets setup for all these objective measures and a lot of times I think they haven't

thought it through. Think about this. I think of them all the time. But they're my colleagues.

10-00:35:00
Burnett: Can you think of an example of the setup of an objective measure that hindered bioequivalence measures to facilitate the development of generic drugs for highly active anti-retroviral therapy?

10-00:35:16
Benet: Oh, for highly active?

10-00:35:18
Burnett: —for example, or another drug that could reach people in developing countries more effectively?

10-00:35:26
Benet: Oh, well. During the Bush Administration they took a position that, yeah, we're going to give five million dollars for giving AIDS drugs to the developing world but we're only going to give that money for AIDS drugs approved in the US. I said, "Well, that's crazy." And this is what Cipla does. Cipla's drugs weren't approved in the US but they eventually went and spent all this money to get them approved in the US, never to sell in the US but so that they could meet these requirements.

10-00:35:59
Burnett: The Bush Administration did?

10-00:36:00
Benet: Yeah, this was the Bush Administration. But actually then the Bush Administration, under pressure, changed it. Yeah.

10-00:36:05
Burnett: So there was pressure from other scientists? Yeah.

10-00:36:07
Benet: Right. There was other pressure. Political and scientific pressure. There's another thing that we haven't talked about. I chaired the IOM committee for RU486. Right. And that was a very controversial aspect. This is before 9/11. This was the first time an IOM committee meeting had security. That you went through a—

10-00:36:35
Burnett: Really?

10-00:36:36
Benet: Yeah. But the aspect of that was if you're going to allow abortion, if it's going to be legal, what the committee said is, what's the safest way to do it? And the committee said RU486 is the safest way to do it. And you might be against it but that isn't what we were asked to do. What we were asked to do was

evaluate, if you're going to allow abortion, what's the safest way to allow abortion?

10-00:37:08
Burnett: And if I recall from that report, which came out in 1993, I think, you also wrote—because you were head of that—

10-00:37:17
Benet: I chaired the committee.

10-00:37:17
Burnett: —committee that produced the report. And it made a big splash. And you also argued that it has all of these other benefits that have nothing to do with abortion. It has preventative effects, I think. Well, you specified what they were in that report. But it was making a case for adopting or reviewing the drug. And you argued that the FDA should review it rapidly by looking at the trial data from Europe as opposed to reinvent. So that was—

10-00:38:06
Benet: Right. No, that is a good example of something you raised before. I didn't know anything about RU486 when I got chosen to chair the committee. I'm a good chairman. That's how I get these. And I know how to get people to work together. But once I started doing that I said, "Hey, there's a whole bunch of things about RU486 that we don't know." And so I did research projects here at UCSF not funded by anybody. What are the enzymes that metabolize RU486? What are the transporters that effect RU486, and what happens in terms of bioequivalence, and how about the other compounds like RU486? How do they compare? So I had a graduate student that wrote his PhD thesis and did all that work and there was a good example of something I would've known nothing about except I became chairman of this committee and realized there's a whole bunch of information that they don't know about this drug that they should know.

10-00:39:06
Burnett: And it's not something you signed up to do but you were asked to do it. As with highly active antiretroviral therapy, was there a sense that this should be available? This should be for you? That you felt that this should be available in the United States?

10-00:39:29
Benet: Yeah, I did feel it should be available. But as I said, the focus of the committee was not on should it be available or not available, the focus on the committee was what's the safest way? If you're going to allow abortion, is this a safe way to do it or is this the safest way to do it? The committee says it's the safest way to do it.

10-00:39:46
Burnett: Right, right. And that's about being objective and answering a very focused specific question and contributing to the debate in that way. So I think we have a little bit of time left.

10-00:40:01
Benet: Sure. Five minutes.

10-00:40:02
Burnett: Five minutes, all right. Well, actually, let's perhaps save this. I did want to talk about Hurel and the Human on a Chip because I think that's an interesting story. But we'll leave it until next time to talk about in our final session.

10-00:40:20
Benet: Yeah.

10-00:40:20
Burnett: Okay.

10-00:40:21
Benet: Okay.

[End of Interview]

Interview #6 January 8, 2015
[Audio File 11]

11-00:00:00

Burnett: This is Paul Burnett interviewing Dr. Les Benet for the Science, Technology, and Medicine series and it is our final session, session six, and this is audio file eleven. And it's January 8, 2015 and we're here on Parnassus Avenue at UCSF. So we are going to follow-up on discussions that we had last time about your work on bioequivalence. But I did want to follow-up on the work you did, and continue to do, with HuRel. Can you talk a little bit about that company and your involvement with it?

11-00:00:51

Benet: Okay. So a number of years ago an investor and a scientist came to see me and they wanted to tell me about their idea, the hypothesis and what they were going to do and to get my opinion on it, of what I thought. And what they wanted to do was to put humans on a chip. And initially they were going to start with the liver. You could put animals on a chip and you could put humans on a chip, and therefore you could study these drugs. If you put the liver on a chip you could study the metabolism and the disposition of the drug before you ever gave it to a human or before you ever gave it to an animal. And they asked me what I thought. I said, "Gee, I think that's a terrific idea and it's something that I've been sort of pondering and thinking about. I'd love to see this kind of thing." And so they said, "Well, okay. We're excited that you're excited and we're going to form a company. We've licensed some patents from Cornell University," that one of the scientists was involved in, "and we're going to try to do this and we're going to market it because we think this would be really good for drug development in the future." And that's what happened. And so I became chairman of the scientific advisory board and we formed the company and it went on and about a year and a half ago now it became commercial. We sell the chips and we're continuing development. We're doing work now on using the chips for toxicology, not just for drug disposition. Can we predict toxicity of molecules very early? And we have a human liver, we have rat, we have dog, we have monkey. Yeah. So we have four. So you can take actually your compound very early and just look and see what happens to it. Specifically the thing that is most hard for the companies very early are compounds that are eliminated very, very slowly because taking isolated livers, the livers don't last that long. And these chips will last for two or three weeks. So it's very good technology and it's exciting and the company's still going. I'm going to make a presentation in San Diego on the toxicology part of it later this year. Some sort of new aspects of it.

11-00:03:21

Burnett: Can you talk a little bit about what the chip is and a little bit about how it works?

11-00:03:24
Benet: It's just a cellular system. You make a living cell system. You take a cell system and you convert it into this cell system on the plate, just like we do in the laboratory in terms of looking at metabolism. But this is something that's human and it'll last for a long time. There's a lot of know-how and technology that allows it to go for three weeks. You can then sort of just ship the plate to a drug company and they can test their drug on it.

11-00:03:58
Burnett: You have cells, liver cells and other organ cells?

11-00:04:04
Benet: Right, right.

11-00:04:05
Burnett: And it makes a passage through these systems?

11-00:04:08
Benet: Right. Well, right now we have like a static system. Basically you just put it on the chip. But we're in the process of developing the flow-through system. Now, we're not the only people doing this. There's a number of other people that are doing this around the country. And, in fact, DARPA, I think I mentioned this last time, DARPA had an initiative on this, that they asked for people. Their systems would be ten different organs that you could do on the chip. But we're not doing that. We're doing more of what the drug companies need early in development.

11-00:04:39
Burnett: Is this related to the work that you've done, that you got an award from PETA from, that you were--

11-00:04:49
Benet: Yeah, yeah. This is related to PETA because this is terrific. You don't need these animals. You don't need animals because you take these cells and you've grown them and you continue to grow them, so you don't need any more animals and you don't need the humans. It's sort of an immortalized cell line that you keep growing. And so PETA gave us an award. And –the more responsible one that takes care of dogs and cats and everything –

11-00:05:21
Burnett: Oh, SPCA?

11-00:05:22
Benet: The SPCA. Our last round of investment, SPCA invested in Hurel. So they have an investment arm and they also thought this was very good and that they should put some money into this, that it would go forward. And PETA said some very nice things about us, besides giving us the award.

11-00:05:39
Burnett: That's fantastic. Wow.

11-00:05:40
Benet: That this is good stuff.

11-00:05:41
Burnett: And it's just coming out now?

11-00:05:43
Benet: We've been commercial for about a year and a half now but we continue to develop it.

11-00:05:52
Burnett: So I just wanted to cover that base a little bit. Now I think we can continue to talk about your work that involves your scientific expertise in other domains. So, in the legal domain. You've described yourself as a crossover guy between science and the business world. You know so much about the patent world. So I was wondering if you could talk a little bit about your—you did eighty to ninety depositions and you've been involved and actually nine trials?

11-00:06:36
Benet: Okay. Yeah. Well, actually, this is a good day to talk about this, Paul, because Impax's first anti-Parkinson drug, our brand drug, was approved today—

11-00:06:47
Burnett: Oh, well, congratulations!

