CHEMICAL HERITAGE FOUNDATION

GEORGE B. RATHMANN

Transcript of an Interview Conducted by

Arnold Thackray, Leo Slater and David Brock

at

Philadelphia, Pennsylvania

on

16 and 17 September 1999

(With Subsequent Corrections and Additions)

CHEMICAL HERITAGE FOUNDATION
Oral History Program
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Chemical Heritage Foundation
Oral History Program
315 Chestnut Street
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GEORGE B. RATHMANN

1927 Born in Milwaukee, Wisconsin on 25 December

Education

1948 B.S., Physical Chemistry, Northwestern University
1952 Ph.D., Physical Chemistry, Princeton University

Professional Experience

3M Company
1951-1955 Research Chemist
1955-1958 Research Manager
1958-1965 Research Director
1965-1969 Group Technical Director
1969-1972 Manager X-Ray Systems

Litton Medical Systems, Inc.
1972-1975 President

Abbott Laboratories
1975-1980 Vice President, Research and Development, Diagnostics Division

Amgen, Inc.
1980-1988 Chairman, President, and Chief Executive Officer
1988-1990 Chairman
1990-present Chairman Emeritus

ICOS Corporation
1990-2000 Chairman
1991-2000 President and Chief Executive Officer
2000-present Chairman Emeritus

Hyseq, Inc.
2000-present Chairman, President, and Chief Executive Officer

Honors

1987	Gold Medallist Biotechnology CEO of the Year
1988	Gift of Life Award, Illinois Chapter of the National Kidney Foundation
1988	Annual Recognition Award, Washington, DC, National Kidney Foundation
1988	Annual Recognition Award, Los Angeles, National Kidney Foundation
1988	Gold Medallist Biotechnology CEO of the Year
1990	Entrepreneur of the Year, Los Angeles area
1992	BioPharm Achievement Award
1995	Glenn T. Seaborg Medal, UCLA
1997	California Lutheran Honorary Doctorate
1997	Bower Award for Business Leadership
1999	Biotechnology Heritage Award, Chemical Heritage Foundation and BIO

ABSTRACT

George Rathmann begins the interview with a discussion of his family background and childhood years in Milwaukee, Wisconsin. At an early age, Rathmann developed an interest in chemistry, which was partially fueled by both his elder brother and brother-in-law, who were chemists, and his high-school chemistry teacher, Mr. Leaker. After high school, Rathmann attended Northwestern University, where he later earned his B.S. in physical chemistry. After receiving his B.S., Rathmann intended to go on to medical school. However, his desire to work on the research end of medicine was strong, and he decided to continue in physical chemistry, receiving his Ph.D. from Princeton University in 1952. Even before Rathmann finished his Ph.D. thesis, he was hired by 3M Company as a research chemist. In is twenty-one years with 3M, Rathmann worked in many capacities, rising through the ranks to become the Manager of X-ray Systems in 1969. Rathmann credits his nurturing and positive experience at 3M as being very influential during his future career. Rathmann left 3M in 1972 to become President of Litton Medical Systems. Disliking the environment and philosophy of Litton, Rathmann left in 1975 to join Abbott Laboratories as Vice President of Research and Development in the Diagnostics Division. Rathmann enjoyed the aspects of managing research and development initiatives. While with Abbott, Rathmann first became interested in recombinant DNA. His desire to learn more about DNA served as the impetus for his career move into the then-emerging field of biotechnology. Rathmann left Abbott and joined Amgen in 1980, where he still serves as Chairman Emeritus. As Amgen's Chairman, President and CEO, Rathmann worked very hard to procure the venture capital needed to start-up a major biotech company. Amgen burst into the world of biotechnological discovery with Dr. Fu Kuen Lin cloning the human erythropoietin gene, which led to the development of Amgen's Epogen and Neupogen. In 1983, Rathmann joined the Board of the newly formed Biotechnology Industry Organization [BIO], serving as Chairman in 1987-88. Working with his colleagues in the biotechnology world, Rathmann felt that his time with BIO was a great learning experience. By 1990, Rathmann felt that he had accomplished all that he could with Amgen and became Chairman of ICOS Corporation. Rathmann concludes the interview with thoughts on his years at ICOS and the future of biotechnology.

INTERVIEWERS

Arnold Thackray is President of the Chemical Heritage Foundation. He majored in the physical sciences before turning to the history of science, receiving a Ph.D. from Cambridge University in 1966. He has held appointments at Oxford, Cambridge, Harvard, the Institute for Advanced Study, the Center for Advanced Study in the Behavioral Sciences, and the Hebrew University of Jerusalem. In 1983 he received the Dexter Award from the American Chemical Society for outstanding contributions to the history of chemistry. He served on the faculty of the University of Pennsylvania for more than a quarter of a century. There, he was the founding chairman of the Department of History and Sociology of Science, where he is the Joseph Priestley Professor Emeritus.

Leo Slater is the currently the John C. Haas Fellow at the Chemical Heritage Foundation in Philadelphia, where he also served as Director of Historical Services from 1997 to 2000. A former research chemist at the Schering-Plough Research Institute, he received his doctorate in History from Princeton University in 1997.

David C. Brock is Program Manager for Educational and Historical Services at the Chemical Heritage Foundation in Philadelphia. He is also currently a Ph.D. candidate in the History Department, Program in the History of Science at Princeton University. In 1995, Mr. Brock received his M.A. in the History of Science from Princeton University and in 1992, he earned a M.Sc. in the Sociology of Scientific Knowledge from the University of Edinburgh.

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INTERVIEWERS: Arnold Thackray, Leo Slater, and David Brock

LOCATION: Philadelphia, Pennsylvania

DATE: 16 and 17 September 1999

THACKRAY: George, we really would like to begin by talking not so much about you, but about your father, mother, and family background. Can you start there?

RATHMANN: Sure. I knew them both! [laughter] I was born in 1927, and I was the fourth in a family of four kids. I was a pretty late arrival. My father was forty at the time I was born and I was the fourth of a brother and two sisters. My mother and father had a relatively limited education. My mother actually went to a finishing school overseas, her maiden name was Blatz. She was from a very prominent Milwaukee family, but of course, the brewery had long since disappeared before I came, because there was prohibition. So the Blatz heritage was mostly one of image, not necessarily of money. Whereas my father was an enterprising young man who decided to leave high school after two years and go into business, I think largely because there wasn't enough money to keep going. So he went and became a businessman at a very early age, and then moved from one business to another, usually from the sales side of the business. But he was very entrepreneurial, much more so than I believe I am. Everything was a self-started kind of activity: it was the granite business, the marble business, and then the insurance business. So the heritage there, if you will, was one of people that were of German background, sort of the typical, hard-working, German family where the work ethic was part of the principles of a good family—a lot of love, and a nice place to live.

THACKRAY: What was the age gap between you and your siblings?

RATHMANN: My oldest sister is still alive. She's thirteen years older than I am. My second oldest sister married a chemist, and that was—as I've indicated to a number of interviewers—certainly important to me. I really admired him. He worked at Eli Lilly after he graduated with his degree in chemistry. Then my brother came along shortly after. He may have been influenced, as I was, by my sister's husband. My brother was seven years older than I was. He went into chemistry and stayed in chemistry for quite a number of years, although eventually he joined my dad in the insurance business. I decided I was going to do it a little differently. I was going to be in medicine, and medicine really intrigued me. But I had no interest in being a physician. I was going to do medical research. It just seemed like that would be a very exciting career. I had mentioned that there are various books that I read, and I happen to remember one, *Microbe Hunters* was influential (1). But probably the most influential thing in my early life

was our chemistry teacher in high school who was kind of cranky, very smart, very demanding, and generally pretty well disliked. [laughter] But I thought he was a remarkable inspiration because he really relished the science. He was not just our chemistry teacher. I was in a school where I had a scholarship in high school, Milwaukee University School it was called, and he taught—as in many of these private schools—general science, biology, chemistry, and physics, the whole bit, and also was the lightweight basketball coach and a few other things. [laughter] But he was good, and I felt truly inspired by—Mr. Leker, was his name. He's long gone, of course, but that was a step toward deciding that chemistry was important to me as well as science. Then the medical side of it was partly because of my brother-in-law being at Eli Lilly, and the idea that he would kind of share with me, you know, all sorts of things that they were doing. I went through his lab once. It was very exciting. And the whole thing of actually trying to find things that would cure people of serious diseases was a very inspiring idea. My brother did not go into medical research, but he was in the chemical field and he actually worked out in New Jersey and at several other places before he decided to go into the insurance business at probably about the age of thirty-five or thereabouts.

THACKRAY: Your brother-in-law and your elder brother, were they bachelor's-level chemists?

RATHMANN: Both my brother-in-law and my brother were bachelor-level chemists. My brother-in-law went on to get his law degree after he'd been at Eli Lilly for about ten years. He became a patent attorney. They were both bachelor chemists.

THACKRAY: And your oldest sister, what did she do?

RATHMANN: Both of my sisters were teachers. They both got married and both ended up with families and long marriages. Both of them were married more than fifty years before they lost their husbands. But there was a big awareness of the education dimension in the family. Obviously, they were both teachers. One taught mentally handicapped, the other one taught fifth grade. So it was really a K to 12 type of education.

THACKRAY: Chemistry and education between them were pretty strong.

RATHMANN: Yes, they were pretty important subjects. In fact, my grandfather on my father's side—I didn't realize this when I was young because he was eighty years older than I was. I did know him for a few years before he died. But he was a teacher at that same school that I went to high school. It was called the German-English Academy at that time, which is kind of a funny thing. The German-English Academy became the Milwaukee University

School. He was a teacher and a well-respected teacher there. So there was a lot of education in the family.

THACKRAY: Did religion have any importance in your parents' lives?

RATHMANN: It was certainly not of paramount significance. My father was a devout agnostic, and my mother always believed that it would be very desirable to have more religion in the family. So with her side of the family being somewhat religious, I was shepherded off to Sunday school when I was about nine. My father didn't object, obviously, but my mother thought this was really essential. I was a pretty devoted student at both—I was a little split personality. I was a Congregationalist and then a Lutheran, and that didn't—oh, excuse me, and an Episcopalian in-between there. So I had something of everything. But the main schools that I attended were Congregation and Lutheran, that is, Sunday school. Actually, I got halfway through confirmation as a Lutheran. But it began to interfere with my high school because I was doing that when I was fourteen and fifteen. I would not call it a religious family, no. My mother, obviously, took it very seriously.

THACKRAY: What were your principal pursuits apart from school when you were in your early teens?

RATHMANN: In high school, I had a couple of objectives. One was not to take courses from really nasty professors, and I managed to miss some awfully good courses that way. But I had a great deal of concern about getting beaten up in classes. I wanted to have the highest grade point average in the school, and I had let that dictate, foolishly; those courses that you could get beat up pretty badly, I just didn't take. I took all the advanced courses that there were. I mean, I took physics and I took solid geometry and trigonometry—those courses. But I did avoid a really nasty American history course that I regretted ever since because it was a great course. So for the most part, I concentrated on science and naturally had to take language courses because of the need, ultimately for science, having had both French and German. It became less important later on. But it was a very, very good school. It's an even better school today. It's now called the University School of Milwaukee, and it involves the merger of three schools, and it is an extraordinary school. We have actually maintained contact with that high school. They're a model school for the state and they do great things in the State of Wisconsin. I mean it's really a remarkable school. We were fortunate. We knew it was a very good school when we were there, and we certainly had a good education. In fact, being a private school, both Joy and I had scholarships. Being a private school, you have the benefit of a high concentration of teachers, to the point where they have time to spend. So I did take calculus, on an informal basis, from my high-school teacher in math who was just an inspired teacher, as far as I was concerned. So it was a very powerful send-off for anybody. I'd strongly recommend it. The benefits of a really good high school can make all the difference in the world, and I certainly was a beneficiary of that.

THACKRAY: How did your ambition, your grade-point ambition fare?

RATHMANN: Oh, I had the best grades in the school! [laughter] Not every time, but most of the time. But I think I was also a frightful teacher's pet. I mean—there was no question about it. When I finally finished my senior year, there were kind people in the school that would reflect for me what I was like during those four years, and they made it very plain: I was a royal pain! Because there would frequently be many, many times where the whole class would be a dialogue between the teacher and George. I thought that was pretty straightforward and normal. The rest of the class thought it was normal also, but weird. I think I was viewed as fairly weird because I took everything very seriously. I can't say I enjoyed school. It was very easy for me. So I suppose I enjoyed it a lot more than if it had been hard for me. But it was a good school and I think the personal opportunities were really remarkable. You could get help from just about anybody any time. They volunteered their time, and it was primarily in math and science that I got the extra attention. In fact, I sort of did penal servitude for Mr. Leker. I took care of his garden and I took care of his plants in his greenhouse and, in turn, I got a lot of private attention whenever I wanted it. I wanted to understand what the word "isotope" meant—I remember that—it just perplexed me. What could an "isotope" be? And I think he had a little trouble explaining it to me, but he was perfectly happy to take the time and try and straighten out this kid that had just learned something about the Periodic Table, but hadn't learned quite enough yet.

THACKRAY: Were your sisters and brother like that at the school, or were you an aberration?

RATHMANN: There were some aberrations—but I wasn't it. My sisters were outstanding students, both of them. My brother came along later and went to the same school they went to. He was an aberration because he decided his role was troublemaker. He was very, very smart, but he just found it was more fun to be smart and cocky and get the teachers upset. So he was the bad boy in the family, and I knew that, too. But I also knew he was very smart. He was a smart guy. He spent a lot of time with me. I got a lot of personal growth from a very, very understanding brother who was seven years ahead. So he would dose me up sometimes with the latest things that he was learning, and I felt privileged to have the chance to hear somebody take the time with me and explain to me what those things all meant. Usually, it was in math and science because he was like I was: very interested in math and science. So that's true. I shouldn't overlook that. That was a fortunate situation to remind me of. My sisters were enough older. By the time I got to that age they were off in college and married before—I think they were married when I was thirteen or fourteen, thereabouts, so my brother was still in college but at least I'd see him on weekends and so on.

THACKRAY: Did you have manual dexterity in experimental pursuits, or was it theory, as it were?

RATHMANN: No. My lab work was always good. I was kind of lazy, so I would try to figure out shortcuts in the lab and sometimes that would backfire and I wouldn't probably do the best work that there was, but I was very satisfactory in those terms. I was interested in lab work but I had a lot of interests in school. I had a lot of sports interests, and I really tried to minimize the amount of time—that was through Northwestern [University], too. At Northwestern I was taking many lab. courses—I had a major in chemistry and I had a minor in physics, a minor in math, and a minor in biology. When you have that much physics and biology, as well as chemistry, you're taking an awful lot of lab courses. I was on the track team, and I was interested in intramurals, and some of my labs got short shrift. I'd have a three-hour lab—I'd be out of there in an hour or an hour and a half so I could get out to practice or do something else. So I probably didn't distinguish myself. You actually see it on your grades. I'd get an "A" on course work, and an "A-" on the lab, and that was kind of a pain. So I wasn't remarkable. I never was remarkably good at independent research. I didn't enter into contests. They weren't so common then, like Westinghouse and things like that. I don't even remember when they had them. But I never attempted to do an independent experimental program. I had to when I was at Northwestern in the honors program, and I did an experimental program and I actually achieved a publication from my senior thesis (2). But it was not remarkable. It was certainly not an inspired piece of either theoretical or experimental work.

THACKRAY: You didn't—back in the slightly earlier, high school era—sort of have chemistry sets, backyard explosions, and so forth?

RATHMANN: Well, that I did. Yes, it was written up in one of these articles: the playing around with explosives. That was irresistible. It was absolutely irresistible. When you find out that you can take a metal and you can put it in water and you can blow up the hydrogen that's being generated, and then you can find it can be sodium or it can be potassium or it can be lithium! Good Lord! You're suddenly catapulted into just the most exciting dimensions. I don't know whether it's the noise or whether it's just the remarkable chemical phenomenon that you're witnessing and the fact that you have control over this. I never even came close to having any kind of an injury or anything like that. I was actually pretty fastidious in how I did these things. But I had some pretty good-sized explosions. There's no doubt about that. A friend was injured playing around with white phosphorus. I didn't like white phosphorus. I was more of a metals man [laughter] sodium and potassium. I loved to use zinc and hydrochloric acid. I was fascinated by the concept that water is made up of hydrogen and oxygen and that you can duplicate the oxygen of air with the oxygen you pull out of electrolysis. From my brother-in-law, I learned how to electrolyze water and take AC to DC, so you have direct current so you can separate the gases. It's not so hard. Sometimes you can put them both together, and then they're all ready to blow with a match. The two areas that I did the most in were electricity and chemistry, and chemistry was—with malice, a fore thought—to have

something quite impressive. And actually, although I ended up impressing my future wife to some degree, I impressed other men. I was more boy-oriented than women-oriented when it came to explosions. We were just bad boys. That's all. We just thought it was more fun than anything to make a lot of noise. Never had any encounters with police or any encounters with injuries. We were spared. Although I look back and I think, "Boy, I probably shouldn't have been doing some of the things I did." But they weren't that bad. It was usually little chunks; maybe of something like 50 grams of sodium or potassium, wrap it up in paper, so you kind of keep the hydrogen around a little bit. You kind of optimized the circumstances for the blow, and then you'd throw it down the sewer or you'd throw it somewhere where you're a fair distance away when it goes off. Some experimental activity I did do. Useful experiments, I can't recall having done many of. [laughter]

THACKRAY: Where did the sodium and so on come from—the school lab?

RATHMANN: Oh, now, that's a terribly unfair question, Arnold! [laughter] Naturally, we sent for it through the Internet! [laughter] No, it turned out that we thought Mr. Leker wouldn't mind if a small chunk of sodium disappeared from his lab once in a while. That's where it came from. We did buy some things in the store. You could buy mercury in a store, which we did. I can't remember what I was doing with mercury, but I know I remember buying mercury. Maybe just fascinated by it—maybe trying to build a manometer or something else, I can't remember. But yes, the chemicals were procured from the chemistry lab.

THACKRAY: Seeing your academic prowess in science at that age—this is remote from both your father's and mother's educational experience. Did they approve of what you were up to?

RATHMANN: Well, their attitude about what people in the family should do is they should do what they love to do. That was it. Except for some bias on my father's side that I should go into business, I should do whatever I wanted to do, as long as I was aware that maybe business was a good opportunity. His dream for me, which I never developed or realized, was that I'd go ahead and get my M.D. if that's what I wanted, and I'd get my Ph.D. after my M.D. if that's what I wanted. But maybe by that time I'd be interested in getting an MBA at Harvard, and that was his contribution to guidance, and that would be that I would be interested enough to try to combine the science with business, because he had a great respect for business. He felt that there was a great deal of public service in a business career. He felt he was serving his customers, and took that very, very seriously. So I felt that he really liked the idea that I would then apply what I learned in a useful way, mainly business. I resisted the business thing pretty hard. He wanted me to run his company more than once, and I decided I didn't want to run a business, namely an insurance company, which he had started from scratch, but I just didn't want to do that. I was very excited about 3M by that time. So after I had kind of redirected myself away from medicine into just plain research, which is what my intent was anyway, I went to 3M and got involved in business most back-handedly. It was certainly not a

preconceived idea that I wanted to be a manager or anything like it. That was a big decision later on, a lot later. So I was going to be an M.D. that did research.

Which reminds me, in the thing that you wrote, by the way, there's one thing that I have to correct because it came out wrong once in another article. I was asked how did I change from pre-med into regular graduate school in physical chemistry. What had happened was, I had applied to medical school when I was eighteen, and I did that because I was going to push through three years of schooling in two years and complete my junior year in two years, and at the end of my junior year, hopefully get admitted into medical school as a three year undergrad, which they did do at that time. Unfortunately, the year I tried to get admitted was the year that veterans were returning. It was 1946, and what actually happened was that the class that started in 1947 had a lot of veterans coming back. The classes were full and they said, "We don't need to take a junior, and anyway you're only eighteen years old." Here I was applying to medical school at eighteen and they thought that was really pretty stupid. That's where the eighteen came in. I didn't get admitted then. I was accepted for medical school after my third year in college, which was in 1948. I sacrificed my fifty bucks and didn't go to medical school, because I just felt that they had done me in. I'd gone to Northwestern primarily because of its great medical school. I'd had a good average all the way through. A very good average. I averaged about A- in college. I just felt they ought to have admitted me. I was a conscientious person. I didn't see any reason not to. I couldn't understand not making it. I didn't apply to any other schools, so by the time I realized I wasn't going to be admitted to Northwestern, it was too late to apply to another medical school. So then, when I was accepted, after my third year, I had been spending a lot of time with my advisor in college. He was a very good guy and he was very encouraging and thought I was a super candidate for physical chemistry—he was a physical chemist—that I had the kind of brain that would be great for physical chemistry, much better than all this medical memorization. I said, "Well, I just like this medical thing." He said, "Well, you weren't going to do medical. You weren't going to be a physician anyway. Why don't you go on and do the research side and if you want to, go back and get your M.D. afterwards, as long as you're just going to do research?" So I thought, "Well, that's not too bad a plan." So I switched over.

But the decision to go to pre-med was very simple. Suddenly I just thought there's nothing more important than medical research. I actually haven't ever changed from there. I do believe that is true. It was just a question of how to get the education necessary so you could do medical research. I thought the pre-requisite would have been the M.D. But the error that's in there was that I received my bachelor's degree at eighteen. I did not. I got my bachelor's degree in June of 1948, at which time I was actually twenty. But I would have gotten into medical school at nineteen, which would have been kind of fun, but they wouldn't let me in.

THACKRAY: So Northwestern was a no-brainer for the reasons that you mentioned?

RATHMANN: You mean going to Northwestern?

THACKRAY: Yes.

RATHMANN: Yes. It was really a very simple thing. It had a wonderful reputation at my high school. A number of graduates had gone there so I had a first-hand feeling that it was a good school, and as compared to the University of Wisconsin—I think today you'd be hard-pressed to say which medical school is better, but in those days, it was clear that Northwestern's medical school was considered exceptional compared to University of Wisconsin. Those are two schools about the same distance away from Milwaukee. I didn't have any huge appetite to go across the country or anything like that. Actually, I had a lady friend in Milwaukee at the time and I liked to be fairly close. She was my future wife, of course. So she was still in high school for one more year, and I went on to Northwestern. But the main thing was the medical school.

THACKRAY: Your father's business was doing well? Were there any financial issues?

RATHMANN: Well, it was interesting. When I got that scholarship—I got a scholarship to Northwestern—my dad's income was extremely modest. It was so modest that I could get a hardship scholarship, yes. Dad had taken an awful beating during the Depression. He'd started a department store in 1927, bought into it in 1928, and got more and more into it. Actually, he was not hit by the crash as much as he was by Sears & Roebuck moving in down the street from him, and he just got wiped out; I mean, we see that today. I bleed every time I see a Wal-Mart destroy six little companies. I just think, "There for the grace of God, goes my dad," because that's what happened. Here was a neat little department store, and all of a sudden, Sears moved in right on the same streetcar line, but six blocks further on. He said he watched his customers go by on the streetcar and that was it. So he was wiped out. The department store was dissolved and he lost all that he put into it. Then he started in the insurance business, and that was a nightmare because nobody could afford buying insurance when the crash came. Nobody could afford to buy insurance in 1930 to 1933. So those were tough years. Now I didn't go off to college until 1945, but he hadn't adequately recovered from the Depression, as the country had not adequately recovered. Right through the beginning of the World War [II] there wasn't much recovery from that Depression. We kind of forget the fact that the World War actually, in a sense, was timed for taking us out of that Depression. So he had suffered, struggling in the insurance business for those years, and then finally he emerged—when he spotted group insurance as a possibility and got into that—as a very successful insurance person and actually started an insurance company. But he started the life insurance company when he was sixty-five. So we had tough years, and when I applied for Northwestern, it was not hard to get a scholarship. That was straightforward, because his income was so low.

THACKRAY: How did you brother make it through?

RATHMANN: My brother worked his tail off in college. He actually did not have a scholarship because he wasn't that great a student. As I say, he was a nice, neat guy, but he certainly didn't have the academic credentials, so he'd take on jobs. He was the guy in the family that would carry three paper routes when he was about thirteen—very young. Then he got off to the University of Wisconsin. He went actually to State Teachers College in Milwaukee, which was largely free because it was a block away from our home. But then when he finally was able to figure out how to get to Wisconsin, he had several jobs in Wisconsin. He had four jobs and he worked at a hotel there, and he just sort of crammed a lot of things in. So he paid his own way all the way, for every bit of it. I didn't pay all mine, although I also did work when I was at Northwestern. I had a Board job and I graded papers, and I did some tutoring. But it wasn't enough to cover everything. I had a scholarship, but I still couldn't cover all my ongoing expenses. So it was a relatively modest drain on my dad. I was actually supported for the extra expenses from the family, but the scholarship was possible because his income was so low.

THACKRAY: All of this sequence must have been very tough on your mother.

RATHMANN: It was. That's a very interesting observation. Because you remember, my mother was a Blatz, and as I said, the Blatzes had gone beyond the point of being a prosperous family, but they were recognized as being very prosperous in Milwaukee. The brewery took its awful beating during prohibition and the family lost control of it and never extracted any assets from the brewery after about 1922. In 1922 my grandfather lost his job as president or something and the thing was going down the tubes, and other people took over the business. So there was no asset there, but there was a lot of pride, and it was difficult for my mother when things went badly. She was a very wise, very, very sharp lady, but she couldn't quite handle the idea that my dad should be able to expand his office when he was trying to grow. Yet she had to be very parsimonious with funds and we lived in a rental place. We just rented, always. My dad never owned any of the property that we lived in. I mean, there are other values that are much more important than your economics, but I think they were tough times for Mother, yes.

THACKRAY: Was your mother enthusiastic about a medical career and your academic record?

RATHMANN: Well, there was no doubt that my concept of doing something in medicine was extremely exciting to my mother. I mean that was inspirational. I mean there's no doubt. She wasn't that enthusiastic about the business world anyway, and the thought that there were three of us in science was very exciting for her. She liked that. The education and science dimension—that's the mother input. The business side, you can see where that came from! [laughter] Both were needed, if you're ever going to do something like biotechnology. Obviously, you have to have the excitement on both sides.

THACKRAY: Yes. In Northwestern, between the physical chemistry and helping to earn your keep, I mean, that must have taken up most of your time. Did you have any time for recreation, diversion as an undergraduate? Also, what age were you when you actually went?

RATHMANN: Well, I actually graduated at twenty, and during that time, I did a lot of things. I mean, school was always easy for me. As I say, I actually could cover a three-hour lab in an hour and a half, usually—now, probably sloppily. I don't mean I was wonderful. It was just so I'd get by, and I'd do it well enough to get a good grade. But I never had to spend a lot of time on homework and stuff. That was not a big problem for me. So I was in every intramural sport that there was. I played touch football, we played basketball, we played baseball, and I was on the track team, and I don't know, I thought I had lots of diversions. I don't recall much in the art dimension, for example. Oh, yes, interestingly enough, I did go down to the Chicago Symphony a number of times. It wasn't that far from Northwestern. But I certainly wasn't really active on anything but school and school-related activities. That was true. But it was pretty broad.

THACKRAY: Were you living on the campus?

RATHMANN: Yes, I lived in a dormitory on campus the whole time at Northwestern for the three years I was there.

THACKRAY: Backtrack a little. You mentioned Joy a couple of times.

RATHMANN: Well, Joy was out at Skidmore [College], and she was a diversion during vacation times, but other than that, we didn't get to see each other very much. She was one year behind me when I started college. She was two years behind me because I went through in three years. We did get to see each other more when I came out to Princeton. My first year at Princeton was the last year of hers at Skidmore, so we got together quite a bit that last year. But I never dated anybody in Northwestern. That's probably a good point. I had probably more time than the average guy because my date was 1000 miles away! [laughter] So that sprung for some time.

SLATER: You met in high school?

RATHMANN: Yes. She was a freshman and I was a sophomore. She came in as a scholarship student in her second year. That sometimes happened in that high school. You didn't get in the first year. You'd get in the second year. She came in the second year. I was immediately charmed. There was no doubt about it. But we didn't date until I was a senior. But she was the

first person I ever dated. That was a big thing in my life that I finally got kind of blackmailed into asking her for a date, and I finally did it, and she accepted finally, and that was the beginning of a relatively long period. [laughter] It's going to be fifty years of marriage this coming June, so it's been a long time.

THACKRAY: Just pause and talk a little about her family background.

RATHMANN: Yes, that's interesting. I don't know how relevant, but it's an interesting background. She was an orphan at the age of two. Her father had served in the First World War—these things today are more anecdotal than they are reality, but at the time it was believed to be reality—and he been given exposure to poison gas in the First World War, and he ended up with a brain tumor. The linkage, which I'm sure medically could not be proved by any manner or means—if you think about Agent Orange and all the rest of the stuff—the assumption in that family was that he contracted the brain tumor as a result of being exposed to gas. It was a dreadful period of about a year of rapid deterioration. It turned out that Joy's mother was so totally devoted to trying to keep him as comfortable as possible during that year that she eventually was badly weakened, got strep throat, and died before he did by about two months. So within an absolutely short span of time, two-year-old Joy was made an orphan, and does not remember her mother or her father. She had a sister, and we still know the sister and they're good friends, but she basically had no family. Her grandparents raised her, one set of grandparents, then another set of grandparents, and finally two cousins, as the grandparents, of course, died. So her childhood was not a wonderful childhood. We contrast it all the time that she doesn't look back on that childhood as something that was wonderful—not through anybody's fault; it was nature that dealt her some tough blows.

THACKRAY: This was in Milwaukee?

RATHMANN: That was in Milwaukee, yes.

THACKRAY: She was of German background?

RATHMANN: No. She's Scotch-English. Yes. So we met when she was a freshman. She came to our school. I'd heard about her before because my best friend had liked her; he had known her before. So I'd heard about her, and when she came and I saw her, I was immediately charmed. There's no doubt about it. I liked her right off the bat. I don't think it was necessarily reciprocal. It took about three years before there was any reciprocity, probably for good reason! [laughter] I was kind of finky in those days. As I say, I learned from my friends what a fink I was later on. But I don't think that ever bothered Joy. I think she liked me as kind of an eager-beaver student. I think she thought that was kind of nice. So we enjoyed each other

right from the first day we met, but we didn't have any dates or anything for a couple more years.

THACKRAY: Just follow that trajectory forward a little. That is, when did you get married? What did Joy do after Skidmore?

RATHMANN: Yes. Well, what happened was we dated when I was in high school, and I went on to college, and she stayed back, and being Northwestern, it was kind of convenient, so we maintained that relationship. It was a little more strained when she was out at Skidmore, but we certainly corresponded like every day, practically. Then I went to Princeton, and during that last year, we saw a lot of each other with the plan of getting married as soon as she graduated, and we did. She graduated in 1950 and on June 24, which also was the day the Korean War started, we went off on our honeymoon from Milwaukee and did not realize the war had started because we went up to the Keweenaw Peninsula in Michigan, which is rather isolated. We got to the newspapers about the third day and there it said, you know, "War this" and "War that." We thought, "What are they talking about? These papers are nuts up here!" But we were at war with the Koreans, of course. That first year, then, was my last year at Princeton. So she'd graduated. I had my last year at Princeton. She worked during that time, even though she was pregnant very quickly. On our first anniversary, two days before that, she gave birth to our oldest son in Princeton. She stopped working on my thesis, which was a real blow because she'd been doing all the artwork for my thesis, all the graphs and charts and everything. So I had to finish up on my own and it was kind of nasty. But then I did submit my thesis and it was accepted, and so that was my last year (3). I completed my orals, final orals in September, but by that time I was already hired by 3M. We of course had been married for a year, we had a young one about to arrive, and we made the decision that we would go to 3M because 3M sounded like it was just a very exciting company. We liked the idea of being back in the Midwest and Minnesota was exciting. It was a good year. I had the choice of about ten different companies.

So the Princeton period was a nice period because when you got to Princeton, one of the first things that everybody did, is they went to the library to read the story about Princeton's philosophy of graduate students. It was that one: they will screen the graduate candidates very carefully; two: if they were right in how well they screened them, then all of them should be capable of graduating, and they would. So you'd have to do something exceptional not to graduate once you got into Princeton; and three: there was no reason in the world for you to stay more than three years for your doctoral degree. The idea of holding onto these people as slaves for four or five or six years was not good. Boy, you read this after you got there, and you were very glad you came to Princeton. You'd think, "This is about the best place in the world," and it turned out to be that way. It did take just three years to get through. It was a <u>fabulous</u> place to learn. I mean, just wonderful. Of course, I really went there in part because I thought I might see [Albert F.] Einstein somewhere along the line. I really did! It's embarrassing to think back how naive you are. I did see Einstein, and it was exciting. So it doesn't sound as if it might be to the average person. I would go past the Institute for Advanced Study every day, and I would

drool thinking about what's going on in there. At one time or another, most of the key people would present at colloquia and seminars and so on. So I saw Einstein quite a number of times and many of the others that are really extraordinary scientists who were there. The Institute was just something you just marveled at, the brainpower that was there. It was quite remarkable and I don't know if it's been matched ever since, because it really was an amazing place. Einstein walked around the campus in his smock and that's the way he looked. He was usually escorted—I think it was his sister that escorted him around. He never made a comment at any symposium or colloquium that I was at when he was there, but it was still just a miraculous feeling to be in the same room.

THACKRAY: Just go back, if you would, into Northwestern. You mentioned earlier the person recruiting you to physical chemistry.