11-00:06:49
Benet: —by the FDA so this is a very good time to talk about this. And one of my former post-docs is the chief scientist at Impax and so we're very excited about that.

11-00:06:59
Burnett: That's great, that's great.

11-00:07:01
Benet: It was really good in terms of the crossover aspect of it.

11-00:07:04
Burnett: Absolutely.

11-00:07:07
Benet: There's a lot of legal cases and some of them have a good basis and some of them don't, because a number of things are just money related. So I'm an expert in pharmacokinetics and in bioequivalence and in patents, and a lot of other aspects, again, somewhat because of this crossover basis. I sort of understand the economics of it, as well as the science of it. So I do a lot of expert witness testimony, both depositions and trials, and I write a lot of expert reports. I don't keep any of that money. All of that money comes back and goes into the laboratory to support research and support the department. But I feel it's really important to have an honest scientific opinion in these critical issues that come up in law cases. And so I will be approached. It's not unusual in a case to be approached by both sides in a case. It's happened a

number of times. But I look at it. I look at what the issues are. I look at the patents. I know how to read patents. I've done patents myself so I know how to read patents pretty well. And I have to agree with it. I have to agree with the position if I'm going to be involved in it. And I think this is an obligation that academics should do.

11-00:08:41
Burnett: Service.

11-00:08:43
Benet: It's service. Many people keep the money. I don't. Therefore I think I'm even—

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Burnett: It's more of a service model.

11-00:08:51
Benet: It's more of a service in terms of what it is. But it's really important. It's really important that you get good opinions because it's easy to skew the data one way or another depending on the legal issues that are involved.

11-00:09:05
Burnett: Right, right. Other scientists that we've interviewed have talked about the amount of work that is done in science that is voluntary. I don't know what percentage of your work is on a voluntary basis.

11-00:09:23
Benet: No, I wouldn't call that voluntary. Money does come in.

11-00:09:28
Burnett: Yeah, that's true. But as you said in the last session, it's not something you need to do.

11-00:09:38
Benet: Right.

11-00:09:39
Burnett: That's what enables you to pick and choose the interesting cases for you, the ones in which you feel you're a good fit in terms of your expertise.

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Benet: I might have said this before, but I'll say it again. I'm very expensive. I charge a lot of money. And one of the things that that does is to keep a lot of cases away from me. So they really have to want me or feel that I can really benefit for them to do this.

11-00:10:07
Burnett: In 2004 Marcia Angell wrote that book, *The Truth about the Drug Companies,* which is this big book that was quite critical of some of the practices of the large pharmaceutical companies. One of the stories is about the ways in which pharmaceutical companies try to keep or extend or expand the patent area

around the drugs that they want to keep under patent. And one of the ways they do it is around the legal challenges. So that a generic drug manufacturer is vulnerable to legal challenges. And just actually mounting a legal challenge to a generic manufacturer. That is, a pharmaceutical company that has a drug under patent, they can challenge a generic company and that challenge alone will guarantee that the drug remains under patent for thirty months or so. So there's a lot of legal wrangling of dubious scientific quality. Because of your expertise in bioequivalence, have you been involved in cases that are about adjudicating bioequivalence matters?

11-00:11:27
Benet: Oh, yeah. Exactly. I do that a lot. I do that a lot. Or pharmacokinetic characteristics of a drug that companies try to patent. And I'm always against that. In other words they say, "You get these kind of blood levels and then we patent it, you get these blood levels." But it's an inherent characteristic of the human that gets these kinds of things, or the way they gave the dose, or it's pretty obvious. So I'm frequently on that side. I do both sides. I do brand name, too, because a lot of times what's being challenged isn't valid. The company patent is a valid patent and they should be allowed to benefit the way the law is. It's not all one-sided.

11-00:12:15
Burnett: Right, right, right. This came out in 2004, the Marcia Angell book. Have things changed in terms of FDA requirements in that time?

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Benet: Yeah.

11-00:12:36
Burnett: Things become a bit more responsible?

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Benet: Right, yeah. FDA requirements have changed a lot because you used to be able to put a citizen's petition in and really stop them from selling it until the FDA made their decision on the citizen's petition. And you could write the citizen petition very cleverly and it took the FDA a long time to respond to it and therefore you got all this extra time. So that got changed. The law has changed and basically now just putting in a citizen's petition doesn't stop a generic from being evaluated by the FDA. That was one of the big issues.

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Burnett: And how is a citizen's petition mounted by a company?

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Benet: Oh, well, the only people that write citizens' petitions are companies. [laughter] They petition the FDA and say, "This is a danger. As a citizen we're worried that this generic is going to come on the market and then patients are going to be compromised by this and therefore you should not approve this and for these reasons."

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Burnett: So it's the corporation as legal citizen that is able to do this.

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Benet: Right.

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Burnett: Okay. So some of the funny business around extending the patent life or using various devices, that has been smoothed out a little bit?

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Benet: Some of that's gone but this is big money. This is huge money. I probably said this last time. But a brand name company with a blockbuster drug, every day they can keep the generic off the market they make a million dollars profit. That's a million-dollar profit every day they keep them off the market, not just total amount of money. So there's a lot of money involved here and so there's a lot of incentive on both sides.

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Burnett: Right, right. And there have been complaints about the ways in which the FDA had failed to regulate sufficiently, that kind of—

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Benet: Yeah. They created environments where it was advantageous for the brand name company, let's see, in this generic issue to bring a case because then they could stop the clock from moving forward. But I said that's really changed. Oh, yeah.

11-00:14:48
Burnett: But as far as your expertise is concerned, you bring your expertise in pharmacokinetics to bear on questions that are specifically to do with the passage of drugs through the body.

11-00:15:01
Benet: Yeah, it could be that. It could be is the product bioequivalent? Is this patent valid? Is there false advertising? Have they misled the regulators? They deliberately misled the regulators by putting this kind of information out? Those are the kinds of questions that I get involved in in terms of the litigation. Or is the drug safe? And the FDA has said it is safe or someone has said it is safe and then it's being questioned by somebody else. And do you agree or not agree? This is personal liability type stuff that happens also. Now, I don't do a lot of that but I will sometimes when I feel it's over the top and really good drugs are being manipulated and made to look like they are not effective.

11-00:15:57
Burnett: This can be time consuming for you, I imagine.

11-00:16:02
Benet: Oh, yeah, it is time consuming but I charge a lot of money for it.

11-00:16:04
Burnett: Okay. Which then goes into your lab, which allows you to do research.

11-00:16:09
Benet: Do other things. And actually, these cases are very interesting, because at least in the beginning, when you're writing the expert report and you're doing all the research, you learn a lot. So I learn a lot. It's just like consulting. When I do consulting I learn a lot in addition to being able to do this. So when I look at all these scientific issues—they wouldn't have me do it if it wasn't a scientific issue—I learn a lot.

11-00:16:37
Burnett: And that informs research projects that you do? As you said, with RU486 you started doing a bunch of research in order to inform the report but also to perhaps go in a different direction for your research projects and advising graduate students and so on. There are aspects of your career that are more or less purely voluntary. One of them is the Institute of Medicine. It depends entirely on unpaid labor that scientists do and it advises on health issues that are of national importance or international importance. Can you talk about some of the work that you've done for IOM?

11-00:17:21
Benet: Sure. I've been very involved. I've been a member of the Institute of Medicine since 1987. Twenty-seven years now. And it's a great honor. You have a responsibility with that honor to provide guidance, because the national academies were setup by Abraham Lincoln to have guidance from experts, to use their information for the benefit of the country. So it's something good to do and I've had the good fortune of being involved in lots of projects and had the opportunity to chair a number of the projects. So that's been a lot of fun. And I learn a lot about that also. And I've been very involved with the Institute of Medicine over the years and very proud of it.

11-00:18:12
Burnett: And you talked about RU486? Are there other projects that stand out in your mind as significant issues? Committees that you've chaired, for example?

11-00:18:23
Benet: Well, I chaired the committee on accelerating the development of countermeasures for bio-warfare agents. I learned a tremendous amount about that. I can't remember if we talked—

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Burnett: A little bit.

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Benet: I got invited to the White House.

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Burnett: No, you didn't tell me. You didn't say that story yet.