RATHMANN: Yes, that was Professor [Robert L.] Burwell, and he was a Princetonian. So I don't think he'd like to be referred to as having recruited me. He simply gave me very sound advice, that his alma mater, Princeton, was the best place to go; that physical chemistry was clearly my career path, and that objective information was provided to me by my counselor at no extra charge. I was, therefore, guided very strongly into applying to graduate school. He was broadminded enough to suggest that I might even want to apply to some others, which I did. I applied to [University of] California and Caltech [California Institute of Technology] and MIT [Massachusetts Institute of Technology] and, oh, about six or seven. So he covered the waterfront, but he made very sure that I applied to Princeton. When I got my Princeton acceptance, he sort of suggested that I wouldn't even have to wait for the others. So, it wasn't a hard call. I was fairly pressured—the University of California was really on me over and over again that it would be a great place to go to school. Caltech turned me down, which later on was a little bit embarrassing, because I had so many good friends at Caltech when I was at Amgen. I didn't want to tell them that I wasn't good enough to get into Caltech! [laughter] That was a heck of a blow! I never did understand it. There was something missing and people don't always enlighten you. I would have liked to have understood that one. But every other place accepted me and beat up on me to try to get me to come. Princeton was not the most enthusiastic. They gave me a relatively prompt acceptance, but they didn't do anything remarkable to try to say, "This would be a great place for you." They did not afford me a scholarship. They did give me a teaching assistantship right away, which was standard at the time. You ordinarily would expect to have your costs of graduate school paid for. Then I did get a scholarship later on, but in the beginning I had a teaching assistantship initially, and then I got a research assistantship. The research assistantships were perfect because what you did was, you did nothing, and you were compensated for it. You did the research you had to do anyway, and that was a nice set-up. So, Princeton was a super place. But I don't think there was anything wrong with Northwestern. When I got to Princeton, I realized that the physical chemistry that I'd had, the organic chemistry I'd had, and the analytical chemistry I'd had, the whole thing was first quality and there was nothing that was left out. And the same thing happened to me from high school. When I left high school to go to Northwestern, I found out

that I cruised right off the bat. So education is so important. I mean, you're a privileged individual, mostly because somebody took the time to give you the education.

[END OF TAPE, SIDE 1]

THACKRAY: Somewhere in that sequence from late Northwestern, you really were pretty much defining yourself as a physical chemist: "This is what I'm going to be when I grow up."

RATHMANN: Yes, that's right. I had really stopped thinking about medical research and had become captivated in a few other disciplines of physical chemistry. One of them that was most exciting was polymer chemistry. There was a man by the name of Arthur Tobolsky at Princeton who was actually a relatively lazy teacher. He was so lazy [laughter] that one day the bell system was off and it rang off schedule. So our class started at 11:00 am, and the bell happened to ring at 11:10 am for no reason, and he dismissed the class! [laughter] As far as he was concerned, he'd done work for the day and by gosh, it sounds a little short today, but it looked all right for him. [laughter] But he was really smart, and he was absolutely inspirational. What he did was bring us into an awareness of why polymers—basically, he did in that course for us in polymers what chemistry is now doing for biotechnology in the speech that I'd like to give. That is, polymers are some weird bunch of stuff—you couldn't dissolve them; you couldn't work with them; they were strange things. And how do you make them? Is it all just luck, just like you cook some ooze together and, like [Charles] Goodyear, you cook stuff up and sometimes that gave you a benefit? What he did was, he showed us the theoretical underpinnings—which are chemistry—behind [Wallace Hume] Carothers, primarily. Carothers was the scientist that invented both nylon and polyester when he was at DuPont [E. I. DuPont de Nemours and Co., Inc.]. In a short period of about three or four years he did all this, and he did this with a tremendous theoretical foundation, and then extraordinarily sophisticated experimental work, because what the theory tells you is, you've got to have highly purified materials. Experiments told you how to actually execute that, and so what happens is that you get nylon in the first experiment that you ever ran in that direction. So it was just so inspiring, because you had this insight and understanding about things you'd seen all your life, but you had no understanding about them, and now you see exactly how they were made, why they were made, and the huge advance that was made possible by that kind of superb science. That was the inspiration. So I decided to be in polymers; so I shopped around at different companies.

Again, those were very nice years. The years when I was looking for graduate school they were hungry for people, and when I was looking for jobs, they were hungry for people. In 1951 when I went looking for jobs, I was offered three different positions at DuPont, and offered a position at 3M and Dow [Chemical Company], and oh gosh, just everywhere I ever went I was offered a job, except one place, American Cyanamid turned me down. American Cyanamid just happened to have a guy there that didn't like Carothers and I just raved on about Carothers. He was just absolutely opposed to him, because I think Carothers had gotten a lot of credit for some stuff that this guy thought that he was really entitled to. [laughter] So that was

the worst interview I've ever had in my life. [laughter] He didn't like me. But every other place, it was easy to get a job, and so why would I pick 3M? I picked 3M because first of all, my brother had told me that 3M was the greatest company in the country. That was big! Here was my brother talking to me when I'm twenty-two saying, "This is the place you ought to pick." So I was still very susceptible to influence by someone I really respected, and he just said, "This is a great company." He'd worked with them when he was at Kendall Oil. They had been exchanging some materials back and forth, and they had done some experiments together. He just said, "They're just a bunch of wonderful people." The person that I went to work for was the man that my brother had actually interacted with at 3M Company; he offered me the job and I took it. It was never a mistake. 3M was just a great place to go to. My own interview trip to 3M told me I wanted to be there because they were doing such extraordinary things. I mean, they were just all over the place in terms of innovation and I just thought, "Wow, this place is alive! This is really what you want." They also offered me the most basic job that I was offered in polymer research. So I could study the structure of polymer molecules by light scattering, by viscosity, by osmometry, by all these techniques, and really begin to understand the molecules of polymers and how they worked and how they filled space and all the rest.

THACKRAY: George, this is your Ph.D. dissertation abstract (3)—

RATHMANN: Oh! Good God! [laughter]

THACKRAY: I've looked at it, but I must say it's not—

RATHMANN: I can't understand it either, so—[laughter]

THACKRAY: What essentially did you do in that?

RATHMANN: Now, this is not a very inspired thesis. I did some inspired things with it later on, but at the time when I did the thesis work, I was getting my Ph.D. That's what the purpose was. What happened was that there was a Professor [Charles Phelps] Smyth, the brother of H. D. Smyth, who was of physics fame, he was—"C. P. Smyth" they called him, "Chemically Pure" Smyth [laughter], and he was just a wonderful person. He brings tears to my eyes whenever I think about him. He was so neat—just a super gentleman, you know. He was not an inspired, creative individual, but he was extremely careful, extremely knowledgeable, extremely kind, very thorough, and a wonderful man to work with.

What had happened was, it gave me a free ride almost, and I shouldn't really fail to acknowledge that, because what happened was that he had managed, over a period of five or six years—recent years—had adapted his background in dielectrics, dipole moments and dielectric

relaxation to be in tune with the new technology that had come along, which we now recognize as microwaves. What he was clever enough to see, was that the availability of microwave equipment, with reasonable reliability so that you could actually work with microwaves of various frequencies, might make it possible to learn about the structure of liquids, and the motion within liquids, because the frequency of microwaves were of the frequency of the relaxation time of these molecules, namely how fast they moved was roughly in sync with the variations and the oscillations of the fields. So he set up a series of experimental procedures at various microwave frequencies, usually measured in wavelengths, instead of frequency, you define the wavelength. He had 1-cm., 3-cm., 5-cm., and 10-cm. equipment. He also had very low-frequency equipment so he could get that. Of course, refractive index is measured at very high frequency, that's light frequencies. So you have the standard frequencies, and therefore it was his belief that that should give you insight into being able to look at molecules and see exactly how readily they moved.

So what we did was then, given that existing equipment—I had to revise my piece. I had the 1 cm. I had to revise it slightly because it wasn't really working all that well when I got there. But I didn't have to do much, I had a piece of equipment and I had a thesis. I mean that's what it amounted to. I could make measurements on this equipment, and as they always say, "Organic chemists make terrible measurements on pure compounds, and physicists make very precise measurements on impure compounds." Guess what physical chemists do! They make imprecise measurements on impure compounds! [laughter] But we did better than that. We had really nice equipment and with some upgrades, it worked very effectively. And then what we did was, we pooled our information. So I would measure at 1 cm., someone else would measure the same liquid at 3 cm. and at 5 cm., someone else at 10, and someone else at longer frequencies. Then what you could do is, you could see where the dispersion occurred. In other words, where was the energy absorption maximum? That was the clue as to what was the average rate of motion of those molecules.

So you could say, "Well, gee, I know the molecule is this big. Is it going to spin fast or slow?" Well, if it's small, it's going to spin faster than if it's big, except if there's internal rotation, so I get some insight into internal rotation; except if there's hydrophilic bonding that's going to slow it down. You begin to make all these correlations between structure and what's going on in the liquid state. Whether it had any profound implications for anything anywhere, I don't know. Actually, it had some implications in proteins and things like that that we never applied it to, but we just did organic liquids, and we went pounding along. My big contribution was, that I decided that since there were some pure chemicals available from a guy down the hall that represented long-chain esters—I knew he had these long-chain esters—I decided to put them in my equipment. The prediction would have been that they're so big that they won't relax in time for us to see anything. But you knew that there was some free rotation in there so it might work. So I just tried it empirically and it worked beautifully, right smack in the middle of the right range, and we learned a lot about these long-chain esters and the effect of rotation. So that's what we ended up writing up. My contribution was esters and alcohols. Somebody else got interested in the halides and so on. So we pooled all of this information and we published quite a number of papers with Charles Smyth doing most of the author work because he was a heck of a fastidious author (4).

THACKRAY: You acknowledge here A. [Alexander] J. Curtis and P. [Patrick] L. McGeer. They were also graduate students?

RATHMANN: Yes, they were. That was the team. In other words, Curtis had 3 cm., McGeer had the 10 cm., I believe, another scientist had the 5 cm.

THACKRAY: So Smyth really had a little group.

RATHMANN: Yes, he had a bigger group than that. He had about two others that worked in the field at the same time.

THACKRAY: The Princeton Ph.D. program in chemistry at that time, how big was it?

RATHMANN: It was very small. There were eighteen kids in our class, of which nine flunked out, defying the little instructions we got at the beginning. I think we had a particularly bad class. I don't know why. Certainly some of the people that flunked out were not really as strong candidates as they should have been. Some of them also had complications in their personal lives and so on, so we had a fairly high mortality. I think it was even more than nine that flunked out—it was very small. Our class of eighteen people was very small, and I don't think it was that much bigger in any of the other years. When you're there for three years, why, you have two other classes you're always there with. I don't think any of those were any larger.

THACKRAY: Have you kept in communication with the successful cohort graduating people?

RATHMANN: Very few. There are a couple of people that I see periodically. The one that I've seen the most is P. L. McGeer. He's up at the University of British Columbia [UBC] and he's doing medical research up there. McGeer went to DuPont, and then he went and got his M.D. after being at DuPont for several years. Then he came out here and became a member of Parliament up here in British Columbia because he's a Canadian. Then he went into medical research at UBC. He and his wife have published many times. He met her at DuPont. So I've kept in very good contact with Pat McGeer. He's quite a remarkable guy. He was on the Canadian Olympic team, and it was partly Pat that made us compete in graduate school. We competed in all the intramural sports and beat everybody! [laughter] But that's because he was a remarkable athlete; and very, very nice. Al Curtis died, and another party, Don Pitt, actually came to 3M eventually, and I don't know what happened. I've lost contact with him. But I maintain contact with Pat McGeer. There are some other members of the class that are well

known in science, and I've seen them when I attend certain symposiums and things like that once in a while.

THACKRAY: I was wondering, regarding the move to industry: did you think of academe? Was Princeton in the air for your career or not?

RATHMANN: Ah, it's interesting. I never did figure it out, Arnold, but I had the feeling that Princeton was very anxious to have a few academic scholars if they could get them. But I don't think they felt I was a suitable enough academic scholar to go out of their way to make sure I stayed in the academic world. I don't know. You see, no one ever said to me, "Don't do it." But no one ever said to me, "Do it." So I went along with the herd. In our year, I don't know of any that went into academic pursuit. It was a very, very easy year to get jobs. The closest thing that anybody came to an academic job was, one of the guys in the group, his name was Bob Crowe, and I know he did die. Bob was kind of pushed by Charlie to his favorite place, which was Murray Hill Labs for Bell Labs. So Charlie would pick one guy each year, and Bob Crowe was not the smartest guy in the lab by a long shot, and I don't know whether Charlie Smyth knew this, but he was the hardest working. Bob Crowe was in that lab fifteen hours a day. I mean—it was just like what you sometimes see in a lot of different graduate schools, which was not common at Princeton. I would work on weekends, but I didn't work all night very often, very rarely. But he did, and I think that suggested that he would be the guy that goes to Murray Hill Labs, and he did. He went to Bell Labs. I'm pretty sure he died at a relatively early age. So that's an interesting question as to why we weren't more attracted, or why we weren't guided, or why we wouldn't think about an academic career. I gave it no thought.

THACKRAY: That's a big switch from your high-school days, as it were, isn't it?

RATHMANN: Well, I don't know. I think maybe there were some other factors here. I'm sure my father had—the concept of being an M.D. was top drawer in our family. The concept of being an M.D. plus an MBA, that was really great. But the idea of going into an academic career was not in the minds of anybody in the family. My brother and brother-in-law had both gone to industry, although they didn't have their Ph.D. I have a feeling that Princeton did guide a few people into an academic slot when they really thought they had remarkable capabilities as independent researchers. I did not distinguish myself as an independent researcher. I think we did some clever things, but it wasn't like very clearly a calling. I certainly didn't distinguish myself as a teacher, in any sense. I don't think anybody had anything against me, but I do know that when I was teaching in the labs there, the fellow that was my partner—his name was James Affleck. Jim Affleck was two years ahead of me in graduate school—and he became the Chairman and CEO of American Cyanamid. If there's any correlation for success in business and being a clown, I think the two of us probably epitomized that correlation [laughter], because we had one hell of a good time! When we were doing the lab supervision, we didn't make anybody mad at us, but he concocted a game that we used to play that involved taking corks and

spinning them like this and then hitting them with your hand. We did this right during lab. While the kids were all working with their notebooks and everything else, here's Affleck and Rathmann playing cork baseball. [laughter] So I probably didn't distinguish myself as a teacher. [laughter] The other thing I did, which was much more innocuous and I think a little bit more credit to me, was when I had another lab mate, named John Shellman. I have not kept track with him. He was the smartest guy in the school. John Shellman and I, when we were lab partners and teaching, we played three-dimensional tic-tac-toe without a piece a paper. I can't do this successfully today, but I did it every single lab day. We'd go in and we'd say, "3A4," which is the third one over and four down—and then the other guy would go "3B2" or something. That would position an "X" in that three-dimensional cube. Then the next guy would come back until a tic-tac-toe, and we never had a dispute. It's like playing blindfolded chess, which I can do, but rather badly. I could play that game very, very well. It was great, because now, you see, it wasn't so obvious as hitting a cork around the lab, [laughter] because you could horse around and not be noticed by anybody. [laughter]

But I don't know, there's something about success that requires people to have a lot of enthusiasm, probably a certain amount of humor, and I think those are factors that are way underestimated in terms of what's important for success. I'd hate to guide kids into hitting corks around the lab and say that's the way to be a successful person, but I have a feeling that there are a lot of characteristics that correlate positively with success, and certainly Jim Affleck was one heck of a success. And his successor at Cyanamid was George E. Sella. George E. Sella was the best football player that we had in the school at the time I was there, at Princeton. So you know, there are some other factors that we don't view. Now, in certain academic pursuits, I don't think that they correlate that well. I think that what counts is just exactly what you expect—a guy that's very, very smart, concentrates very heavily on narrow objectives, and so on. But some other characteristics are interesting. Anyway, I think Princeton—as far as I was concerned—was a fully acceptable place. The process of getting your degree was pretty straightforward—the course work was very effective, professors were, in general, quite dedicated professors—again, you had small classes; a pretty nice place. But we were quite active on the social scene in the form of intramurals, because Pat McGeer insisted on that. He had to have his sports going on continuously. So we probably were the beneficiaries of a pretty healthy environment.

THACKRAY: Polymers was kind of a pretty active and hot field at that time, I think. You mentioned Carothers. There was [Paul J.] Flory.

RATHMANN: Yes, Flory came by. Paul Flory was actually a pretty good friend. The other guy that we saw a lot, in fact one of my best friends in Princeton went there; Allan [R.] Shultz went to—oh, what was his name? Dr. [Walter H.] Stockmayer, a theoretical guy up at Dartmouth [College]. So we got acquainted with them. You're right. There were a lot of prominent people in the field of polymers because it—like biotechnology—sort of matured with these new insights into why they were the way they were. And that's true. It was an exciting time for polymers.

THACKRAY: Everybody was hoping that they'd "do a nylon," as it were—commercially.