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Benet: So when the report came out, the day before it came out I was invited to the White House to brief the president. Didn't talk to the president, I talked to his chief bio-warfare guy, who was named General Gordon. But I went to the situation room in the White House that you see on all the TVs. Doesn't look like the TV but it's also a very interesting room. Briefed General Gordon of what the report was going to say and what our recommendations were going to be. This was a committee that was mandated by Congress. So many things at the Institute of Medicine or national academies do are actually—Congress says to the Department of Defense, "You should do this study at the National Academy or someplace like that and pay for it." And so the Department of Defense paid for this study but they didn't like it because we actually criticized them and made a bunch of different recommendations. And when we made the report, they basically said, "Well, some of this stuff is okay but a lot of it we don't agree with." But subsequent to that they actually followed almost all our recommendations. They didn't admit they had followed our recommendations. [laughter]

11-00:19:59
Burnett: But after a suitable period had passed.

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Benet: But I felt very good about what that report had done in terms of accelerating the developing of bio-warfare agents. Most of the recommendations that we made in the report the Department of Defense followed, even though they never basically said they did.

11-00:20:16
Burnett: Well, the development of countermeasures. So this is ideally to understand antidotes or to understand—

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Benet: Oh, they have antidotes. To be able to stop the bug or some other kind of characteristic thing that was going to be done by a terrorist group. But through a disease, bio-warfare. So that was what this was about. So I chaired that committee. I chaired the committee on improving drugs, pharmacokinetics, and accessibility in underserved populations. That committee was an IOM committee. Report did pretty well. It was primarily interested with African-American patients who had different characteristics in terms of how they might respond to certain drugs. It was felt that the drug companies or the scientific community wasn't paying enough attention to this. And so that report basically said, "Here are things you need to pay attention to," and things like that. So that was a good report to do, too.

11-00:21:27
Burnett: Could we open a parenthesis there because I am curious about how race and, say, gender fit into pharmacokinetics research. Is there a lot of research that's been done on how drugs move through the body differently for—

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Benet: Right. There definitely is. And a lot of what is called personalized medicine is exactly that. The new idea that we could personalize medicine. In other words, do you give this drug to Asians or do you give it to African Americans? Does it work the same way? Do they handle it the same way? Do men and women handle it the same way? There's a lot of that. And, in fact, some of our recent work was with one of the statin drugs, the cholesterol-lowering drugs. It's called Crestor, which many people are taking right now. The label for Crestor, with the recommendation of the FDA, says that Asians should take it at a lower dose than Caucasians. And people thought that was genetics, that you could explain by the genetics but nobody could find that out. And we found some drug interactions that looked like they were only occurring in Caucasians, not in Asians, and we think it's not because it's the genetics, it's actually the amount of protein that's there. In other words, this transporter in Asians doesn't have as much protein there and therefore you don't see as big an effect, and so they have higher levels. This is a transporter that gets the drug into the liver. And so Asians have higher levels, we think, because this transporter is less active. Not from a genetic, we believe because of how much of the transporter is there is different as a function of race. So you could have activity be different as a function of race, or how much is there. How much of the transporter is there to make it happen.

11-00:23:26
Burnett: That's governed epigenetically? Or it could be?

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Benet: It could be. Yeah, it could be.

11-00:23:30
Burnett: So it's not necessarily—

11-00:23:32
Benet: Right.

11-00:23:32
Burnett: Right, okay.

11-00:23:34
Benet: So we sort of came upon this discovery. We looked at this drug interaction that nobody had looked at before and the only people that encountered it were Caucasians. Well, the reason we believe the Caucasians saw it was because they had good transporter that was putting in. You block the transporter, you saw an effect. The Asians, they didn't have enough of the transporter there in the first place, so they had high levels. And you block the transporter, it didn't make any difference. So that's one of our newest things that is really directly related to that issue. Is it a race issue, is it a gender issue?

11-00:24:06
Burnett: Yeah. And are there genetic things it could be? Because the dream of personalized medicine is you can get your genome mapped, sequenced

individually, and then they'd look at that profile and say, "Well, you need this much of this drug." And you're somewhat skeptical of that extreme precision or idiosyncratic, shall we say—

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Benet: Okay. What I'm not skeptical about is that you can tell differences within a population and you can understand what'll happen and it can be a genetic basis. What I am skeptical about, that you'll use this to dose in an individual patient and you'll be able to get it to the right level. Because if you've got a small level, small characteristics, there's just too much variability in my mind for that to work. But I'm not saying pharmacogenomics isn't important. It is. But I think it's more important to get the right drug in the right patient. In other words, this patient shouldn't be taking this drug because it's not going to work and because it can't do this or it can't do that. But this drug should work in that patient for those reasons.

11-00:25:14
Burnett: And UCSF has really gone into pharmacogenomics under Dr. Giacomini, right?

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Benet: Giacomini. Yeah. But our emphasis on transporters, which is the new area, as opposed to the enzymes. The enzymes were there before. But this has been a long time. I think I told you this story of going to Taiwan and Israel.

11-00:25:38
Burnett: Yeah, no. Yeah, yeah. I was thinking about it as you were telling that story. Right.

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Benet: That was an enzyme.

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Burnett: Right, right.

11-00:25:43
Benet: But now the emphasis is on transporters. So this last example I gave you is a transporter example, of what's happening with Crestor between Asians and Caucasians.

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Burnett: That's really exciting. And, of course, gender is a huge issue, as well. So women and men respond differently.

11-00:26:01
Benet: Right. Yeah, yeah. I have a couple of highly cited papers reviewing that kind of thing.

11-00:26:08
Burnett: So we can close the parenthesis and go back to talking about the IOM and the committees. So you chaired this committee on countermeasures to bioterrorism and you did the work on RU486.

11-00:26:28
Benet: RU486 and underserved African Americans.

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Burnett: Underserved, yeah.

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Benet: I think those are the three committees that I chaired. I also chaired a bunch of review committees because each IOM report is reviewed by an outside panel of experts and I have frequently been called upon to chair those review committees. But you get listed in the beginning of the book but you really didn't do anything but make comments one way or another, or something, or opposed to—and I've been very involved in a lot of IOM committees, and particularly the ones that I've been involved in, because of my area of expertise, is what are called the drug forums. In other words, where issues related to drug development and the drug lag and how we're going to do things better. The IOM has had three drug forums. The third one is still going on now. And I've served on all of those right from the beginning. When I was on the first one, I was the young pup in the room; this one I was the old guy in the room. [laughter]

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Burnett: So these don't happen very, very often or they're –?

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Benet: Well, the way the IOM works, there's got to be somebody that funds it and wants this in some issue, and the majority of funding has to come from non-profit aspects or government aspects. But this is a big issue. Big issue for the FDA. FDA has funded these forums over the years.

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Burnett: And so it's high-level policy considerations or just trying to understand not just the technological but the political and social, legal, economic aspects as to—

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Benet: So out of one of the drug forums I think the IOM could really say that the emphasis on having drugs in pediatrics really got pushed very well by one of the IOM drug forums. Because IOM is usually taken as having a non-partisan view and the IOM said this was really important that the FDA spend more time studying drugs for pediatrics. And there is. And the laws changed and there became incentives for drug companies to do that. And that really was really driven by one of the drug forums at the FDA. And there's a number of other good changes that have happened. For example, something called the Animal Rule, which is a bio-warfare issue. So for the FDA to approve the

drug it has to be safe and efficacious but how do you test a bio-warfare agent as efficacious if you don't have a situation. So the Animal Rule that was created was to say, "Okay, you can test safety in humans but you can't test efficacy because you don't have the situation." And so they come up with different alternatives. And that came out of one of the drug forum committees.

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Burnett: What alternatives do they have in testing—

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Benet: Oh, it's animals. That's why it's called the Animal Rule.

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Burnett: Oh, I see, all right. Yeah. And so these are some of the policy issues for the FDA. The drugs that are very important, really crucial, but they're small. They're insignificant—

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Benet: Yeah, orphan drugs.

11-00:29:49
Burnett: Orphan drugs. And so the IOM can flag areas that are important and recommend that the FDA take a greater role or that those become—

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Benet: Right. A lot of times those are being funded by the FDA looking for recommendations of what to do or how to do it or how to approach it. The big study showing of all the problems of patients in hospitals and having patients dying from the wrong drug and the wrong dose, that was an IOM study and it really made everybody aware that we need to pay a lot more attention to how we treat patients in hospitals and how we care for their drugs and that they get the right drugs and that there's the right controls that are going on. That was a very impactful study.

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Burnett: When was that?

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Benet: It was about six, seven years ago. Yeah.

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Burnett: And was this the Forum on Drug Discovery, Development, and Translation?

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Benet: No, no, that's a forum. That's a standing forum. The IOM has a number of different ways that it works in terms of looking—basically what that does is actually think up things that should be studied. Okay. So the forum actually doesn't really study anything. It says, "This is something that should be studied and this is a problem and so on." And then you appoint a committee that studies it.

11-00:31:18
Burnett: So in the years that you were involved in that forum, were there things that you flagged that you thought were important that needed to be explored and studied?