RATHMANN: Yes. Well, what we did when I got to 3M was—my first interest was to understand structure-property relationships. So why does a polymer behave like it does? Why is one sluggish and one elastic? And what's really going on if you put a plasticizer in there? What are the molecular mechanisms by which these things are changing? And why is natural rubber the only good rubber for tires? Which it turns out not to be, but at the time it was the only really good rubber for tires. During the war you ended up with reclaimed rubber and it was a disaster. Your bicycle tires were rupturing all the time and they didn't have the tensile strength—and what is tensile strength? All this stuff where you got a basic interpretation and understanding was exciting and fun.

SLATER: Do you recognize this paper?

RATHMANN: This is [Marshall R.] Hatfield's work more than Rathmann's. He was a neat guy. I forgot all this! Yes. I wonder why he put me on this paper (5). He did most of the work. Yes, that's interesting. Paul Flory came by, and I presented to Paul Flory the work on the light scattering of fluorochemicals (6). We had a lot of fun. He was a great guy. Right. Exciting times.

SLATER: Were there other areas of P-chem that seemed particularly engaging alongside polymers?

RATHMANN: Well, you see, the amazing thing is that if you take a microwave study like I did when I was at Princeton, and then you study light scattering, the equations, much to my surprise—and boy, did I look good at 3M—the equations are almost identical, so you go through the same sets of equations. They're very complicated equations, but you've gotten so familiar with them that it's very easy to apply to light scattering, what you've learned from the microwave studies that I did. So in physical chemistry, practically anything is exciting for me because I'm going to understand what's going on. So whether it's kinetics, or thermodynamics, or molecular structure, you always feel like you've got a running start to understanding it, and it's very stimulating. So that's what these things were all about. I've seen publications—I sent one to Marsh Hatfield about six months ago—publications as to why adhesives behave the way that they do. It's never been totally clear why everything is just the way it is. But there are new insights all the time. We had an approach that was unusual, that came out of Princeton kind of thing, which is using absolute rate theory to explain adhesion, but the whole process by which you relate the physical properties of an elastomer to how it's going to behave as an adhesive give you very interesting insights. All of a sudden you sort of get the feeling, "I know how to

make a better one. I can see what it takes. I have to have certain properties that I have to achieve." I don't know, it's just, that was why physical chemistry is so fascinating for me—any part of it. If you're looking at studies of light, electricity, studies of chemistry, electro-chemistry, anything; you tend to just be able to get one step further into understanding than you might have done if you had done more of a phenomenological type of examination. That of course is what made biotechnology so exciting, I mean, I loved biology! I was a minor in biology in college, and the part I didn't like about it was all the empiricism and all the memory and all that stuff. If you didn't remember the interrelationships of a whole bunch of stuff you didn't understand, you couldn't do biology. Look at a cell, you've got this thing to find, that thing to find, that thing to find, and all these things are happening, and you don't know anything about what the molecules look like or what they're doing. All of a sudden biotechnology comes along and says, "You want to know what factor eight is? Here, I'll give it to you. And here's the total structure from one end of the molecule to the other. You want to know what erythropoietin is: a hundred sixty-five amino acids, and I'll tell you what every one is, I'll tell you the sequence, I'll tell you how it's folded, and I'll show you why it behaves the way it does. And you want to know what happens when a receptor gets activated? I'll show you. It couples with another receptor molecule and you've got yourself an activation state and that it phosphorylates something." And wow! I mean, this is really exciting, instead of just sort of saying there's a factor one, a factor two, a factor thee, and you get up to twelve, and you think you know twelve times as much as the guy that only knew about one. Well, you know a lot, but you can't reconstruct. The really bright physical chemists that I knew, and physicists and others, have some of these same characteristics, they can almost start from scratch with anything and sort of deduce what's happening from first principles. And I think there's something very satisfying about that. Where you don't need to memorize everything. You just have to have some principles, and then you can kind of reconstruct what's probably happening and why it's happening, and if you finally get a chemical interpretation of a biological phenomenon, it's there forever. I mean, now you know. That's going to happen that way, and that's why it happens, and now I want to interfere with it. I can start to design the molecules that are going to do that. I don't have to just try them in a whole series of empirical reactions. So, yes, I'd say all branches of physical chemistry I think are fascinating.

Boy, you really dug some stuff out of here. None of this would be viewed as remarkable by anybody. I think some of the insights that I got, which I never published after I did all the work in Princeton, I felt were kind of remarkable, but the work at Princeton was basically an experimental study that was guaranteed to win. I'm going to look at a bunch of liquids, and I'm going to study the relaxation frequencies, and once I find that I'm in the right frequency range, I'm going to have data that no one's ever had before, and I'm going to be able, therefore, to interpret it in ways that it had never been interpreted before. So it's a guaranteed thesis, and I'm not particularly proud of that, but it was not an unastute thing to do, if what you really want to do is get on with your career.

The job at 3M was intriguing because it was so basic, and what they had there—this paper—the 1,1-dihydroperfluorobutyl acrylate one (6). You showed it to me here somewhere. Here it is. The thing was that 3M had acquired the rights to make certain fluorochemicals from Joe Simon's—Simon's fluorochemical cell, and they now could make fluorochemicals [fluorine

containing molecules]. And there were all sorts of unusual properties in fluorochemicals, one of which of course is that it has a very low refractive index, a very low cohesive energy density. You're going to get remarkable properties supposedly out of everything you make that's a fluorochemical. In fact, you do. But the dimension that we were going to hopefully exploit, which we didn't do very well on, was that if you made a fluorochemical polymer, it would be solvent-resistant and be extremely interesting as a gasket for military purposes, where you'd be solvent-resistant and still have very good low temperature properties. Silicones have very good low temperature properties, but they are not solvent-resistant, so you needed something better. Neoprene has very good solvent-resistance, and that was a Carothers product, by the way—polychloroprene. Neoprene has great solvent-resistance, but it has very poor low temperature properties. So these hoses that would carry gasoline—you could handle the gasoline because it was solvent-resistant, but when you got really cold, the hose would break. That's the kind of problem that happened in the shuttle, obviously. So you wanted a low temperature rubber that was solvent-resistant. Maybe fluorochemicals would do that. So, before I got there, they made poly-1,1-dihydroper-fluorobutyl acrylate. They found out that it was a lousy low-temperature rubber; it was sluggish and it didn't bounce. I used to have a chunk of it around to say to people, "Here we're going to have this great rubber," and you'd drop it on the table and it goes "thud" and you know you don't have a great rubber. So what's wrong with it? There must be something wrong. Maybe we're not making the structure, the molecules the right shape. Maybe we're not getting high enough molecular weight. Maybe we're not doing this or doing that. So we made all these measurements to determine that, yes, we were doing things right, and we still weren't there. We then began to explain, because of the nature of the chains that are there, why in fact it would be a sluggish rubber. They turn out, after the fact, you could predict it very nicely as a very inferior type of rubber, and it never made the grade. That one never made the grade as a rubber, but it was the first molecule that was useful as Scotchguard. So that was the break that we got. My assistant had spilled some on her shoe, and came back and said, "You know, I got this spot on my canvas tennis shoe. It just doesn't go away. It's permanent. And look at this: when I put water on it, it spreads away from it." Which is what you expect a fluorochemical to do. What you don't expect is that it's going to stick on there. Another thing you don't expect is that it's going to stick like <u>anything</u>. As a matter of fact, poly-1,1-dihydroperfluorobutyl acrylate had been tried many times as a textile treatment and it always failed. Well, how come we were so successful? Because everybody was so sure it would not stick that they primed the cloth before they put it on and they wrecked it's ability to bind to the cloth. They primed the cloth with fluorinated materials to get it ready for this poly-1,1-dihydroperfluorobutyl acrylate, and then the cloth was already damaged enough so you didn't get a useful result.

As soon as she told me this, I said, "Well, let's coat-up some fabric." I coated up some fabric, and I did it in two different ways. I used a solution and I used the latex where you just dipped it in the water-based latex, and pulled it out. You knew that would be an awfully practical way to do it. And of course, it was. That's exactly what the treatments were later based on, a latex application. We found out that it was very nice and water-repellent. So I sent it over to the fluorochemical group and said, "Try this, you guys. See if you like that." After about a month, I called them again, you know, "How about it?" They said, "Oh, we haven't gotten around to it yet." Then I forgot about it. Then Joanne Mullens, my assistant, came back

to me in about three more months and she said, "Whatever happened to those samples that we prepared for them?" I said, "Oh, shoot. I don't know. I didn't check on it. Let me check again." Well, it was a new guy that just arrived. His name was Bill [William] Peterson, and Bill Peterson said, "I'll run them." I said, "Well, that's a great piece of news. You're going to run them after all this time—they've never been looked at?" "Well, that's right. Never been looked at." So he looked at them, and he said, "They're the best things we've ever seen. How did you do this?" I explained to him how we did it, and he said, "Oh, my God! This is fabulous." That became the basis for developing a whole new polymer family that worked much better than poly-1,1-dihydroperfluorobutyl acrylate. But the whole thing came out of the fact that she was preparing these solutions for these light scattering studies and we were getting very good solutions. We knew how to make the solutions correctly. There were a lot of reasons why those solutions were better than anybody else's that ever were tried before. But the main thing was that the experiment to test them had just not been done even though we tested them and said, "My God! It does look pretty good." They had told us, "No. We haven't tested them yet. We've done it before anyway, so it won't work." Well, it <u>does</u> work and it works very well. So that was a big success out of a big failure. It was a lousy rubber, but it was a great start for a textile treatment. Of course, the whole thing that's fun about 3M, which I think <u>is</u> the prototype for biotechnology companies, is that you had this idea that what you might want to try, you tried. I mean, at 3M if you had an idea to try something, you almost felt like you had the obligation to try it. You never could use as an excuse, you know, that you had other jobs that were more important. There was no job more important than your curiosity, and that was a really, really nice program they had there. I mean, 3M was really remarkable in that regard, and it's a lot like biotech in the way that there's a lot of bottoms-up type of thinking and innovation and energy. I think some people feel you have to push innovation into the organization, and in a lot of ways you just have to let it blossom, and that was the 3M approach.

THACKRAY: How do they manage to keep nurturing that orientation?

RATHMANN: Well, they of course, brag about it a lot. I suppose you get bragging values, it's going to get to people. They really feel that a very important part of the charter for every scientist there is that they have 15 percent of their time—they use that number all the time—15 percent of their time to do independent things that you think are of interest. You're not accountable for that 15 percent of your time. Well, you might wonder how many hours a day and how many hours a month? Or do you do it all at one time—well, they don't tell you that. They don't say, "I want you to use no more than four hours a week," or something like that. They just simply say, "You've got 15 percent of your time." What that means is, it takes the heat off, so that if you really are doing something that's not strictly on the track of your main program, and even if your program is under some pressure, no one's going to come by and slap your hands for having taken the time to look down a side road that you happen to spot was interesting. So that's one of the things.

The other thing is that they have a lot of individual recognition for when an innovation has occurred. They're quite fastidious about how patent applications are filed and how

recognition is given to the people that do things. So you have a lot of incentive to try to be one of those people that's done something unusual. There's a lot of excitement in the company. They consider the real test of a program, how much you learn that you didn't expect to learn, as much as how fast you pursued the objectives that you had. So they consider it a highlight if there is a high, what they call "discovery potential." So if you have a program in which "I've learned this that I didn't expect, and this that I didn't expect," those are hallmarks of a good program.

THACKRAY: Was this research labeled "basic research?"

RATHMANN: It was called "exploratory research."

THACKRAY: And you were hired into exploratory research?

RATHMANN: Oh, I was hired into the Central Research Department. When you did these things, it was called Project 99 Exploratory Research. What I actually did the rest of my time would have been called "Fundamental Research," but it really isn't quite true, because I was fully aware that what we were trying to do was get a polymer that would be useful in hoses for the government. Later on, I was very well aware that we were optimizing a product for Scotchguard. So "fundamental" isn't quite the right word, but somewhere between basic and fundamental and exploratory. I think "exploratory" is probably the best word for when you're doing something that you don't quite know what the answer's going to be, but you hope that it has a commercial dimension. What I did at Princeton was clearly basic research, where it challenged me. Every once in a while I tried to take up the challenge. "Now what have I learned that could affect human society here in some way or another?" Sometimes there's just no obvious, no even un-obvious linkage as to affecting humankind with this work. So all you're saying is "I've learned something and have filed it away and there's a building block here somewhere that's going to build something some day, but I sure can't translate that one building block into anything commercially interesting." I think 3M basically did a lot of exploratory research. Your program was usually an exploratory research program. So I was exploring how you could make a polymer more sprayable. So obviously, a very practical potential, but at the same time, I was examining the light scattering—a whole series of different molecules and how their branches occurred and how frequently they occurred and so on. This one paper that you showed me here is a very good example of not seeing a linkage between an exploratory program and reality.

Many years later, when I got up to Amgen, I interacted with a company called Raychem, and Raychem said, "I know your work." I said, "You know my work?" "Yours and Allan Shultz's, yes." Well, you know, Stockmayer—the guy at Dartmouth, by the way—Allan Shultz worked with Stockmayer, and Stockmayer was a wonderful, wonderful person. I don't know if he's still alive, but he's a great guy, a theoretical physical chemist in polymers. Anyway, so

Allan Shultz and I published on some things that had to do with cross-linking of polymers with radiation (7). Allan was a very bright physical chemist, pretty straightforward, not unusually imaginative, but just gets the job done. He began to correlate what happens when you radiate plastics and rubbers and things like that. What are the changes due to? There's two processes going on: one is you're cross-linking, the other is you're breaking chains. You begin to see the balance of these properties and you can do certain things.

Raychem built a business on that process. So they began to affect polyethylene insulation by radiation to the point where they could have the fusion point of polyethylene, the melting point, because you've got a cross-link, and they knew exactly where to put that in terms of commercial reality. We published on this stuff and told everybody how to do it (7). We knew that people were saying, "Well, if you change polymer structure, you're going to have big benefits. There'll be lots of commercial products." But there aren't just any old commercial products. If you try to affect tires this way and so on, it's totally impractical. But little tiny connectors that are in electronic circuits—that's where this becomes very important. It changes the penetration temperature, so this thing will stay intact as it heats up to 100 degrees. Otherwise, you've shorted it out. That was Raychem's whole business. It was kind of funny to see. I realized, suddenly, that asking yourself that question over and over again: "Is there some way in which this has a really important implication for human beings?" It is always worthwhile, because you really feel stupid when you've worked in a field for a couple of years and you've missed it completely that there were immediate implications to something of great importance.

Well, I think we're getting close to the time when I'd better start getting ready for this afternoon. What day will we finish this? Tomorrow, at noon?

THACKRAY: All right. Good.

[END OF TAPE, SIDE 2]

SLATER: We were, I think at 3M and research and development there. If you wanted to maybe expand a little bit on your career at 3M.

RATHMANN: Sure. Well, I joined the company, and I picked the person I wanted to work for, I picked the company I wanted to work for, and I picked the program. I was lucky that all three coincided. The company was 3M and it had a wonderful reputation. I liked the idea that they were in magnetic recording tape, something really quite revolutionary, and had the chance to get exposed to it. Scotchlite reflective sheeting was something that impressed me that glowed back at you, and I didn't understand the optics of that, because that's not supposed to happen. If light hits an object at glancing blow, it's supposed to bounce off that way, not back to the source, and they had to control the optics to make that. So that's pretty clever. And they had a whole bunch

of other products. I was very excited about the company because of its tendency for innovation and generating novel new ideas.

There was a particular individual, a very bright guy, [Frank A. Bovey], who eventually left the company and went to Bell Labs to do independent research in health care, in medical things. That had an influence on me at that time, because at the time I thought, "Gosh, he's such a great polymer chemist. Why would he go back and start to do basic science in medical directions?" I couldn't quite understand it until later on when I got re-bitten by the medical bug. But he was a very wonderful scientist in the sense that when we had our interview, when I came to 3M, the interview was entirely about real things. In other words, "We have this problem. How would we improve the elasticity of a fluorochemical? What kind of structure would you think would be better than this structure, which is one of our structures here? Now, what would you do to make it so it would be stronger?" All sorts of questions like that. And "Why would it be as sluggish as this?" So we actually kicked around ideas, and I know that I impressed him because I was willing to embrace his problem and try to contemplate ways to solve it. They impressed me that this is a lot more interesting discussion than telling me how great 3M was and a lot of platitudes and about a lot of sort of philosophical stuff, which, by the way, can be awfully important, too, but this was impressive. He was absolutely dedicated. As a matter of fact, they called him "Eager Beaver Bovey"—his last name was Bovey, as you noticed on some of the publications. He was just so intense. Everything was exciting to him. Every piece of science was exciting. He was a little bit cynical about the business side of the company. He felt that researchers were never paid enough, they weren't treated well enough; kind of a little chip on his shoulder, which I wasn't that sympathetic with, because I kind of felt like we have a pretty good deal; we get to do what we want to do and get paid for it. That sounds pretty good to me. But he was a little cynical, other than that, he was a wonderful, wonderful supervisor. I have not kept up with him. When he left town, he left to go to Bell Labs. He really had reasons to go out of town. I think he was getting a divorce, a whole bunch of stuff. So we never followed up. I was just lucky that I found those three things all in one place, the right company, the right boss, and the right program.