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Benet: Oh, yeah, yeah, yeah. We did a lot of pharmacogenomic stuff in that forum. It wasn't just me. There were other people that did it also. Because there's a drug lag and things take a long time people say, "Okay, how are we going to solve this? We're going to solve it and solve it." We're going to do it over and over again. And we talk about the ways that we're going to solve it and why they didn't work after people spent billions of dollars trying to do it. But that's how science progresses.

11-00:32:07
Burnett: Well, and any problem that is intractable, it's going to require all of these stabs at it to get any kind of traction. So that's an important service element. And you've talked a little bit about your FDA advising and you talked about the new FDA rules on bioequivalence that you were—

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Benet: I'm in the process of writing a paper.

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Burnett: I lifted a quote from our previous session: "A bunch of statisticians making the rules without the scientists." So that you're trying to bring the science back to the policy element. And Dr. Lawrence Yu talked about your important work in advising the FDA on—

11-00:33:07
Benet: That was in bioequivalence.

11-00:33:08
Burnett: On bioequivalence. And that this resulted in changes.

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Benet: Oh, yeah, definitely. A couple of major changes that have happened. I think I was really the driving force to push it to happen, along with other people. I'm a big supporter of the FDA and I want them to do it right. If I think they're doing it wrong I want to correct it but I want them to do something and I want them to change rules when things become too onerous, that it's not going to be successful, or there are unusual requirements that they're making. If you give a highly variable drug, it's really a very safe drug. A drug that gets on the market that's highly variable. Now, highly variable, I'm not talking about across the population, I'm talking about within an individual. If you take the same drug over and over again, and one time you get levels up here, and another time you level down here and here, that's a highly variable drug. It says coefficient or variation greater than 30 percent. But if it gets on the market you've shown it's safe and it'll work. Okay. So those are really safe

drugs. But because they've got so much variability it's really hard to show bioequivalence because that's—

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Benet: —a statistical issue. So what we wanted to do was to change the rules so that we would sort of weight the bioequivalence test with the variability of the innovator product. If the innovator product is very, very variable and it still works, you don't want to have a very small criteria for showing bioequivalence. You want to take—

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Burnett: Increase the range, right.

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Benet: —into consideration. Yeah.

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Burnett: Because that was the discussion. Obviously the molecules are very similar?

11-00:35:04
Benet: Well, the drug molecules are the same.

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Burnett: The drug molecules are the same but they may behave differently in the body.

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Benet: Well, they could be affected by the formulation. They could be affected by the formulation. Okay. But the drug is the same in the bioequivalence. Yesterday the FDA advisory committee recommended approval of a biosimilar for the first time in the United States for Epogen and that's always been a big issue. For small molecules it's really easy. It's exactly the same molecule. But for biotech it's hard because these are made by human cells or animal cells. Mostly by human cells and therefore it could be slightly different from time to time. So how do you prove that they're exactly the same?

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Burnett: And they're so large. These are—

11-00:35:51
Benet: Yeah. And they're these huge molecules, right. In Europe they've approved biosimilars for a while. But yesterday an advisory committee for the first time in the US recommended unanimously, fifteen-to-one, that this Epogen drug be approved. But I'm not a large-molecule person. I'm a small-molecule person.

11-00:36:11
Burnett: Okay. You'll remain silent on that issue.

11-00:36:14
Benet: Yeah. I'm a small-molecule person, where the drug is exactly the same. The only thing that can happen is the way you deliver it. That could have an effect on how the drug works and that's what you're trying to test in the

bioequivalence, that you're delivering exactly the same and you get the same blood levels.

11-00:36:33
Burnett: Right, right. And in clinical trials they don't typically, unless it's—there are special exceptions, like I think with the HIV drugs, where they're comparing two drugs and a placebo, right? But typically in the clinical trials they're just comparing against –?

11-00:36:53
Benet: Yeah, but this isn't for proving efficacy. It's bioequivalency versus efficacy here.

11-00:36:57
Burnett: Yeah, yeah. So yeah, okay. So bioequivalence is looking at the formulation. That's the only—

11-00:37:20
Benet: Well, it's blood levels. Do the blood levels turn out to be the same? There's no significant difference in the blood levels. If there's no significant difference in the blood levels, the drug's going to work the same because it's the exact same molecule.

11-00:37:28
Burnett: Right. And there we go.

11-00:37:31
Benet: But how to do that and the statistics and all that is not easy, not simple. It's not simple.

11-00:37:36
Burnett: Right. It's an acceptable range, right?

11-00:37:40
Benet: Right. And when bioequivalence was started in' 84 with the Hatch-Waxman Act, you had to have new statistics because we didn't have any statistics that said things are not—we weren't proving that things are different. You were proving that they're *not* different. That's harder. New statistics had to be developed for bioequivalence and that's why the statisticians, they're still developing new statistics. Some of them are good, some of them aren't. [laughter]

11-00:38:10
Burnett: But you did a lot of consulting for the FDA on that.

11-00:38:14
Benet: I did.

11-00:38:14
Burnett: Expert panel on Individual Bioequivalence, the FDA Science Board, and the Generics Drug Advisory Committee.

11-00:38:22
Benet: Advisory committee.

11-00:38:24
Burnett: And the FDA Center for Biologics Peer Review.

11-00:38:29
Benet: okay. I was asked by the director of the Center for Biologics to chair a committee to review science in biologics. And that was also very interesting. I learned a lot. [laughter]

11-00:38:46
Burnett: Did that pull you out of your domain a little bit or—

11-00:38:48
Benet: Yeah, because I'm a drug person, not so much a biologics person. But people think I'm a good chairman, so that's why I get picked a lot of times.

11-00:38:59
Burnett: And it seems, from one of your talks, and I hope I haven't misunderstood this, that you've argued against the need for some conventional aspects of the double-blind clinical trial?

11-00:39:11
Benet: Oh, yeah, I have a new paper that's just out now. That just says I think that we're doing a lot of things we don't need to do early in drug development. There's just sort of a historical view, that people think you need to do this. But my view is if you can't get any real information from it – and that's what we're arguing – you don't really get any useful information from this, why are you spending all this time and all this money doing this when you're first looking at a drug. And it has to do with when you're running your first studies to look at efficacy and toxicity. Very few people, six people and a control, very often they will add two placebos to validate their studies. But they can't validate anything. That's what this article is about.

11-00:40:04
Burnett: With such small numbers.

11-00:40:06
Benet: Yeah, you're not validating anything. And what we tried to show is most of the time you really don't know anything anyway. It doesn't help you. And so you've spent a lot of money blinding the clinicians and doing all this stuff and you've added these placebo patients. And what we're arguing is that there's very little benefit from this.

11-00:40:26
Burnett: This is just an inherited practice that—

11-00:40:28
Benet: Oh, yeah, it's definitely. And it is so controversial because the clinicians who do it, they just think I'm the devil—

11-00:40:35
Burnett: Wow.

11-00:40:36
Benet: —for proposing this. That I don't understand anything. I don't understand drug-development process. That you need to do this.

11-00:40:43
Burnett: But it seems to be a statistical question, too, right?

11-00:40:46
Benet: It is a statistical. It is.

11-00:40:47
Burnett: Because there is such a small—

11-00:40:48
Benet: But they have a different view on this. You need to validate it.

11-00:40:52
Burnett: It's a best practice or something?

11-00:40:54
Benet: It's a best practice and if you don't do it the guy doing the evaluation is going to be biased. Because if you have these two placebo people then they're not going to be biased because they don't know who the placebo is and who is not. What we document in there is the kinds of things that you measure, you're going to measure anyway, and you could be just as wrong with the placebo or not with the placebo. But it's controversial and we'll see what happens. The paper's coming out. It's now online. People can read it. And I've been asked to present it at sort of a forum and discussion at the American College of Clinical Pharmacology meeting in San Francisco next September..

11-00:41:35
Burnett: And you have had a kind of role as a public intellectual to some degree, right? You've weighed in on important cases of the boundary between industry and public scientific research. And things have evolved now but in the 1990s there was this case of a researcher at UCSF named Betty Dong. And I was wondering if you could talk a little bit about that case.

11-00:42:13
Benet: Okay. That's a very interesting case. Okay. Betty was a faculty member in the School of Pharmacy. She had done some earlier work, along with Frank Greenspan, who just recently passed away, in endocrinology related to thyroid drugs. Some of the generics that were coming out were not good and they really wouldn't give you the right clinical response. So she got funded by a company to carry out a clinical study in detail that would do this and document it really well. Well, what happened in this study was that actually things had improved and she came out with the result that there was no

difference. There was no clinical difference. And, of course, the company who funded this study was really upset.

11-00:43:07
Burnett: Surprised.