So, when I started out, it was a matter of doing studies of basic molecular shapes of polymers, and following the principles of Paul Flory and [Paul M.] Doty and a number of the other key people at that time. I found myself learning about the structures and then being able to get some insights into what to do to change structures. So one of the things we figured out we could easily do is make a sprayable adhesive that had never been sprayable before. We knew exactly what to do about how to do that and change the strength of an adhesive by modifying structure and so it was a great deal of fun.

It was true that I had a boss for whom I had a very high regard, who was the guy that gave me my first promotion. He came by and he said, "You know, Frank Bovey's leaving. We're going to have to replace him. Have you ever thought about being a manager? Or would you rather have a Nobel Prize?" I thought that was kind of an interesting thing. I said, "Well, hands down, I'd rather have the Nobel Prize." He said, "Well, if you become a manager, chances are you're going to be going down a path in a way that you will never again be able to pursue the other pathway." I said, "Well, I'm not likely to be that successful with the other

pathway anyway." I said, "I guess I'd accept being a manager as something that I could try and see what happens." He didn't know that I had a father that probably relished the idea of being a manager more than being a scientist. So I think he was afraid I might have found it repulsive to be a manager. I didn't at all, but I wasn't at all sure that that's something I was going to be good at.

What he did was, he split up the group and said, "You can manage part of this, we're not going to take that full a chance on having you try to do the whole job." He also said that he looked very hard for somebody else to fill these shoes, that they tried to recruit from outside, and they hadn't found the kind of person they really were looking for. So kind of by default, I was made a supervisor, not a manager, of part of the polymer group, and that was the beginning of a pathway that never stayed very steady. I was a supervisor, then I was a section head, and I was a section head of polymer and physical chemistry. Then there was an opportunity to go into the tape group as a research director reporting to the group as a whole. Then there was one thing after another, and I never had a job at 3M for more than about three years at a time, and that I found probably was the necessary part of the stimulation of keeping me there for twenty-one years. Somebody was smart enough to figure out that I probably needed stimulus. So the career at 3M was just an awful lot of fun right from the beginning. There was evidence, I think, that the company took a lot of pains to make sure that if they think you were doing a good job, they really let you know that you were doing a good job. So that was very stimulating, and you had this enormous amount of freedom. There was no question about it. I could start a program tomorrow, if I limited my time to 15 percent, and one way of looking at that is that 15 percent is roughly a sixth of your time. There's twelve months in a year. If I wanted to, I could take two months right now for this year, and I did that. I would rationalize that I could go and embark on something. So this whole idea of how you make a sprayable adhesive came about by virtue of my thinking that it would be a fun thing to figure out how to do it. I had a relatively conservative boss [Dr. Al Borders], the one who put me into the job, who would ask questions like, "Why are you doing this? [laughter] You really think you're going to be able to do anything useful?" At the time, I wasn't that sure. It just seemed kind of an intriguing thing. So he had a little bit of discomfort, but he had a great deal of faith, and so he was helpful, too. That was the boss that was still there after Frank Bovey left.

So I had many mentors. I notice one of the things you people ask about is mentors. I'm always a little suspicious of a mentor relationship because I think it can be a dominant one, I think it can be painful, and I think you can have all sorts of associations. I think if your mentor begins to look like your father, one of the two of you is going to have some problems, unless you had a perfect relationship with your dad. I happened to have had a perfect relationship with my dad, but with people that I've tried to mentor, sometimes I encounter this fact that I'm suddenly getting attributes I didn't need, which are kind of baggage from some prior part of this person's experience.

I was a little bit privileged because I was viewed as having performed well. The 15 percent mandate at 3M was tied a little bit to when your programs have generally gone pretty well. You weren't supposed to take 15 percent if you were on a critical program and it was falling way behind. That wouldn't be a prudent thing to do. But most of the time things worked

out for me well enough, and I thought my performance was good enough that I had the ability to just branch into things that just fascinated me and hoped I could convince people later that what I was doing was worthwhile.

But the other thing about 3M is, you did not have to—they called this "bootlegging"—but you didn't have to literally bootleg; you didn't have to be illegal, or so surreptitious that no one knew you were doing it. You could bring it out and share it with your supervisor and with others that you were investigating these kinds of things. So it was a great set-up, and there was a lot of stimulation because the other thing 3M had was a strong commitment that a very significant percentage of their sales was going to come from things that were introduced into the market in the last five years. So you knew that if you're going to keep doing that, you're going to have to start stuff that you can't predict beforehand where it's going to be and how effective you're going to be. So there has to be a fair amount of latitude. The other thing that was a fundamental principle at 3M is that 3M-ers should be allowed to fail. It's an official pronouncement, in those words, and I've got them on my slides, by the way. "3M-ers should never be afraid to fail." The idea is, if you're going to be encouraged to take high risk programs, you've got to have it that you're not going to be beaten to death whenever you take one that didn't work. In fact, William [L.] McKnight who—talking mentors—was certainly not my mentor because he was Chairman of the Board when I got there, but when I interacted with him I found it to be a wonderful, wonderful experience. He was a down-to-earth, very soft-spoken, but very powerful individual. He ran the company for quite a number of years, and had had a fifty-year career with 3M and worked his way from accountant right on up to the top. He had great confidence in research, great confidence in the initiative of the people at 3M, and great awareness of the importance of not being punitive when people make mistakes. That was the thing. He said, "We've got to be so careful because as we get bigger, and that's the challenge in getting bigger, we're going to be finding out that we're going to be suppressing risk-taking because it's so easy to sit in judgment as compared to joining the individual and be on his side of the equation—that he tried and he learned something." That is the question that we would be asked at 3M. "Well, what did you learn? Gee, that didn't work out. What did you learn?" And if you learned something, that's the end of any despair about that.

So I thought there were some wonderful, wonderful philosophies at 3M. I've embodied them in the talk that I was planning to give today. I actually mentioned quite a few of them. One of them is, "Policy is a point of departure." When you get to a company in which policy is the last word and the managers and executives and even supervisors can lean on the word "policy" and say, "No, you can't do that. It's outside of policy." At 3M, you couldn't make that statement because the person would come right back with, "Wait a minute. I thought policy was a point of departure." Which means that in this particular case, the "policy" may not be the appropriate course of action. Now, I admit I'm not going to just embark on something the company feels is a bad thing to do, but I'm going to have a chance at least to do that. So those were some of the philosophical things that I thought were underpinnings to why 3M—and to answer your question: how could they sustain these levels of innovation over the years? Of course, when I go back to 3M, and I've given a few talks back there, I found out they feel they've lost it compared to what they had. They think there's much more bureaucracy and resistance to some of the exciting ability to start something new. Yet, I think for its size, 3M is

still absolutely remarkable in the number of things it does and how really different things are. I mean, there are many things that they showed me on my last trip there a couple of years ago that I just thought were vintage 3M. That's where you'd expect that sort of thing to start. Some guy starts to make micro-surfaces. What's he going to do with micro-surfaces? Don't even ask what micro-surfaces are. When you finally find out what they are, you'd say I'm never going to find out anything useful for a micro-surface, in which I've created a surface of pre-determined structure that I can create by certain techniques that he had, and what do I find? My God! It becomes a very unusual abrasive. It becomes an interesting optical material. It becomes a reflective material that outperforms Scotchlite. On and on and on and on for this guy that does this. Another guy says, "I'm going to make webs of stuff." Why are you going to do that? "Well, I just think it's going to have lots of benefits." The first thing was going to be brassiere cups, of all things. And then they turned out to be—I don't know, people got into their business a little bit too closely—face masks. You know, this sort of thing. Success breeds success.

That's the other thing that you learned very clearly, and that is, if you want to analyze why morale is bad, and then try to figure out what to do to correct morale, you could spend an awful lot of time dwelling on what's wrong with your company and it doesn't work. What works is having some successes. So if you say, "Come on, that's not very logical. If I have success, I have high morale. And if I have high morale, I'm going to have success. But how do I get into that cycle?" You've got to start it with success. You can't start it by scrutinizing what caused your bad morale, because it just seems to me that takes your morale down the tubes. I haven't heard that in so many words from 3M, but I do know that success breeds success. When you get a few good things and everybody shares in the good news, that section and that department has some good news—we're all winners. We're all winners. Then pretty soon, it spreads. And I think that that's how they sustain the level of innovation. So, not being punitive, and rewarding success, and sharing success, I think those are all things that they do very well.

SLATER: In some sense, you learned to be a manager at 3M. How did you find that experience of learning that as opposed to other kinds of learning you've done?

RATHMANN: You know, for me, it never bothered me that there were no formal management training courses. There were some later on, in the later years that I was there, but the first fifteen years I was at 3M, I don't think I took a single formal course. I never felt that I was missing anything because there were plenty of role models, and I liked the concept of role models better than mentors. I believe that I can look around me, and if I'm perceptive, I'm going to learn all the things I'm going to have to know because I see how that fellow performs and how that person performs and how that male or female, not important—they're role models if I see things that seem to happen that are good that seem to result from certain qualities and I can make linkages. And if I'm perceptive, I'll do this. I don't need someone to tell me, "Now, did you notice how he did this or she did that?" So it was clear to me that there were people I really respected, that I could picture myself trying to emulate. They ranged from people like William McKnight, the soft-spoken Chairman of the Board, who on one occasion made a very simple summary of a very vigorous and painful discussion in which the lawyers were on one

side, the scientists were on the other, and he said, "Well, I realize why the scientists here don't want to take on that company in a lawsuit, but, I'm listening to both sides of this and I'm afraid what we're going to have to do is go ahead, but let's not make it a rancorous lawsuit. Let's see if there's such a thing as a low-profile lawsuit. I know that's very hard, but, I think that's what we're going to have to do." And the most soft-spoken, even-handed, wonderful way in which you could see he weighed everybody's comments very, very carefully. I was just dazzled—wow! How would you like to be a Chairman of the Board that had the wisdom that that guy has? It just seemed like a wonderful thing.

There was another guy [Richard Drew] who I felt was a wonderful role model. Not a mentor in any sense. But a role model in the sense that he was the guy that was responsible for more innovations at 3M than anybody else—one thing after another. You couldn't help but want to find out how he did this. You could ask him, and he'd tell you. I used to say, "How do you get so many good ideas?" I've got a slide on that. You know, "Where do all these good ideas come from? Where do you get these ideas?" Transparent tape, masking tape, Scotch-Brite, facemasks—I mean, you name it. He was responsible for a dozen of these things, and he had the same explanation for all of them. He said, "You encourage people to do things that are new and different." Well, you say, "Well, what? You encourage just everybody?" "Yes." "Everybody?" "Yes!" "Well, what if it's a bad idea?" He said, "That's great! Let's encourage it anyway. The guy will rush down toward the goal, and he'll come to the end of this blind alley, and he'll come tearing back knowing it was a bad way to go. But, you drag on him and slow him down and challenge him, it'll take him forever to find out it's a bad idea." So he said, "No! Just encourage everybody." You say, "It can't be that simple." Well, this guy proved that it was. I mean, he just came up with stuff over and over and over again. The idea was, you're going to be smart enough to know if it's a bad idea. I don't have to tell you that before you start. If I challenge your idea too early, I'll kill some good ideas.

So there were so many people in the company that you could listen to and learn from. I never was aware, other than I had the feeling that I had wonderful examples to look at; I never had the feeling I was being trained as a manager. 3M did use the expression "On-the-job training." Maybe that was just sheer rationalization for not spending the money on education and training, but they really zealously believed that you could go into a lot of formalized stuff. In fact, Dick Drew himself, the guy that invented Scotch Tape, was very cynical about a lot of formal training, including Ph.D.'s. I felt I was very privileged because he'd talk to me. Most Ph.D.'s he didn't have any time for because he figured that they'd already stunted their innovation capabilities completely by having so much formal education. But if you could convince him that you were kind of open-minded, then he'd be willing to talk to you. So I think that the role model idea was an easy way to become, I think, quite proficient in management skills. It also speaks well for the kind of style that I think is most fun to be part of, and that is a kind of a bottoms-up style, where the people that are making the calls on what's good and what's bad and what's interesting and what's exciting to pursue are the people that are doing the pursuing, not somebody looking at it from a loft somewhere.

SLATER: Did you have much R&D contact outside of Central Research, or outside of 3M? I mean, consultants' meetings?

RATHMANN: You mentioned two types. Within 3M, they recognized that it was very important to fix responsibility, so they had varied numbers of divisions, but let's say twenty-five divisions, and the responsibility was fixed. This is your division, this is your job. Don't worry about the rest of 3M. You get your job done as the general manager. I was not a general manager, but that's the mentality of a divisional structure. However, they recognized also that there are some risks that you're going to have competitive activities between different divisions, maybe lose the synergy that you could have by the strength of 3M, so they wanted to have some feeling of responsibility across the structure. What they did was, they organized themselves in such a way that all of the technical directors who were like vice presidents of research for each division, all of the marketing directors, which were like the vice president of marketing for each division, and so on—they would have formalized sessions together two or three times a year, and they would frequently be off-site; many times at the lodge that 3M had up in northern Minnesota. You would become very closely affiliated with the rest of the people that were in your corresponding position in other parts of the company. So that was a very strong fabric that they wove into the structure that otherwise would have been self-standing strands or silos, and I think that was very important. The general managers also had a council and the council would meet several times a year, off-site again. So there was a structure there that cross cut the individual divisions.

As far as outside the company was concerned, the company was very cautious about publication. It was not understood that every scientist had the right to publish every time he wanted to. That was far from the 3M system. It was a bit secretive, and there were some people that were offended by this. They felt that their light was being pushed under a bushel because they didn't get a chance to go to every important conference and tell the world everything they were doing. But the incentive once in a while—it was kind of a reverse incentive—that induced you to do the kind of research which was not linked to something practical so that then you could claim there was no big loss if you published it. On the other hand, that particular strategy was fraught with risk because your boss was in a very good position to say, "Let me understand, again, why you want to publish this? It's because it had no relevance to anything we're doing here? Now, is that exactly your position?" [laughter] Well, you kind of hesitate to take that position because you'd get caught with that one. On the other hand, if you say, "Oh, no, it's really got a lot of relevance," then you can't publish it. So it was a tricky area.

But I did present many publications, you know. As you can see, I had quite a few publications and even more times, more informally, would be asked to participate in a Gordon Conference, which was like heaven. You'd go off to New Hampshire and you'd have like three days of vacation because it's so beautiful there, and very stimulating because you're kind of in an elite group that's talking about some subject that not everybody can understand. So it was quite an impressive opportunity when it came. But I think in general, scientists in industry are relatively insulated from national and international recognition. I think the price that's paid there is when companies like an Amgen are started, it is quite likely that the head of scientific

activities for the company, or the head of the company as a matter of fact, will be selected more from academic people who have much broader visibility around the world than some person who might have been doing a great job in a company, and is truly hidden from view. So it was kind of an unusual circumstance that someone like who I was, actually got involved with the people starting Amgen. When I watch the recruiting going on for who's going to start a company, it involves people who have a lot more visibility than, let's say, a research and development director at a 3M company division. That guy's buried and he's out of—he has virtually no contact. Once he gets to be a head of a research activity, he doesn't even have these kinds of publications. These may have predated his becoming an executive by five years or something. So you're out of contact, and there are a few cross cutting organizations around the country for young executives. But I never got to the level where those people were, where I was participating. The Industrial Research Institute, for example, is such an organization; it's people meet and get acquainted with each other. But even that, they're not in the stream of things as a candidate for a CEO position. I think it's an oversight. I think maybe it's to the benefit of companies that these people are kind of held out of the limelight, but I think it's kind of too bad, because some of those people are wonderful candidates. In other words, when I've thought about it, I think of 3M and I think there's probably not a junior executive at 3M that couldn't run a biotech company very, very well. Except people don't know about it, and that person probably is pretty comfortable up in St. Paul, and so you know, it doesn't happen.

SLATER: Can you say a little about leaving 3M to go to Litton [Medical Systems, Inc.]?

RATHMANN: God! The less I say, the happier I'll be! [laughter]

SLATER: Yes, I've gathered that from some of the materials I've read.

RATHMANN: All right, sure. Well, after having literally vowed I'd never leave 3M because they were so wonderful to me, I reached a stage where I was so much more interested in medical things than in other things, and 3M is primarily not a medical activity. So the jobs that were likely to emerge for me, if I were going to get promotions to general-management level, were likely to be in adhesives or abrasives. As it was, I was in photographic. I suddenly yearned for something that was more vital from a health care standpoint.

SLATER: Your last slot at 3M was in the Medical Imaging.

RATHMANN: Medical x-ray. So I took on a business-oriented job in medical x-ray, and that was very exciting for me, and it really whetted my appetite for being heavily into a medical field. If I saw that that business was going to grow and be one of the biggest businesses in 3M, and it was—it did grow, and it was an interesting business—but I recognized that the next step

would be a different kind of an assignment, and very likely it would be—and there were people angling for me in some other areas. And very likely I was going to be faced with, "How would you like to head up the chemical division? How would you like to head up something in adhesives or abrasives, or something?" I didn't think that was a very attractive idea.

So when I thought that I could really expand my role in the medical field, with medical x-ray and other types of equipment, ultrasound, and other things that Litton was doing, that combination was just like my original decision to come to 3M. It looked like I had all things. The company that I was going to go with was exclusively medical. The boss that I was going to work with was Alan Enthoven, one of the brightest guys in this country even to this day. The area I'd gotten acquainted with—the x-ray field—was extremely exciting to me because x-ray was in the process of a revolution. It was growing from very slow, hand-dipped films and all the rest to automation and much more rapid response, a ninety-second processor and things like that. Then of course the revolution that really came, which I didn't predict at all, was the revolution of CAT scanning and other ways of doing imaging that goes far beyond x-ray.

But it looked like a perfect fit to me, and the other dimension that was important was, I was going to be a General Manager <u>now</u>. Not in two years, not in three years, not in some place where I wasn't sure I wanted to do it, but right in the place where I wanted to be. I was going to be made a General Manager. That was President of what was called Profexray, and later on we changed the name to Litton Medical Systems. So it was the right-level job as well as these other factors. So it was just about perfect.

What I had overlooked was the nature of the company itself, Litton versus the nature of 3M. Although this particular part of Litton was medical and fitted that bill of the right company, Litton was the <u>wrong</u> company for me. Litton, at that time, was a conglomerate that had expanded rapidly on the principle that there's a lot of synergy between divisions, even if they don't know each other and don't know what they're doing. The principle of conglomerates had seemed to be established as a wonderful way to expand your business because you could buy stuff relatively cheaply and then benefit from the price-to-earnings ratio of this growth stock that you were and actually enhance your growth rate. The equation is quite simple. It's an economic equation, it's not a science equation, but the economic equation is very clear. If you buy something with a price-to-earnings ratio of ten, and you happen to have one of thirty, immediately, your earnings go up for the amount of money you've just expended. So the number of shares that you have to put out is less than the average number of shares you have for every dollar of earnings. So your earnings go up per share, and it looks like you're doing something very smart. All you've done is bought a company that's got a very poor price-to-earnings ratio. [laughter] So it's self-fulfilling in a way.

So anyway they rode higher and higher, and the stock was up in the hundreds, and then it started to fade. When I joined, the stock had dropped to thirteen, and I got my stock options at thirteen, and they said, "You're only going to get very few because these are so valuable." I was just dumb enough to argue but not to do anything about it. I said, "Four thousand shares is not a lot of stock options at thirteen." They said, "Well, it was just a hundred recently, so that's like, you know, a half a million dollars." I said, "Yes, if it goes to a hundred, but how do we

know it's not going to go down?" They said, "Well, there's no chance of it going down." I said, "Fine." I was a real jerk! I said, "Fine. Why don't I take half my shares at the price of the stock a year from now? If you're so sure it can't go down, I'll take half the shares at that price." They said, "That's a foolish thing. We won't let you make that mistake." Well, a year from then the stock was at seven, and the year after that the stock was at three. So it didn't guarantee that it was going to go back up to a hundred. But that was an indication of the problems at Litton. Litton was having problems in every direction. They had problems at a big government ship building installation that they were running for the Navy. They were off schedule and they had punitive actions there. They had bought these marginal companies that were all bought for the wrong reasons that no one understood. They had enormous pressure on the presidents. So what's the good news? The good news was that, as the President of this division, I came up a learning curve that was straight up because I had to try to perform under the very, very worst conditions possible. The company's products cost too much to make. They did not meet all government regulations, and there wasn't enough money for the research to do it, so you couldn't meet government regulations. You'd lost credibility with all your customers. You had lawsuits because your products weren't working. So the x-ray activity of Litton was by far its least successful activity. They had some good divisions. They had Microwave, and they had Geophysical—Western Geo, I guess it was called—and they had a bunch of things that were not bad. But this division was a disaster. The pressure was sky-high to turn it around and I had thought I had gone in to run a successful division because they'd shown profits for the preceding four years. I learned the hard way that those profits did not reflect the true health of the business. There are ways of reporting profits without necessarily having a healthy operating statement. That's what had happened. There were huge increases in inventory, huge increases in receivables, and the place was in real trouble. I didn't catch on that it was in trouble for six months. After I caught on, I couldn't convince my bosses that I could ever get out of that trouble, and I wasn't sure I could either. They eventually got out of the business, but it took them about five more presidents that they went through, because the Litton system was that if you don't succeed, you're out of here, and I'll get somebody that can. So I beat them to the punch. I resigned. But I would have been out of there, too. I would have been fired along with the succeeding Presidents.

SLATER: When you first made the transition, did you approach them? Did they approach you?

RATHMANN: They approached me. In the x-ray field, 3M had picked Profexray as our distributor. We felt that we had to have an exclusive to compete with [Eastman] Kodak and DuPont who sold to everybody.

SLATER: Please explain.

RATHMANN: Yes. 3M felt that if we're going to be in the x-ray film business, we will need an edge to compete, and one way to do that is to have a bias at the distributor level. So instead

of distributing through everybody, we will offer Profexray an extra discount over other films. They had big film sales, as a matter of fact. The idea was, give them an extra cut as an exclusive distributor, and that would maybe balance off the fact that these others have great reputations. So we'd give the Profexray salesman a little bit more of the action. The other guys didn't have to make gifts to their customers because they had a standard 20 percent discount, and most of that was passed on to the customer. So they'd sell the x-ray film. It was really amazing. They'd sell x-ray film at 20 percent off the list price and a 2 percent cash discount extra. So it was 20 plus 2, and most of these distributors would sell the product for 20 percent off. So they would be capturing 2 percent, but they'd have huge sales. They'd have one customer and they'd drop ship directly from DuPont or Kodak right to the customer four hundred thousand-dollars worth of product a year. That was not unusual. They'd get their eight thousand dollars for literally having to just talk to the guy once, and they had huge sales. I mean, thirty to forty million dollars of x-ray film sales, and it also would help to facilitate other kinds of sales because you'd get into the lab there to see how the film was doing, and so on. So you had kind of an automatic business.

We had to break that with the 3M film that was a good film, and initially it was not as good as Kodak or DuPont, so we had to offer an extra little bonus. Later on, at 3M, while I was still there, we developed a higher speed film that neither of them had and we offered some unusual benefits. But we still used the extra discount, so we offered them 25 percent instead of 20 percent. Unfortunately, sometimes the distributor would pass on the extra 5 percent, so he didn't have any real incentive to sell it because he didn't retain any more than he was retaining with the Kodak film.

But, that was the idea: that Litton could help us enter the x-ray film business. We did develop a multi million-dollar business this way, relatively quickly, and so then they knew me at Litton. Alan Enthoven, who was running Litton Medical Products, invited me in to become President, and he was thrilled to death. He thought he'd picked the plum of the world because I had a very fine reputation at 3M, and 3M had a great reputation. So I got captivated by the idea that I would be running what would soon be a hundred million-dollar division. I'd be one of the top executives in Litton itself. I didn't ask myself whether the quality of Litton as a company had anywhere near the texture of a 3M. It did not. I mean, the standards by which they did business, the kinds of products they had, and the kinds of leverage they had—many years later I saw a diagram of the businesses that 3M was in and the businesses that Litton was in, and how they came out on the diagram of your market share and growth of the business and all the rest, and 3M's businesses like Kodak's businesses, by the way, were all in the segment of this chart that said, "Very, very desirable." Litton's businesses were all in the segment of the chart that said, "Dog!" So when you're running a dog, you really know it. I realized it very quickly. It was really difficult.

But as I say, you come straight up a learning curve until suddenly you recognize what accepting responsibility is. I think when you first eye a job that is the possibility of a big job, a general manager's job, the first thing to think about is all the pluses. You have more authority and more things to be done; you have more resources; you have more of this and more of that. You don't always recognize the tremendous responsibility that goes along with being the boss

of something that's got to thrive, and if it doesn't thrive, you suffer and many others suffer. When you're in one that doesn't thrive and you suffer, you've learned some experiences I never had when I was at 3M. So I thought—at least the rationalization was—a great learning experience.

SLATER: Did that change your vision of like what your career would be? How you saw yourself?

RATHMANN: Well, it did initially, but probably in a funny direction. It changed my vision to the point where I became very skeptical about being in a big company. I certainly was skeptical of my ability to be a president. So I was prepared to sort of drop out of the work force almost, and do some consulting or something like that, as a full-time job, except I suddenly realized that that's a terribly difficult thing to try to be gainfully employed. So while I was wrestling with the idea of being a full-time consultant, I was approached by someone who had a friend at Abbott [Laboratories] and they were looking for a head of R&D for the diagnostics division. I thought, "Well, at least it isn't taking on the CEO job," which I didn't want, or the President's job. I loved diagnostics. It was very fascinating for me because that's what medical x-ray was, and what ultrasound was, and medical electronics. All the things I did at Litton. I really liked the technology at Litton. If we had been fully competitive it would have been a lot of fun.

So I thought, well, a diagnostics thing would be very exciting. It's strictly R&D. In a sense, I redirected my thinking from being an executive, which was my father's goal for me. I followed his other advice, "Do what you enjoy doing." My dad decided that he liked being Chairman of the Board a lot better than he liked being an employee, or even President, and so I had considered the concept of being Chairman of the Board the very thing. When there's a William L. McKnight who's Chairman of the Board, and you just worship this guy, you just hope someday you're going to be qualified to be Chairman of the Board. It's kind of a wild dream, and it probably won't happen. Well, I got disenchanted with that idea in a big hurry, and I was very happy to be back in the research lab, and away from the responsibility of running a company and getting beat up by my boss every week on my profits and my cash flow and having ten percent staff cuts.

So I took a huge step in the direction of back to science, and loved it. The job at Abbott was just perfect. It was just what I wanted. They needed a new way of looking at things, I felt, which was to have a much broader product strategy than they had, and I knew how to do that. I knew that there were plenty of opportunities in this field. I could see the numbers and I could tell how far it was going to go. So I just loved the job for five years at Abbott, and I took the job knowing full well that I would not be CEO. I did not want to be CEO. They asked me a few times along the way, "Is there anything else I'd really like to do," and I didn't have any appetite for anything but what I was doing there.

SLATER: So managing R&D has sort of been qualitatively different than this other kind of business?

RATHMANN: Yes. Well, you still have a lot of business responsibility, but the areas where your time is spent—a very high percentage of your time—wrestling with actual problems that have to do with facts and opportunities and, although there's a people dimension, the part that makes it fun is the real challenge of bucking up against nature. The competition is another part of nature, in a way, but it's fun to be attacking something like that rather than trying to manipulate numbers and come up with something that looks better than it is, and a whole bunch of things that are very unpleasant. Having to spend too much time, literally meeting on the subject of what our numbers are, and every possibly nook and cranny of our numbers, I find that to be much less interesting than, "My gosh, we've got a new product, and if we could get it to market, we'll totally change our business profile." It's still a business issue, but the meat of it is something I can get my hands on and understand, and feel like I can contribute to. So I liked that change right away, and I would have stayed at Abbott forever because it was a great company and treated me well, except there was one strong pull and a small push. The strong pull was: I really wanted to know more about recombinant DNA [deoxyribonucleic acid], and when I went to the group at Abbott, they were neat people, but they were not responsive. Abbott had kind of handcuffed these people because they had a lot of bureaucracy at Abbott that was preventing them from doing very many experiments. They had taken all too literally the idea that this was dangerous stuff and had to be done with super-protection and all the rest. It was not that dangerous, but they were on the safe side, and the safe side was the dull side. So they couldn't offer me the kind of fun of doing new things in recombinant DNA that I was anxious to do. And I wasn't smart enough to do it. You know, I could have had the freedom to initiate some programs, except I didn't even know what recombinant DNA was. All I knew was a rough idea that it was a new frontier and it was very exciting.

I decided to learn more about it and that was the idea that prompted me to leave Abbott. The push was a very slight push, and that was that we had taken a potential cut in our staff because part of our division had a real bad year. We faced the reality that we had to take a staff cut, and yet I knew we were going to grow over the years, so I asked for some kind of relief and the management said, "Well, you don't have to take the cut, really. We'll just plan it and then if things look up, you won't ever have to get rid of those twenty-one people." But the rest of the division was aware that I was supposed to lose twenty-one people, and they weren't being told that if things went well, I wouldn't have to do it. So I got a lot of people asking me when these twenty-one people were going to leave. I'm looking around me and I don't want to have twenty-one people leave because I knew what was going to happen, and it did happen. Within two years, the research group was almost twice as big as when I was there at the time. I knew they weren't going to leave. It wasn't sensible to cut the research group. In fact, the bosses recognized it wasn't sensible. It was just sort of like everybody's tightening their belts so we've got to take some out of research.

It was an unpleasant time. I just felt like it was unfair. I mean, I had to drop staff a lot when I was at Litton, but it was justified because we weren't successful. But the diagnostic part

of Abbott was extremely successful, and the R&D was paying off enormously. So it was a bad call, even on a temporary basis, to say, "Let's reduce staff." It was a minor "push." The main thing really was the pull of recombinant DNA. I was fascinated by the R&D associated with recombinant DNA, and there was no way to do it through Abbott.

Then I said, "Well, there's a company on the west coast and I think they've got some interest to us as a potential partner, and they've asked me to consider being CEO and it hasn't even started yet. I mean, it's just a group of scientists and a couple of venture capitalists and they're going to start forming it and it's called Amgen." And I said, "I think they would like me as CEO, of all the funny things!" The Chairman of the Board and the Chief Operating Officer of Abbott said, "We'll do it with you here at Abbott. You start a company here within the company and we'll let you do that." It took them one day to make that decision. I was really impressed. We met together that evening and they said, "What would you need?" I said, "Well, I don't think it's possible to do it with Abbott. I might need an awful lot of money. I might have to go public." "That's all right. You could go public. As long as you leave us with 52 percent of the stock, you can take the company public." I said, "Well, I might have to have other companies invest. One of the ones that's already out there has Standard Oil in there as an investor. You know, the big bucks in oil might be necessary to finance recombinant DNA at the magnitude you might need, and so I might have to have another company in as a partial owner." "That's okay. If you want to do that, you could do it." I said, "Well, I might have to have some shortcuts on some of the, you know, approval cycle that we have here. If I have to stick with the RCE [request for capital expense] system, the AFE [authority for expenditure] system, and the rest of the procedures for getting budgets authorized, I don't think I could move as fast I might have to move in this field. It'll be very dynamic." They said, "You can set up your own systems. We'll respect the system. Whatever system you want to put in place." I said, "Okay. You've answered my questions. I'll do it. I'll start a biotech company right within Abbott in exactly the way you've described."

Then I thought about it. And I thought, "There's Cetus, and there's Genentech, and there's Biogen." I'd studied them fairly well. Look what they are doing. They're controlling their destiny. They are going to go wherever it leads them. They're going to be able to promise the people that come to work there that if they hit the home run, they're going to have very lucrative returns on their stock. But a company that's owned 52 percent by Abbott might not have the freedom to go and launch a product to make, let's say, excessive profits because they might be siphoned off to Abbott and correctly so. Why is Abbott doing this?

I thought I'd love to be in the company that's financed by Abbott. It's a lot safer and more secure, but I'm afraid it's a little bit more secure than it is an opportunity. I took two days and I said, "I feel terrible. You guys—Bob [Robert Schelhorn] and [G.] Kirk [Raab]—are wonderful to propose this. But I'm going to turn you down. I'm going to take the job at Amgen." I never regretted it, as it turned out. But what made it really work, amazingly enough, was Abbott. They said, "Well, that's up to you George. We respect you for that, but I hope you're not confused into thinking that we might be so enthusiastic in supporting you that we'd go and invest in Amgen. So don't come around expecting any financing of your independent

company. We like you, and it's fine that you're doing just what you should do. It's a fine thing. But don't expect anything from us."

I said, "You don't have to worry. These venture capitalists, they can raise any amount of money that they need." The venture capitalists had already promised me five going on ten, and then Genentech announced it would "go public." They were going to go sell stock to the public; they hadn't quite done it yet. They were going to have an IPO [initial public offering] in the middle of October for thirty-five million dollars. I thought, "Oh! We'll get five or ten million dollars and we aren't going to be able to keep pace with these guys. They're just racing—they're going to go ahead—they're ahead of us by four years already anyway. It's just going to make it worse." I said, "We're going to have to raise fifteen million." The venture capitalists said, "That's okay with us. We'll try to raise fifteen," but when we went out and talked to the other venture capitalists, there wasn't fifteen out there. There was very little. We thought, gosh, Genentech went public and we were out there trying to solicit, and we should have an easy time because they were so popular. And, yes, they were popular, but they were also four years ahead of us, and so a lot of people said, "What do you have that's all that wonderful? You don't have any products. You don't have anything." I couldn't get much investment—maybe a couple of million dollars is all I could get. You know, so I thought, "It was guaranteed that the venture capitalists would deliver the money, and all they could deliver was a couple million bucks."