11-00:43:08
Benet: Not necessarily some of the scientists but certainly the businesspeople were upset. And so they tried to do everything they could to discredit. And back in those days there wasn't as much control by the university in terms of how people would sign agreements to do with companies. So Betty had signed an agreement that the company had the right whether she could publish it or not publish it.

11-00:43:30
Burnett: Yeah, they required permission. Right. Yeah.

11-00:43:31
Benet: Yeah, the permission. Right. And Betty had actually gone to the corporate counsel, the UC counsel at that time, and he had looked it over and said, "Oh, it's probably not a problem." But then the company really wanted to skewer Betty and show that she was an incompetent and that this study didn't deserve to be published, and then they were going to sue the university if it did get published. And the university took a very cowardly position and said, "You can't publish it." And I wrote a letter to *Science* in those days and said that the university is taking a bad position and I actually wrote to the FDA and said, "This is what the company's doing," to my friends at the FDA. Lou Sullivan, who was the former HHS secretary, was brought in to negotiate this thing, and he was here for about two weeks and I think that settled because I had written this letter to the FDA and told him what was going on. The FDA told the company, "You back down." And so the whole thing got settled and it got published in *New England Journal*. But there was a lot of really rough stuff going on and Betty, she really was scarred by everything that happened on this.

11-00:44:56
Burnett: I bet. That's quite a significant—

11-00:44:58
Benet: And Jere Goyan, who was the dean at that time, asked me when it was first going on to do the scientific evaluation. The company was going to do a scientific evaluation. He asked me to do the scientific evaluation of what was going on. I looked at the science and said it was fine and what the company was doing was just trying to badger her and to threaten the university with lawsuits and things like that.

11-00:45:24
Burnett: According to one source, even after the initial crew at the company accepted the settlement, the informal settlement of this arrangement, a new crew came

in later and tried to pressure the *New England Journal of Medicine* and [the issue] just refused to die for a few years afterwards.

11-00:45:52
Benet: Yeah. There was a lot of back and forth and this kind of stuff. And Drummond Rennie, who was the editor for the paper and was the one involved, he wrote an editorial. He said some nice things about me, what I had done in terms of all of this. And it got all written up in the *Wall Street Journal* because somebody from the *Wall Street Journal* discovered it and wrote the whole thing up. And I was the leak on that. [laughter]

11-00:46:22
Burnett: So you had a public voice in something that gets cited a lot in histories of the commercialization of scientific research. If they don't argue that this is what happens on a regular basis, they argue that this is what can happen if we're not careful.

11-00:46:52
Benet: What I did was *sub rosa*. Only in Drummond's editorial does it actually say some of the things that I actually did. [laughter] Because I just sort of did this informally. I wrote my friends at the FDA and said, "Look what this company's doing."

11-00:47:09
Burnett: "This is nonsense." Yeah. So what were the lessons learned at UCSF or were there any?

11-00:47:18
Benet: Well, there were. Yeah, definitely. Well, first of all, UCSF became much more careful in terms of what faculty could sign and what they couldn't sign and under no condition was faculty going to sign something that if you run the study the company has to agree that you can publish the study. So that changed a lot. And just a lot of the industry/university regulations subsequently changed. We've talked about that. I was very involved with that in terms of seeing that we did it right or at least right in terms of the way I thought we should do it in that time. And I think it was a good lesson for the university, too. That you really need to support your faculty. It's not good when the university goes against their faculty.

11-00:48:08
Burnett: I think they just sort of left her to twist in the wind. It's like, "They could sue you and we're not going to provide you with any support." That's a challenge for any academic and could potentially have had a chilling effect if there had not been support.

11-00:48:30
Benet: That all changed.

11-00:48:30
Burnett: It all changed. And so that was resolved. There are other issues that you've been involved in. Education. Pharmaceutical education. You're on a number of boards and committees. Could you talk about your interest in promoting pharmaceutical education or excellence in pharmaceutical education?

11-00:48:56
Benet: Well, I was president of the American Association of Colleges of Pharmacy and do have a view in terms of the importance of academic freedom and that it serves the world and that it's not something that serves only these ivory-towered people; the ivory-towered people are doing something that's important. Very much involved in that. And very much involved in making sure that the curriculum in pharmacy moved with the times and we were one of the leaders in saying you have to have a clinically oriented curriculum. I think I was involved, not as much as other people here, but certainly was involved. And also, as we've discussed, there needed to be a scientific association that represented the science within the school, in the academic disciplines. That that's again how they had big impact in terms of not only in education but also in terms of public policy. And you needed associations and that was one of the driving forces of founding the American Association of Pharmaceutical Scientists.

11-00:50:10
Burnett: And this is also not just restricted to an interest at the national level. You've been interested in broadening the scope and getting a global organization together. Can you talk a little bit about that?

11-00:50:25
Benet: Right, right. Right. So after I founded AAPS, American Association of Pharmaceutical Scientists, I got approached by the scientific leadership of the International Pharmaceutical Federation to become the head guy of the science within the organization. And I said I would do it but I had some conditions of what I wanted to do. One of them is I wanted to have a world congress. Second, that the practitioners and the scientists had independent voices within the association. It's the same thing I tried to do in the American Pharmacists Association with AAPS. I wanted to do it at a national level. And the association did it and I think it's been very successful. FIP, International Pharmaceutical Federation, was basically a European organization and I wanted to see it globalized. I wanted to see the Americans become much more involved in it. I wanted to see the Asians becoming much more. And so during my four-year tenure of heading that I really feel that that was my big goal. Was to get everybody. And I think that's been a great success, not only through me but through other people who have worked in making this happen. So the International Pharmaceutical Federation didn't make the mistake that the American Pharmacist Association made in trying to say, well, the scientists have to be here and the clinicians here. And it's sort of a parallel situation and I think it helps in moving forward. Yeah.

11-00:52:03
Burnett: Yeah. And it has increased opportunities for pharmaceutical scientists to work together, to have a common professional identity, I suppose?

11-00:52:12
Benet: Right, right. Yeah. Definitely. Definitely. I wanted the international meeting because I wanted this group of people to get together on an international level and interact in terms of their science.

11-00:52:23
Burnett: So there are other societies that you've been involved in. I don't know about the degree to them because on your résumé it mentions your involvement but I don't know the extent.

11-00:52:43
Benet: I've been an officer in a lot of other associations. I've been president of three organizations, so I figure that's enough. So I got to be treasurer of ISSX, International Society for the Study of Xenobiotics and I thought, "Oh, I better not go any farther than this because this is a whole other commitment." And I've been active in the clinical pharmacology societies but never beyond just being a member.

11-00:53:12
Burnett: Associated with it.

11-00:53:13
Benet: Yeah, yeah. With the science aspects of it.

11-00:53:17
Burnett: And just bring us up to date a little bit on the Department of Biopharmaceutical Sciences, where it is now and where you'd like to see it go in the future.

11-00:53:34
Benet: Okay. So we have a new chair. Now it's a new name called Bioengineering and Therapeutic Sciences and a new chair, Tejal Desai, who's been chair since October. And she's doing a wonderful job. And basically my view has always been that the way you succeed in science is to keep moving in lots of different directions and you don't necessarily concentrate on a single area because that area can get out of fashion. And we're moving in completely different directions. Recruiting outstanding young faculty members and good leadership of the department and good interactions. Now I'm two chairs removed from the chair. I wasn't the past chair, I'm the past past chair now. And so that's even better. And very proud of it. Very proud of what's happening and our impact on campus and our impact internationally and we're moving in new directions and it's very exciting. And in today's environment, in terms of what happens at the NIH and funding and things like that, you've got to be moving in new directions. If you're continuing to do the same things, you're going to have to retire. That's why I'm not retired. [laughter]

11-00:54:50
Burnett: Because it's bioengineering, it's a lot more genomic work, a lot more—

11-00:54:57
Benet: Well, it's called bioengineering and therapeutic sciences. But we've got five different disciplines in it. One of them is drug development, which would be sort of the one, and there's a genetics, there's a bioengineering part of it. Well, we do a lot of computational work in the department and we're a leader in using models and computational models to predict not only pharmacokinetics, pharmacodynamics, but how drug molecules move in the body and go to different places. And Kathy Giacomini really emphasized that when she was chair and really brought in some outstanding people. So it's a great place to be. I'm always pleased to be here.

11-00:55:37
Burnett: This is the *in silico* kind of modeling?

11-00:55:40
Benet: Yeah. Right, right. Right.

11-00:55:41
Burnett: Right. And it's becoming more sophisticated.

11-00:55:42
Benet: Right. Becoming more sophisticated. And paying attention to the important parameters. I think we've talked about that I'm concerned about the *in silico* guys because the *in silico* guys are always using *in silico* for everything and they shouldn't be doing *in silico* for everything. The things you can easily measure, measure. You don't have to do *in silico* for that stuff.

11-00:56:06
Burnett: Well, I suppose that's the flip side of going in new directions. The flip side is that one can become enamored of the newest thing. And so there's a real emphasis on genetics research or there's a real emphasis on using computer processing to solve problems. And your approach seems to be always question the conventional wisdom, even if the conventional wisdom is brand new.

11-00:56:39
Benet: Right, right. It's what makes it exciting and makes it fun to do. I feel I've got a whole new thing within the last couple of days. I'm really excited about it.

11-00:56:55
Burnett: What's your whole new thing?

11-00:56:57
Benet: I think that the general belief of how drugs get into the brain is not correct.

11-00:57:07
Burnett: Like crossing the—

11-00:57:08
Benet: Yeah. Because the general belief now is that you need transporters and I don't believe that's true in a large number of cases. And I think now I've got some really good data and good evidence that suggests that this may not be true. From my perspective, if you believe that you need transporters to get into the brain all the time, well, then, you're going to be limited in terms of how you're going to develop it. There is a possibility that it can just get in there because they're highly permeable. So we're going back. One of the things I told you is that I create these databases. I create these huge databases that allow me then to go back and test the information. So I did the BDDCS database where I have these 900 drugs. I've got all this information that I curated and said, "I believe it." It wasn't somebody else who just put it in the database. So now I can go back and ask specific questions in that database and so now I'm going back and asking the database some questions about brain delivery. We've actually published one paper but people don't pay a lot of attention to it because that's not my area. But I'm really excited because I think something's being missed in terms of it and that's the kind of stuff I like to do. I could be wrong. This is a lot of—

11-00:58:30
Burnett: Right. And this is brand new for you.

11-00:58:31
Benet: Yeah, this is brand new. I just sat down with one of my graduate students this morning and said, "Hey, look at this. Look at this. Go look at that. Let's go back and look at our database and see what you can find for this kind of information." Yeah.

11-00:58:46
Burnett: And this is part of the quest for the unifying relationship?

11-00:58:55
Benet: No, no.

11-00:58:56
Burnett: No? This isn't—

11-00:58:56
Benet: It's not that at all. It's my BDDCS part. Okay. So the unifying relationship is PKPD. The BDDCS, Biopharmaceutics Drug Disposition Classification System, can tell you a lot of things that you didn't realize before and allows you to make some guesses. And so that's what we're doing. We've actually published two papers on it. But because I'm not in the area and we were just more simple in that area people don't pay attention to it. So I'm used to that. I'm used to people not paying attention to me. [laughter] So we go on and we do more work until they start paying attention.

11-00:59:37
Burnett: We have talked about it a little bit but the unifying PKPD relationship to predict drug-dosing regimens –

11-00:59:50

Benet: Right. So this is a paper that we will submit. I'm going to speak about it at the FDA in the Abrams Lecture in April, the end of April. And I've spoke about it a number of times. It appears that many, many drugs in many, many disease states fit the Emax model that just basically says if you increase concentrations, effects reach a plateau. Okay. You can't keep going up all the time. And so the question was if all drugs in all disease states do this, is there something within the Emax model that we hadn't seen? Because this has to be PKPD. The blood levels are PK [pharmacokinetic] and the effects are PD [pharmacodynamics]. And so we played around with it a lot and we felt that we found something that says that in fact there is another relationship that people haven't seen that relates a parameter that is a characteristic of the equilibration time between pharmacokinetics and pharmacodynamics. In other words, you get a blood level, how fast does the effect occur? Okay. So for a drug like warfarin that you're taking for blood clotting and stuff like that, it would be days. You get a blood level, days later you get the effect. But an anesthetic, one minute later you get the effect. Okay. So that parameter is a characteristic that all guys doing PD and PK usually characterize. And there's different ways of getting that number. So that's one of the parameters. And the other parameter is something that said, "Okay, let's just look across all drugs and see if we can see something in all these drugs related to how you dose it and how the pharmacokinetics are," related to the EC50 because that also comes out of the Emax modeling. In the Emax model that's the concentration that gives you half the effect. That's in the denominator of the equation. And so what we've done is it looks to us like if you look at the fraction of time that a drug molecule is above EC50 during a dosing interval, for only drugs that are approved, that are on the market, that there's a general relationship between that number and this other parameter of the time to equilibration and it's a single line, that molecules fit on it. If that time is very long, like warfarin, the time above the EC50 is very short. If it's like an anesthetic, it's all the time. You have to have blood levels there all the time. And so we think there's a general relationship that actually probably all drugs fit on and if you know this general relationship, and we have an equation that says what it is, you can run very early in your studies and say, "Well, if it fits the general relationship, this is how you should dose it." That's what we think we've discovered. I think it's really big. I think it's really big. And so it's really interesting that you have this oral history because people will be able to go look, when they listen to this thing a few years later, and say, "That dummy. He didn't get it right at all." Or, "He got it right." [laughter]

11-01:03:07

Burnett: Well, you were willing to take that risk. So we have risk-taking evidence here in this oral history. Do you think you're ever going to stop?

11-01:03:18

Benet: I hope not. I don't feel like I have any reason to stop.

11-01:03:25
Burnett: This is the kind of dream job that people talk about that you don't want to retire from.

11-01:03:27
Benet: Right. This is a dream job. I told you, I get paid really well here at the university and I get to do whatever I want. Why should I retire?

11-01:03:46
Burnett: That's a ringing endorsement of the career that you've had. Definitely. So we have talked about your scientific career and we've talked about your service, your academic service and your public service. There are three things that define a professor at a research university. They have to have a service requirement and there's a research—

11-01:04:17
Benet: Research.

11-01:04:18
Burnett: —requirement and teaching is the other third of that equation. And so I'd like you to talk a little bit about teaching and how it figures in your academic career.

11-01:04:31
Benet: Okay. So I enjoy teaching and I am good at it. I've won the campus teaching award and I won a mentoring award on campus for graduate students. I have definite philosophies of what my responsibilities are as a teacher and I feel strongly that I need to meet those. Because of where I am sort of in stature in the department, the only course that I actually teach that I have responsibility for, besides all of my graduate students and the seminars and things, is every other year I teach "advanced pharmacokinetics." So otherwise I'm teaching in lots of courses but they sort of match my time. In other words, when I'm in town, or they schedule it ahead of time and do that. So I don't have the responsibility that many academics do, that they have to be there for this even though frequently I teach the most in the department. There's been a number of quarters where I'm doing the most teaching in the department.

11-01:05:45
Burnett: And these are—

11-01:05:45
Benet: Professional classes and graduate classes.

11-01:05:49
Burnett: Yeah. And Advanced Pharmacokinetics is a fairly large class?

11-01:05:52
Benet: No, it's not.

11-01:05:53
Burnett: That's not? It's not?

11-01:05:55
Benet: They take basic pharmacokinetics and so it's really that are the aficionados. And if you're in my lab you have to take it, of course. So it maybe has about eight or nine people. And I only teach it every other year because it only has about eight or nine people.

11-01:06:11
Burnett: That's like a seminar.

11-01:06:12
Benet: Yeah, it is. It is. But to do pharmacokinetics you got to actually do the problems and do the workshops, so there's a lot of work in it for the students. They have to do a lot of work between each class. You don't learn it by just listening to it. You actually have to do it. Grading those things also takes a long time because you want real data that they're analyzing and there isn't one answer to this stuff. Depending on how they look at it, they could have lots of different answers. So that takes a lot of time to do but I like it because what I'm interested in, and I think what all faculty are interested in, is teaching people to think. And especially for my graduate students, that's my objective. I want them, by the time they finish here, to be able to think on their own. And it's really gratifying to watch them over the years. We have a weekly seminar in our group where we rotate all the people that are talking. And it's just so gratifying to me to see them progress, that they're asking the tough questions or asking the questions that you haven't thought about before. And that's what you like to do. It's hard with the professional students to do that as much but I try to do it. I'm not a big person on new techniques in teaching and things like that. I haven't been involved in that. I'm still sort of a, "Here's the information."

11-01:07:42
Burnett: You talked about your disappointment when you were a student with rote learning. In terms of pharmacology, old-school pharmacology, which was like "Here's the formulations. Learn them, go forth, and practice." And that was so disappointing to you and that's why you became a pharmaceutical scientist. And that's what it is for you. So there's a Socratic approach that you take?

11-01:08:12
Benet: Right. I always take the Socratic approach. It wouldn't be a modern good teacher that's doing new techniques in terms of getting the students to be involved. But I actually teaching some classes where some faculty are doing that and I do it because they've set up the format of how to do it, and that's kind of fun. They have to listen to my lecture before they come to class.