I went back to Abbott and I said, "You know, I heard you when I left, and very smugly I thought I was going to have no trouble raising the money because I sort of thought that was the venture capitalists job. But I think it's going to be my job, and I'm going to start with you and I'd like you to consider putting in three million bucks." I put the pitch together that was a very sophisticated pitch for Abbott. I knew everything that was going on in Abbott in the chemical division, the Ross [infant nutritional] division, the diagnostics division, and the pharmaceutical division. I had potential product candidates for each one of those based on recombinant DNA, and I convinced them to put in the three million dollars. The venture capitalists, were lining up three million dollars from Tosco [Corporation], so we had six out of the fifteen, and if we could just get it up to ten somehow we'd probably be able to get it.

I went back to Abbott and said, "We've got some opportunities to put another pharmaceutical company into this thing, but it would be better if you guys just upped the ante, because if you upped your ante and Tosco upped their ante, why, we could get there without another pharmaceutical company." Abbott came along and they put in five, but Tosco couldn't reach the five; they put in three and a half. But that eight and a half was enough to whet the appetites of the venture capitalists that were left on the fence. They said, "Gee, if Abbott is putting in five million, they've never bought a minority stock in anything; they must really like this guy." So we raised nineteen. I never had to look back because it was just the greatest idea in the world. The recombinant DNA turned out to be just as exciting as I expected it to be. The interesting thing was, of course, "How did I get the line on Amgen in the first place?" It was that I was going to do a sabbatical to concentrate on learning recombinant DNA. I was going to do a sabbatical with Winston Salser, the professor at UCLA [University of California, Los Angeles] that I knew. So when I called him in April and said, "Well, I've gotten leave. I've gotten a six-month leave." They wanted to limit me to three and I insisted it had to be six. "I

got my six-month leave, Winston. I'm ready to come and work with you." He said, "Aw, gee, I think I'm not going to be around very much. I'm going to be part time in this new company I'm trying to get started." In April 1980, he was starting Amgen. So I said, "Well, that's a heck of a note. I was going to come out and work in your lab, you know? That's what we said." He said, "Well, you can come and do that. You can still work in my lab. I've got some space for you. I've got another guy that's kind of on a sabbatical here with me, and it's going very well. His name is Marty [Martin] Cline. He's doing the first experiments on gene therapy that have ever been done. It'll be wonderful. You can just do a sabbatical with me anyway." I said, "Well, it doesn't seem right, if you're not even going to be in the lab there. I mean, how am I going to learn from you?" But he said, "It could be wonderful."

Then he said, "But you know, you might be interested in the company that I'm going to try to form. Would you like to come out and be on our Board?" I said, "Well, I can certainly contemplate being on the Board." He said, "How'd you like to be CEO?" I said, "Well, gee, that would be a most unusual thing. I don't really want to be a CEO." So we talked back and forth. But I said, "I'll use my own money to come out and see you. I am intrigued. I really do want to do something in recombinant DNA, and maybe the company's a better vehicle than being on a sabbatical." As soon as I talked to him and some of the scientists that were already signed up for the Board, that was just the most exciting thing in the world. I mean these people understand recombinant DNA! They're going to teach me faster than anything I could ever learn in books or anything else. I'd read a lot by that time, but still, I had no feel for this subject. I didn't have any feel for how to go about doing this. These scientists all had had some contact and experience with the earlier biotech companies like Genentech and Biogen. This is how we're going to get started, you know. We're going to do this, this, and this. The scientists were wonderful. Actually, some of them took great pains to explain to me what was really involved, what you had to do, what you have to put together to make a company that would work. They'd help with the recruiting of the scientists. Gee, everything was great.

A cute story, by the way, and I don't think we'll need it in, but it's such a wonderful story. One of the key scientists said, "I don't think I want to take the stock." He was a key guy. He was head of a department at UCLA [Arnold Berk]. I said, "Arnie, why don't you want to take the stock?" He said, "Well, my dad's told me it's a bad idea to take the stock." I said, "Well, Arnie, I understand. Let's go through this. We want to give you twelve hundred shares for twenty-five cents a share. That's three hundred dollars. You got paid—let me understand this—you got paid three hundred dollars for the last scientific advisory Board meeting. So, if you just give us the three hundred dollars back that you got—now you had to pay some taxes on the three hundred dollars, I understand that. But if you give us that back, and you're going to get twelve hundred shares of stock, I really think you ought to do that." He said, "Well, my dad says that's a terrible idea." He said, "Stocks in companies like this could be absolutely worthless." I said, "How old is your dad?" "My dad is fifty-two." I said, "I want to talk to your dad. I'm fifty-two. I think I can talk to your dad."

So I talked to Arnie Berk's dad and I said, "Mr. Berk, you should understand that the advice you've given your son is wonderful. It's true that someone can offer you twelve hundred shares or ten thousand shares or a hundred thousand shares, and it can be a complete fraud and it

can be absolutely worthless. The number of shares means nothing. It's absolutely true, and you can't really be sure with a company at this stage what it's worth. But I'm telling you, I'm betting on this company and I've got my life in this thing, and those twelve hundred shares could easily be worth a very significant figure. We're going to build a company that is going to devote itself to trying to make every shareholder get a good return, and my gosh, we're going to be selling twelve hundred shares for something like five thousand dollars instead of three hundred dollars. So I've got a lot more at stake with the fellow I'm taking five thousand dollars from than you. I think this is a no-brainer. You should do it."

He said, "Okay, Arnie, you can go do it." I can't give you the total numbers, but it comes out to something like twenty-six hundred times that number of shares at one hundred dollars per share—it's twenty-six times one hundred thousand dollars—yes, that's it. So it's about fifteen million-dollars worth of stock that he was about to pass up because he thought it was going to be too risky. But it was a huge number. Whether he ever kept it long enough, I don't know.

Abbott's input of five million dollars is worth a couple of billion today, although they sold out at two hundred thirty million. They were quite satisfied taking their five million up to two hundred thirty million. They were very proud of themselves when they did it, thinking that they really captured the thing at the peak. They gave away a factor of ten before they're done. The whole experience at Amgen was just a miraculously wonderful experience.

SLATER: Can I just take it back one moment? You were saying, when your curiosity was first piqued about recombinant DNA, you knew what Abbott did in its different divisions, especially diagnostics where you worked, and you felt that this technology could somehow address this set of problems. Is there anything that stands out in your mind there? I mean, had they done anything in that direction, in diagnostics there?

RATHMANN: Yes, what it had done is this. I had been very concerned that Abbott was moving in a very conservative direction with respect to government regulation. There was good reason for that. They had a very bad experience in 1971 in which they'd had a flaw in their manufacturing and there were a lot of deaths. They almost went out of business because they didn't have satisfactory quality control of a particular area. It was actually a very unusual thing that happened, but it happened. Therefore they were determined never, ever again to do less than what was the most you should do in conforming with the best, most conservative practices, including all regulations. So, what we had in the factory, which was very burdensome, was that we treated everything that we touched as an etiologic agent, or a toxic material, potentially biologically active. That was because our products involved hepatitis, and we obtained one of the materials for the hepatitis test from infected blood. We had to categorize everything as potentially infective, or potentially an etiologic agent. Therefore, all the precautions for the entire plant, whenever you brought a new product in, if you were in that same plant, you had to treat it as though it was toxic, biologically active and toxic.

It seemed to me that there was only one thing that was in that plant that was toxic, and that was the material we brought in, in order to get the hepatitis B surface antigen. The hepatitis B surface antigen was the candidate for a vaccine. So the hepatitis B surface antigen was known to be absolutely safe. If you made pure antigen, it would be safe. If you made it in recombinant cells, in other words, it would be a very safe product, and you'd need none of this etiologic agent precautions and all this stuff—stainless steel here, and other stuff there—huge burdens on bringing out new products. I wanted to try and bring out new products faster. I hated that burden on every product that had to be put into that plant and had to be treated like it was toxic.

So, I asked the recombinant group to make hepatitis B surface antigen, and they said, "That'll cost you a million dollars." I said, "Well, it isn't that valuable to us. We don't have to buy that much. But it would really simplify our plant and everything if we had it. Can't you make me some?" "To make you some is going to cost a million dollars." Well, I didn't have a million dollars. I was an R&D director. I had a budget of about ten million, but I wasn't going to take one of it and set it off for that. So I talked to a friend of mine, and he said, "Well, my advisor, Winston Salser, out at UCLA, has a clone of hepatitis. Why don't you go get it from him?" So I went out to see Winston Salser, personally, paid him a call and said, "I'm really interested in hepatitis B surface antigen. If you've got a clone, we might be able to get it expressed and make stuff and that way avoid all this plant problem." He said, "Yes, I'll sell it to you." He was very enterprising. I said, "How much would it cost?" He said, "Ten thousand bucks." I said, "It's a deal. Abbott will buy the clone for ten thousand dollars."

SLATER: That was a good trip!

RATHMANN: Yes! He sent the clone in. I handed it over to the recombinant DNA group and said, "I'd really like some surface antigen. Now you don't have to spend all the front end money to get the clone, so here it is." We went ahead for about three months. It was sort of like the Scotchguard thing. I didn't do much for three months, and then I came by and said, "Well, how did it look? What does the surface antigen look like?" "Oh, the stuff is still in the refrigerator!" It turns out, two years later it was still in the refrigerator. For some reason, nobody was sure enough that it would be okay to investigate. It's not a matter of risk in terms of biology. It was just a matter that it was a hard job to figure out how to get it expressed, and they weren't going to take a lot of time. It was not one of their main programs. Even though I was prepared to spend the money, whatever that would have taken—it surely wasn't going to be a million—but they didn't touch it. They left it in the refrigerator.

But there was a useful outcome. What had happened was, Winston had remembered this contact. A year later, when he decided to start Amgen, he called me, and said, "Are you still interested in recombinant DNA?" At that time, Amgen began to form, and that was the reason that he talked to me, and that's how the whole relationship with Amgen started. It was because I had wanted recombinant DNA to be applied to surface antigen.

Now, when you say, well, you knew about all the other things at Abbott—that was a matter of selling them on investing. I had not thought it was all that important. Yet some of those things were a lot more important than surface antigen. In other words, if you can put things into Similac that made it more resemble mother's milk, then that would be a huge thing. Well, how do you do that? Well, you analyze mother's milk for proteins that are there that are not in cow's milk. Today we know many. Some day we'll make them all and add them to cow's milk to make it more like mother's milk. One is a product that ICOS [Corporation] has. There were a few things that we knew about such possibilities. Certain antibodies that we could make that might be a good addition to Similac. That was one. There were certain growth factors. For the chemical division we could mimic a microbial pesticide if we could make a key protein by recombinant DNA. It turns out to be a billion-dollar idea, by the way. We said we'd work on it for Abbott but that program was never started. We had a whole bunch of programs like that.

But the motivation for me was—because of my diagnostics interests—to get surface antigen without having any infective material to be there. Abbott did convert their diagnostics over into recombinant hepatitis surface antigen. That's the way they do it today. So it was a good idea, but it wasn't a monumental idea. But it precipitated things. If you're in a company and a good idea can't be worked on, your lucky to find another place where it can be done. That was the call.

SLATER: This is sort of a side question: When were you first aware that there was this biotech thing out there?

RATHMANN: That's interesting. You know, sometimes I disappoint myself because I wasn't the prime mover at the company, at Abbott, to say that recombinant DNA is an exciting field. It took somebody else to say to me, "Recombinant DNA is an exciting field!" I said, "What is it?" There were two people there. One of them worked for me in research, Dr. Lacy Overby, who was very knowledgeable, and he was the guy that was then put in charge of the recombinant program at Abbott. He said, "We've just got to start a recombinant program." So that program was started under him. I had responsibility for his effort, but he was an independent guy. He was in the central research part and we kind of financed a fair amount of what he did. But the recombinant portion of what he did was funded by the company, so I had responsibility for much of his work, but not the recombinant program. He was telling me all the time, "This was the wave of the future." So, I wasn't the inspired guy. He was.

The other guy that was inspired was the head of the pharmaceutical research activity, Ira Ringler, and he was even more than inspired. He was aggressive and active. He said, "George, I want to go on a trip with you because I think the two of us could ferret out whether it's good for Abbott to be more involved in recombinant DNA. There are some companies on the West Coast. There's a company called Cetus and there's Hybertech and there's Monoclonal Antibodies." He didn't think of Genentech. But he said, "These companies are doing things in this field that are really exciting." I said, "Okay. I'll go out there with you." We visited Cetus,

and I met a couple of people that I've known ever since, and one of them is a very good friend, Ron [Ronald] Cape, who was Chairman of Cetus. We talked about the possibility of doing some collaboration with Abbott. But it was pretty remote that there was that much interest by Cetus. I mean, Cetus wanted to be a pharmaceutical company, but they had a lot of investors. They didn't need us, and they didn't exclusively think about pharmaceuticals. They thought about a lot of other things. They certainly weren't thinking about diagnostics of interest to Abbott. So we didn't have a lot in common, but it did make me realize: "Hey, there's a world out there that's starting to do things that were impossible just a few months before! Impossible!" As a matter of fact, in December of 1979—1980 was the year I suddenly got turned on to recombinant DNA. In December of 1979 there was a meeting at Abbott to decide whether or not to try to make Interferon from cell culture, isolating it from places where natural interferon would actually occur. Because I'd now heard the word "recombinant DNA," I raised the question whether this wouldn't be better done by recombinant DNA. All the recombinant DNA pros came down on me very hard and said, "You don't understand. Interferon is too difficult to make by recombinant DNA. It will not be done by recombinant DNA. You just don't understand!" So I admitted I didn't understand. The program actually started at that time, to make Interferon by these methods.

One month later—and I've got the slide—[Charles] Weissmann announced the cloning of Interferon. I didn't run around the company saying, "You idiots, you all told me I was stupid." I was stupid! I didn't know enough to know whether it could happen or it couldn't happen when I was talked out of it. It was all right with me, and if they want to go ahead and make it from tissue culture, that's fine. But then a few months after that, they abandoned the program that they'd initiated in December of 1979 because it was clear that Interferon at least was going to be better handled by recombinant DNA. But it still didn't mean much to very many people at Abbott. That this was going to be a universal source of products for pharmaceuticals. I mean, it still was just barely recognized.

It was in October of 1980 that I interested Kirk Raab in investing in Amgen because he saw that there were implications beyond what people at Abbott had seen up to that time. He had been in charge of the recombinant program that year at Abbott and they went nowhere for a year. So he saw that they weren't going anywhere and he listened to me tell them about how great it was going to be at Amgen, and he put in the initial three then upped it to five million and made it all possible. So I was not the guy that was the first guy to think about it. I'm kind of embarrassed about that because I should have been. I mean, I should have been the guy that was smart enough to see that this is terribly important. But I was smart enough to decide I was going to get more knowledgeable anyway.

SLATER: Let me ask you a development-related question. It's too difficult to clone Interferon. That's what the assertion was, which proved to be incorrect. But these things weren't easy. I'm interested, for instance, Schering [Plough Corporation] got three molecules from their interaction with Biogen, one was alpha-interferon and another one was erythropoietin. Biogen couldn't get it to work. But other people got it to work. Is there a management story? Is there a resource story?

RATHMANN: I'd love to tell you the whole story. I could give you a slant of it, but again, you may have to get many views to get it right. It's a very interesting story. First of all, there wasn't that much justification for saying that interferon would not work. That was not a good statement. The basis for the statement was very simple, and that is, the molecules that had been made up to that time, somatostatin and insulin, were both much smaller molecules. You could have argued, though there's no real good basis for it, you could have argued that the small molecules maybe were easier to make, because you don't have to assemble such a long chain. It actually turns out that recombinant DNA is great for big molecules, so that's not a good generalization. But there was a basis for making the distinction at least. Hey, they're small; this is big; it's going to be hard.

The first thing is: what size molecule is it? The second thing is really more important, and that is, what if the molecule is not just a polyamino acid? What if it's got glycosylation? Now, if it's got glycosylation, you're not going to be able to do it in the same way that you assembled a polyamino acid in *E. coli*. *E. coli* does not have the equipment for putting on sugar groups or glycosylation, and then you're "out of luck." Now, the question is, does anybody know whether it's absolutely essential that you had the sugars? Well, that's a pretty tricky question. You can make the assumption that nature wouldn't have put them on there if they didn't need them. But it's still a valid concern to say, "But I might not need them anyway. I might get close enough without them that I don't need them." So there was a second reason to say Interferon won't work, but it's not a very good reason because I haven't proved that I have to have the sugars. In fact, there are very few sugars. It's not a big deal. In fact, you can make interferon fully active in *E. coli*. No doubt about it. But you might have thought there might be a lot of sugars, and it might have been important.