11-01:08:38
Burnett: Oh, the flipped classroom?

11-01:08:39
Benet: Yeah. They have to listen to the lecture before they come to class and then I ask questions that are a case and then they have to respond to that case based

on what's in the lecture and stuff. And so that's fun. I've been doing that for a couple of years in one of the classes. But that faculty member spent so much time in making that happen. I enjoy it but I'm only giving one lecture in that class.

11-01:09:03
Burnett: Right, right. But you prefer governing how the students are going to encounter the knowledge, right? So a lecture format. Not the flipped classroom but definitely enabling discussion?

11-01:09:26
Benet: Right. But what I teach people, you can't just sit there and listen to it and do it back. You've got to actually do it. You've got to solve the problems and think about it and analyze the data and things like—because that's what I'm always doing, yeah.

11-01:09:40
Burnett: Can you break it down for me, what an advanced pharmacokinetics class is?

11-01:09:45
Benet: There's three hours. You spend one and a half hours going over the problems that you assigned the previous time and they go up and we discuss the problems, where did you get it right, where did you get it wrong. Does anyone in the class understand this problem or how would you solve this problem? Things like that. And then the next part of the class you say, "Okay, so here's what the new problems are and here's the background for it." Okay. This is the kind of information you need and now these are the problems you're going to have to solve: "you were in a company and you ran this study and this is the data that you got and now how are you going to analyze it and what does it tell you?" Yeah, yeah.

11-01:10:33
Burnett: So it's like a case study for these kinds of problems.

11-01:10:37
Benet: Right, yeah.

11-01:10:39
Burnett: And at the graduate level we've talked a little bit about your mentorship of—

11-01:10:49
Benet: Fifty-two people—

11-01:10:51
Burnett: Fifty. I was going to say over—

11-01:10:51
Benet: Fifty-two PhD graduates right now and one, two, three, four in the lab and two rotating. So maybe two new ones coming in.

11-01:11:01
Burnett: Yeah. And your former graduate students that I've talked to talk about your mentorship and we've talked about that before. And we've talked also about the relationship between teaching and research. Can you talk a little bit more about that?

11-01:11:24
Benet: Yeah, okay. So I think that's really important. In one of the first-year classes that I teach in the pharmacy curriculum, the person that runs the class said to me, "Your lectures are different every year." And I said, "Yeah, because the topics change and I update it because I'm usually talking about stuff, how the FDA does this and what happens, and things change, and I learn more." So I do. I change my lecture every year. And it's different. It's really nice with slides because you can just change the slide.

11-01:12:03
Burnett: Swap them out.

11-01:12:04
Benet: Right. No, that's been a great advance over the years in terms of having to write it on the board. So you get through a lot more things. What I learned in my consulting and in the legal cases and in my interactions with the FDA, I'm always doing stuff that's directly relevant to what I think the students ought to know. And so I'm trying to translate that over to them in the lectures so they know the latest stuff, what's happening and where it's going to be. I will say to them, "When you get out, somebody's going to ask you this question." The answer may change but here's what the answer is now and here's why it is and here's what may be changing and here's what's going on right now." But I'm fortunate again because I'm not talking about something that is really the same thing over and over again, physical chemistry at the basic level. I'm talking about the FDA practice. I'm talking about bioequivalence. Those rules are changing all the time. Okay. I'm not sure I said this, Paul. I am very fortunate. I get to lecture about what I do. Even at the most basic level, even when I'm teaching first-year students I get to lecture. Now, very few people get to do that.

11-01:13:28
Burnett: They're usually stretched in different domains because there's a departmental requirement that we need someone to teach this area. And you learn as much as you need to for that area. But this is all the stuff that you're doing currently or have done in the past.

11-01:13:43
Benet: Right. It's a joy to teach it even because it's different. A couple of times students complained. "Wait a minute. This wasn't on last year's exam. The topic wasn't on last year's exam." [laughter]

11-01:14:00
Burnett: What, are they looking at old exams?

11-01:14:00
Benet: Yeah, right. And, "What are we going to study?"

11-01:14:07
Burnett: It sounds like it's such a dynamic field. You're at the cutting edge of it. And it's a privilege for those students. I imagine students come to UCSF knowing that they're going to be at the frontier.

11-01:14:28
Benet: Yeah, I think they do. But if I think back when I first started teaching, I was teaching, because I do analytical chemistry because I measure drugs, so I was teaching analytical pharmaceutical analysis. And I was teaching what was called physical pharmacy, which is physical chemistry applied to pharmaceutical systems. So that didn't change. But I don't teach those courses anymore. [laughter] I teach the stuff that I have the expertise in and that they need to know.

11-01:15:00
Burnett: But you are recognized for being good at this, whatever this is, the thing called teaching. Whether your techniques are old-fashioned or not, you've been repeatedly recognized for them. Can you talk about those awards a little bit?

11-01:15:17
Benet: Okay. So the teaching award is when I first got here, like the fourth year I was here. So I'm not sure that carries over anymore.

11-01:15:28
Burnett: By testimony of others and evidence, more recent evidence of teaching excellence.

11-01:15:36
Benet: Right. But the mentorship award is pretty recent.

11-01:15:41
Burnett: Yeah. Distinguished lecturer, distinguished teaching award, and—

11-01:15:44
Benet: This thing here is the distinguished men—

11-01:15:47
Burnett: Outstanding faculty mentorship 2001.

11-01:15:48
Benet: Yeah. That's 2001. That's training graduate students and teaching them to think.

11-01:16:00
Burnett: When I was teaching regularly there's something about the process of translating something complicated to something that a student at a certain level, whatever it is, can understand. There's something about that activity

that's really important kind of cognitively, at least for me. It helps me to think about the work that I'm doing. And there's always that old adage, like if you want to really learn something, teach it.

11-01:16:28
Benet: Oh, definitely. Right.

11-01:16:29
Burnett: Because it requires a level of engagement. And you seem to excel at teaching. And I'm wondering if you could reflect on how that teaching skill helps you in the other domains.

11-01:16:46
Benet: Oh, well, it definitely does. If I have to go before a jury, I have to teach a jury. I've done nine trials. We've won eight of the nine. So I've got a good record.

11-01:17:01
Burnett: And the subject matter in those trials was –?

11-01:17:03
Benet: Those are science issues. A patent issue or false advertising or something. You got to teach the jury how to analyze the data and what it means. And the other side's trying to teach them something else. And you've got to teach them that this is the right way to look at it and then this is how you interpret it and that's why this is what I believe and this is why you should come down on this side of the argument, because here's the facts that I think are important for you. So that's real teaching. That's the hardest teaching. Teaching a jury is probably the hardest teaching.

11-01:17:41
Burnett: You did it nine times, but before you did it once did you get counseling from the legal team as to the nature of the jury's level of comprehension?

11-01:17:52
Benet: Yeah, yeah, definitely. Definitely.

11-01:17:54
Burnett: And they'd say, like, "Think of this as grade-ten level," or somebody with a grade ten —

11-01:17:59
Benet: Right, no, definitely. Because the lawyers are very experienced. In reality it's not the experts that win the case, it's the lawyers that win the case. And if they can use the experts well then they're going to win the case.

11-01:18:12
Burnett: Right, right. But your testimony, I'm sure, helped. So you need to translate to a certain level to think about—

11-01:18:19

Benet: Right. And sometimes it's not the jury, it's a judge. Sometimes it's a judge trial. But the judge also has no experience usually in this and you're trying to teach the judge. He's probably at a different level than the jury but you're dealing with people who sometimes surprise you. I remember once in one of the trials I was in I was telling the judge, and it was that the FDA presented a poster at a meeting that matched my view of what the correct answer was. Now, the judge thought, "That's nonsense." He says, "That's just a poster at a meeting. That doesn't mean anything." Because he didn't understand for the FDA to come out and do science and say this is the correct thing and we're going to even publish that this is the correct thing, that's pretty powerful. But the judge didn't think that. He thought, "Oh, it's a poster." It's not peer reviewed, this kind of stuff. "Anybody can present a poster at a meeting." That really opened my eyes. I had to think about this differently. He doesn't come with it saying, "Everybody in the pharmaceutical industry says the FDA prints a poster at a meeting, this is what they think and this is going to govern how they evaluate this data because they don't get to present that poster unless the FDA agrees that's the position they're going to take." But he didn't recognize that at all. And so I had to step back and realize, "Wait a minute. I've got to treat this completely differently in terms of how I'm going to present it to him and how he can react to it or the kind of information he needs to know." Yeah.

11-01:20:04

Burnett: Right. Because I think judges are looking for what's the generally recognized authority because they know that it's beyond their area of expertise and so they're like, "Just point me to the institution or the party line as far as what a particular scientific fact is." Did these encounters with translation of the complicated science that you're involved with for the public or different publics, has that made you think about the public understanding of science?

11-01:20:44

Benet: Yeah, definitely so. Before I get to that I want to say the same thing happens on the boards of directors of companies. Because most of the directors of the companies are not scientists. They're business people or financial people. And so you're trying to teach them also that this is the way we think the company should go. This presentation that's being presented to us we should buy into because it's the right thing. Again that's sort of a different group of people that you're dealing with. No, I'm very interested in and sensitive to making the public aware of the science that I do and how it could benefit them and how they could understand it and want them to understand. It's not easy. It's very hard.

11-01:21:38

Burnett: No, it isn't, especially since the work that you do is very complex. But also there's a question of general science education in the United States. Is that something that you feel strongly about in terms of—

11-01:21:57
Benet: Yeah. All my grandkids do science projects and they call me up and, "Gramps, what's the answer for this and how about this as a project? What do you think?" So that's fun to do. Sixth-grade kids. They're always doing that. And then they win prizes and stuff and that's fun. That's fun to do. So no, I'm very pleased that my grandchildren, as opposed to my children, who didn't pay any attention to science, that my grandchildren, they're all interested in science.

11-01:22:33
Burnett: Right. It's interesting. Does it skip a generation?

11-01:22:35
Benet: Yeah, maybe. Your father does that. Absolutely not. They're not going to have anything to do with it. But the grandkids, they all think, "God, that's kind of neat."

11-01:22:44
Burnett: Is it one of your grandchildren is starting at UC? Is that correct?

11-01:22:48
Benet: No, he's a senior at Michigan.

11-01:22:50
Burnett: He's a senior at Michigan.

11-01:22:51
Benet: Applying to graduate school now.

11-01:22:52
Burnett: Oh, wow.

11-01:22:53
Benet: Yeah, yeah. My oldest grandson is a senior at Michigan studying pharmaceutical sciences and applying to graduate school now for next year.

11-01:23:01
Burnett: That's exciting. Yeah, yeah. And what's the age ranges of your grandchildren?

11-01:23:07
Benet: So he's twenty-two and the youngest is eight.

11-01:23:13
Burnett: One of the interviews I did, the background, I asked, "What are some important things I should know about Dr. Benet?" and they said, "One of the things you should know is he's really a family man. Family is so important to him. He'll stop on his way from one conference to another if it's close by to where some of his grandkids are. He'll stop over and visit." So can you talk about I guess the work-life balance of someone who's as busy as yourself?

11-01:23:58
Benet: Well, I really felt it was important to be there for my kids when they were young. And so I always lived close to the university when the kids were young. So come home for dinner, you'd be there for dinner, they'd go to bed and then you'd come back [to work]. So I did that a lot. And also in my first job in Washington State University. It was very easy to always be home for dinner and to interact with them. And we'd travel a lot and we'd take our kids a lot of places around the world and that's good interaction. We're big on teaching while we travel. So yeah. I'm kind of surprised that someone said that because I didn't know that was a recognized trait.

11-01:24:51
Burnett: For the people that know you well, they know that family's really important to you and that you take time for your family. You wouldn't necessarily know that. If you look at someone – we were joking earlier about the size of your résumé, like physically the size of it. And I think that you might make assumptions about someone with that level of activity, of professional activity, about what kind of time they have for the rest of the life that is not sort of on the clock.

11-01:25:25
Benet: Okay. So we're very proud of our kids and our grandkids. They're all good and Carol and I feel that what we've done, that that's been a priority. That we want to make sure that they have a good life and a good environment. And so we're proud of it. No divorces. [laughter] Everybody's still together and the kids are all doing well in school and nobody's in jail.

11-01:25:55
Burnett: Excellent.

11-01:25:59
Benet: One of the things, though, I think was important. We did talk about this with our kids. Because we traveled so much and lived in different countries so much, we really sort of broke the bonds of our kids with their friends. The family was a really important unit. More like a European family because we were always together and dependent on each other. So we never felt we lost our children or our grandchildren to their companions. In a lot of families that's what's happened. And the father's not there or the mother's not there. We thought about it. We thought about it all the time.

11-01:26:45
Burnett: Us against the world.

11-01:26:46
Benet: Well, it wasn't us against the world. We do things together and we enjoy it. The whole family together enjoys it. And that's why we just took our granddaughter to India with us. The trip that we went to India, we took our elder granddaughter with us.

11-01:27:04
Burnett: And how old is she?

11-01:27:05
Benet: She's sixteen.

11-01:27:06
Burnett: She's sixteen and seeing India. Wow. That's an experience. You've mentioned offhand leisure pursuits, like an interest in music, and I think Carol is more interested in music.

11-01:27:25
Benet: Right. Well, Carol is. They did this thing on the UCSF magazine where I got featured in the Graduate Division and they asked me what my hobbies were. I didn't list any hobbies. But what I should have said, because my hobbies really are ballet. I had it alphabetical. Ballet, opera, theater, symphony. Symphony, theater, and running. Those are my hobbies. Because I go every night. Because Carol's a critic we go to things all the time. Yeah.

11-01:27:59
Burnett: Oh, so can you talk about her? She's an opera critic?

11-01:28:01
Benet: Well, she's an arts critic.

11-01:28:02
Burnett: Arts critic. Okay.

11-01:28:03
Benet: Okay. So she's got a PhD in comparative literature from Berkeley and at one time she was the academic placement advisor at Berkeley. In other words, guys get PhDs at Berkeley and they want to find a job? That was her job to be the academic placement advisor. Really for everybody. People that came to see her were primarily the liberal-arts people as opposed to the scientists but some scientists came, too. But she's a good piano player. She's a good musician. She's really good. And she's been the critic for the local newspaper in Belvedere-Tiburon, it's a weekly newspaper called *The Ark*, since 1975.

11-01:28:43
Burnett: Wow.

11-01:28:44
Benet: And so she does the arts. And she doesn't do Marin. Somebody else does Marin. She does the city [San Francisco] and Berkeley. And so we're going to things all the time.

11-01:28:55
Burnett: That keeps you busy.

11-01:28:55
Benet: Yeah, right. Right.

11-01:28:58
Burnett: But you are interested in the arts, as well? This is something—

11-01:29:02
Benet: Yeah, I am, too. I had an undergraduate liberal arts English degree and I was a musician also. There's a lot of things. Opera was *my* passion. That was what I liked when I was young. I attended opera and actually served as a super at operas in Cincinnati when I was a young kid in high school and stuff like that.

11-01:29:25
Burnett: You served as a—

11-01:29:27
Benet: Super. Super. The guys that hold the spears and stuff like that.

11-01:29:33
Burnett: You were like the extra.

11-01:29:34
Benet: Yeah, yeah. You're on stage and you're doing something but you don't have any lines. You don't sing and stuff but you march in, you march out. [laughter]

11-01:29:41
Burnett: Oh, that's wonderful. That's wonderful. So there's a passion for the arts that you can fulfill. And, again, it's a question of making time I imagine.

11-01:29:53
Benet: Yeah, but we do it. My wife is a terrific reader. She leads book groups and stuff. And I do pretty good. I read also. I still read non-scientific stuff. [laughter]

11-01:30:11
Burnett: I wanted to leave this open for you to have the last word. Is there anything you'd like to talk about in terms of your career or the path of UCSF, the direction that it's gone?

11-01:30:26
Benet: Well, it's just I'm very lucky. I'm a very lucky guy. Everything works. And I work hard. There's no doubt about it. But I get so much benefit from what I do. Yeah. So many nice things. Like this. This is a really nice thing that doesn't happen to everybody. So this is a great place to be and I've said it on videos and everything. This is a very interactive campus. Me or my students can approach anybody here and say, "We'd like to do this," and they help you and they come to our labs and they help us. And we help them. So it's a pleasure to be here. It's also a really hard place to get in so all of your students are terrific and, as I said before, I don't really need to know anything. I just say, "Just do something and then give me the credit for it." So that's good. And you get ideas and the students take it and the post-docs take it and they run with it and do wonderful things. And I think I'm a good consultant. It's

easy for me to look at a set of data and see things people haven't seen before. I'm really good at that. And to understand or see implications that people didn't think about before. So that translates over in consulting. It also translates over in research. And I think it's why I sort of see what's in there and this is what the general belief is but maybe it's not right. That's, I think, my own capabilities and so I'm proud of that. But it's just so much fun. I get to do so many things and I get so much recognition for it. And in addition I get all this business stuff that I get to do, too. So I couldn't have a better life. Yeah.

11-01:32:29

Burnett: Well, thank you very much for your time.

[End of Interview]