There were many instances like this in recombinant DNA. One of the first things I wanted to do, and I got talked out of it by Winston Salser, was pheromones. I said, "Pheromones are incredibly expensive things and if we could be able to do that by recombinant DNA—." He said, "George, don't be silly! You'd have to have a pathway that's very much more complicated than just assembling a polyamino acid. You'd have to go ahead and make a whole lot of other things that have to work together." It turned out that one of the first things we made at Amgen was indigo, and in making indigo, you are basically putting a pathway in there to make about six different molecules that finally assemble the pathway necessary to make indigo [sic], and you happen to be able to do it with surprising ease, because the pathway that leads to an oxidation pathway puts all the genes in a cluster, and you find one cluster and you've got the whole pathway. This idea that you'll never be able to hook it all together is ridiculous.

It's very easy to find reasons why something doesn't work, and lots of times there's some logic there, and that was the basis for saying interferon would not be done. It was bigger, and it hadn't been done. So therefore it can't be done, or very likely it was going to take a very long time. It took one month and that was a big surprise.

But the erythropoietin story was somewhat different. One of our original candidate products was erythropoietin. The people at Abbott found that very distressing when they found out that they'd invested five million dollars in a company and one of the things we were going to do is erythropoietin, and they'd had Gene Goldwasser beating on their door for the last five years telling them that they should go into erythropoietin because he could make some by separation from urine. They always passed it up because it was foolish. You couldn't get more than a few micrograms from urine. So they thought it was the dumbest idea in the world to try to make it by recombinant DNA. Goldwasser had been pushing this stuff on everybody for years. Apparently he couldn't make it, or it was going to be very hard.

So the first thing was, it was highly glycosylated. You certainly had to do it in mammalian cells. But tissue plasminogen activator [TPA] was made by Genentech in mammalian cells and that proved that you could it. You don't have to use human mammalian cells. You can use Chinese hamster ovary cells, and you get good product, even though it probably is not the same glycosylation. But it's good enough to make it biologically as active as the human one.

But the second thing that did catch Amgen for a while was that all the ways of cloning up until that time had been from CDNAs. So you find the tissue that makes the stuff; you find the message in the tissue by taking the poly chains and pulling them on, finding the messages, and then getting the message for that particular protein, and then you make the CDNA of that message and you have a gene that you can put anywhere you want. You put it into a plasmid [small sequence of DNA] and then you put the plasmid into the cell that becomes a production factory. So what you had was a standard way of making recombinant molecules that was irresistibly attractive because you go right from the CDNA to a plasmid to a system that makes the molecule.

Everybody knows that since the body produces erythropoietin, there's got to be some cells somewhere in the body that make that message. Since 1947 it's been known that the kidney makes that message and produces erythropoietin. But the kidney's a big organ. It's got a lot of different kinds of tissue. No one has ever isolated specifically that tissue that produces the message. If you look for the message in kidney tissue you cannot find any quantity of that message because erythropoietin is <u>extremely</u> rare in the blood stream. It's extremely rarely produced. It's very potent material, and so the combination of not having much around and not having the specific tissue that makes it, you could not get the message. Try as you would, you could not get the message.

Now, eventually, we did get the message, and we did it by treating a juvenile monkey with hydrazine and when you treat them with hydrazine, it increases the production of erythropoietin and when you do that, you can actually isolate the message. I think it was actually produced in the liver, but I can't remember now. It's been a long time. So we were going to collect prenatal livers together; we were going to collect lots of kidneys and do various things to simulate it and so on. And the scientist that was on the job simply said, "I'm going to get it out of the total gene, the human gene." Everybody said that couldn't be done. It's impossible to find it. You've got this huge genome and you're never going to find it. He went

ahead and found it, and he did it by getting enough information from fragments of protein that Gene Goldwasser supplied that he could in fact make the probes and he could do it.

Biogen and Julian Davies testified on our behalf in the courtroom. "I tried it. I tried it and I couldn't make erythropoietin." [Richard A.] Flavell, who was a subsequent research director at Biogen, testified for the other side and he said, "I could have done it. If I'd have had Gene Goldwasser's stuff, I could have done it. It would have been very straightforward." A lot of people testified on both sides. Axel Ulrich from Genentech said, "We tried it. We couldn't do it." But they all felt it was too impossible to try to do it from a cell's DNA. They all felt that was too hard to find. A scientist at Genetics Institute tried to do it from the gene, but he didn't try until after Dr. [Fu-Kuen] Lin had done it. But, other than that, nobody even tried it. They thought it was too hard to do. So that explains the failures.

Now, the number of failures was not just the ones mentioned. Biogen, Genentech, Integrated Genetics, Suntory [Ltd.], Takeda [Chemical], and a lot of the foreign companies, and Schering-Plough for all I know, might have tried it independently of Biogen. It was simply that you had to go after it. You had to have two things. You had to have at least some sequence data. That was hard to get because pure erythropoietin was almost impossible to get. Gene had figured out a way to make very tiny quantities, and it was a real tough process. You had to have urine from people that were non-treated aplastic anemics. If they were treated with transfusions, that suppressed the level of erythropoietin being made, but if you didn't transfuse them, their hematocrit went very low and they produced a lot of erythropoietin and it spilled over into the urine. So you needed urine of an abnormal patient who had been abnormally treated. That's kind of hard to do. There had been a Japanese population like that. So it was only Japanese urine that was used by Gene with his Japanese associate, Dr. Myake, and they developed this very tricky process for isolating, and there were very tiny quantities available. Now, he shipped it around. We weren't the only guys that got it. Then we sequenced it and the terminal sequence, which is easy to get, is not useful because of redundancy. From the sequence, as you know, you cannot deduce absolutely what the gene is. So you say, "Well this is an alanine." Well, there are three different possibilities. This is a glycine—well, there are six different possibilities. You need a DNA sequence long enough to be useful, which is about fifteen bases, which is five amino acids. For five amino acids, if you get two hundred fifty possibilities, you can't get there from here. So our scientist, Fu-Kuen Lin, couldn't do it from just that sequence alone, but if he got another stretch of sequence, now you see which ones match up, and those that hit both places are likely to be okay. They are the true genes. So that's how he did it.

But it was a tricky game and it actually was harder in 1983 than it would be today. Somebody could do it a lot easier today. One of the reasons is that when you're hybridizing an unknown gene to an unknown hybrid from a combination—in other words, you're making the probe match, you don't know the conditions to use, back in 1983, because you knew that the CGs [cytidine and guanoine] are bonded much more tightly than the AT [adenosine and thymidine] bonds. Therefore, you make an estimate for the probe that you're going to use, which has all the different structures in it. In other words, because of the redundancy, you've got two hundred fifty-six different probes, and some of them are heavy in CG and some of them are heavy in AT, and some are both. If you put the temperature too high, and you had a lot of

ATs, they're not going to hybridize. They're going to fall apart because it's too warm. If you have a lot of CGs and if you have the temperature too low, then mismatches are going to crystallize and you're going to have a lot of genes you didn't want. So you really would like to predict the temperature of hybridization for the exact one you have. It turns out that between 1983 and 1984, a new molecule was discovered that tended to wash out the temperature differences between AT and CG bonds. It's tri-methyl ammonium per-chlorate. So if you put in the per-chlorate when you're doing this job, now you can peg the hybridization temperature without knowing which gene is the one that you want. That was not available, so Dr. Lin had a much more tricky game to do. That's another reason why it was not done by anybody else.

SLATER: It's a nice piece of physical chemistry there to be able to figure that out.

RATHMANN: That's right.

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SLATER: One of the things that's interesting about biotechnology is that you have a lot of fine science that allows you to identify, clone, produce on a very small scale these things. When you want to be Amgen, where do you find the expertise for manufacturing, particularly if you're talking about manufacturing something in the early 1980s?

RATHMANN: When we started there were a lot of revelations. The whole thing was new to me. I was not knowledgeable about recombinant DNA. I had interest, but it was certainly not knowledge. One of the things I didn't have was the understanding of how to go about doing all this stuff and everything else. What I was surprised to find out when I started the company were things like this: that there was no message for erythropoietin. If your scientific genius said it was a great program, and we don't have any way to get the gene, then a lot of posturing, but it was true. It had been a total gap in people's thinking. They had just not thought about the fact that there was no source of message, and they hadn't even tried to isolate message. They simply thought, "Oh, you know, we'll get large amounts of kidney, we'll get fetal livers, we'll treat animals to enhance erythropoietin message levels." But tissues were hard to get and early treatments didn't work. So, that was a real shocker, and I was not impressed with our status. I was just lucky we had a very obstinate Taiwanese who said, "I can do it anyway," because that was all that we had. But in the summer of 1981 the proposed solution was to "timetable" the discovery of the gene. So Dr. Martin Cline, who had been trying gene therapy experiments, said he would lead the project. It came through. He said, "Why, we'll have this in the clinic within three months." But in three months and then six months we still had nothing. I finally said, "Hey, we're not going to run these things as in any industrial research group and Scientific Advisory Board members will advise but will not run these programs. We're going to run them with scientists because they're the ones that are in the lab. Some advisor coming in every two

months and saying, 'Why don't you do this? Why don't you do that?' It's a terrible idea. It's a terrible way to manage." I know where I learned that. I learned it in the very early days at 3M. The guy that's doing the work is the guy that knows the most, and the guy that knows the most is the guy that should be deciding where he's going to go, and nobody should tell him what to do. That's really terrible. I remember several times when I learned that.

Anyway, what happened was that we had a bitter pill there. Well, the next bitter pill is that—and Schering-Plough never seemed to learn this one, by the way—and that is that the academic world had provided us with: how to clone genes, splice genes, put them into organisms, get them in, and get the gene that you wanted by determining the sequence of the gene you wanted and know the peptide that you have. But the academic scientist was much less interested in reaching practical levels of publication. There was little or no interest in figuring out how to make even 1 gram, much less 10 kilograms or more. He was pretty happy if he could prove he made what he said he was making. So Weissmann cloned interferon in 1980 and it's still today questionable that he had more than a sniff of interferon in that January 1980 publication. In fact, he made extremely low quantities, and it was just barely detectable that he had any. They proved that they made a new gene and they cloned it. But you had to think: how about production?

So at Amgen, we said, "Well, based on the yields we presently have, we're going to need a plant. And based on some regulations that were occurring in the wonderful city of Sacramento, it's a good chance that we won't have this plant up here because they're going to start putting some limits on how big you can go with a recombinant organism." There was this "enlightened" concern. We were able to turn that around over a year with a lot of lobbying and a lot of education and the so-called Biotechnology Control Bill, became the Biotechnology Facilitation Bill. It stayed as a biotech bill but encouraged rather than suppressed biotech. Some others in the state were really good at this and convinced the legislature that we wanted biotechnology enhancement rather than biotechnology eliminated.

So at first we said, "We probably can't scale up to the huge quantities that we're going to need here. We're going to need over 10,000 liters or more, and they're talking about stopping everyone at 100 liters or less. So, what are we going to do?" Well, we're going to go to Chicago. So we authorized a plant in Chicago, a forty thousand square-foot plant that was going to be built in Chicago, because we knew that we were not going to be constrained by the California legislature.

Now, as we went ahead there, a lot of things changed. Jane Byrne was not reelected. She got ruled out by her own party and she was the mayor we'd worked with. I really liked Jane Byrne. My Joy was very jealous. She said, "Every time you go see Jane Byrne, you're walking on the clouds." She was just so charming! She was just a dynamic little lady that loved Chicago. I'd lived in Chicago, of course, for years and we just thought she was great. She was going to help us get this plant. So that was what we had, and we had authorization to get a government grant and a whole bunch of help to build in Chicago.

So we got underway. We broke ground. We put up the walls. Meanwhile, back in California, we were looking at how to expand the yields. We weren't the only company doing this, but it did fall to the companies to do this. We found ourselves with some leads that were provided by Dan [Daniel] Vapnek, who had come from the academic world and had been working with so-called "runaway plasmids," which meant that after you put the plasmid in, it might multiply itself before the product started being produced. So if you put in one gene in a cell, you might have a hundred genes, you might have five hundred genes. It was itself a bad idea because you had a runaway type of experiment and you had a hard time controlling whether you were going to have a huge number or double the number or triple the number or whatever. Actually one of our scientists, after we did the runaways, did what he called the "walkaway." It is was a way of getting it to a certain level and then stopping there so that almost all the cells had roughly the right multiplier.

Once we did that, and accepted one more thing, and that is that we could make cells like this—that's interferon. It's one of the early experiments at Amgen, and you can see the look of that *E. coli*. It's been elongated and distorted. In fact, that inclusion body there represents almost pure gamma-interferon, almost pure interferon. It's like one step to go to practically pure stuff, except you're stuck with a changed molecule because it's denatured, which is why it's separated out. So it's almost pure, but it's denatured. So what you have to have is some insights as to how you re-nature denatured proteins. It's mildly denatured. It's not like fried into a fried egg and then try to restore it back into a regular egg, but it is denatured. So you have to carefully sort of digest it so that it gradually goes back into the best-folded state it could.

Now, when we dealt with Schering-Plough, as I said, we loved those guys; they were really nice. They confided in us what their yields were, and we couldn't believe it. Well, they didn't confide in us. They said, "This is our reactor." We said, "For heaven's sake! That's big!!" Because by this time, we had decided we could make all we needed of most of these materials in a three-hundred-liter fermenter, and these guys were pushing them much, much bigger. It was impossible to understand. So we asked them, "Why do you stop at those kinds of yields? Can't you get a higher yield?" They said, "What we found out is, when you go to a higher yield, you get this precipitation of the protein. So we want to keep the yield below this very low level. That way it stays soluble and it stays maximally active." We said, "Well, maybe when it's coming out of solution like that, it's going to be inactive, but can't you do anything to restore it?" They said, "Well, we wouldn't want to add that step. We think it's much better to keep it below the levels where you have that problem, and then you're automatically producing maximally active molecules."

There was always this worry that you have no perfect reference of what is maximally active material. Sure you might have isolated something from human tissue or something, but the fact is, you might have messed it up a bit already. So you're always worried that you're not maximally active. You might freeze on something that's really not the best. But if you're a little trusting and say, "I think I've got a really nice re-digestion process here, and I've got this great yield, I don't think I can pass that up on just the remote possibility that when I'm done I've made some sacrifice relative to so-called maximal activity. Now, there's nothing I've ever measured that's more active, but the proper thing to do is to run it the Schering-Plough way and

our way and see what the biological assay tells you." Of course, biological assays are only good to a factor of two, so you might not prove it even then.

But anyway, they were wedded to a process that we would never have used. What happened was, we could forget about Chicago because now, along with our lobbying in California that had permitted us to go somewhat higher scales without risk—you could go over 10 liters; you could go to 50 liters or something—we had plenty of latitude. We could make as much as we needed without ever going to Chicago. We closed down the Chicago plant and proceeded. That was a key call because that meant that we could keep our research right next to our plant and although you might think it's great to put your plant somewhere where your scientists can't get hold of it, that's a bad idea. If you have good scientists, having them not so far—and an example of that was in our EPO [Epogen] plant. We followed all the key areas of EPO that we could learn from the CHO [Chinese hamster ovary] cells that other people had worked with. We turned on the EPO plant, and the first day I was out there where they were collecting the first drops of what we thought would contain erythropoietin, and they had the receiving container on an angle. It was propped up with a block of wood, in this twenty-million-dollar plant, [laughter] and this canister that was going to be picking the EPO was propped up on a block of wood, so it was on a slope, and I said, "What's going on here? Why don't you do this right?" They said, "This is right. Steve [Steven Elliot] told us to do it this way." I said, "Well, why did Steve Elliot tell you to do it that way?" "He was worried that the way we were collecting the EPO—it was coming out the spigot and dropping down about four feet to the bottom of this collector, and it probably would denature the EPO—so we wanted it to hit the wall and just kind of slowly drain down the side." So, I mean, it makes good sense, except you say, "Well, gee, did you know that it was really denaturing if it dropped?" "He had the sense that it probably would, so he suggested we do this." Of course, the first yield of the product was perfect, and eventually they didn't use that configuration where they had to tip it, but it was very interesting. It had always occurred to me—talk about luck—if that plant had been started the way it was intended to be configured, by the engineers, the EPO would have plopped down on the bottom; they'd have been producing that stuff, and they would have said, "No activity, or very little activity," for possibly a substantial period of time it could have been. You might choose to adjust around with something in the process somewhere else, and try to fix your activity, when in fact it was right here and the guy put it in place, and you never missed a beat, you know. So that's why it's nice to have your scientists near your plant.

Now EPO was a separate story because, as I said, it had to be done in mammalian cells. But EPO as a yield is a very interesting game. The first plant was designed at 7 ounces a year, 200 grams a year. That was sufficient to support a two hundred million-dollar business. It was an extraordinarily potent material. If you're on EPO for the rest of your life, you'll consume about 500 mg in the course of your lifetime. Mammalian cells are a lot tougher than *E. coli* to use, but it still all comes together.

Somatogen was producing an *E. coli* product and, although they were getting wonderful yields, it was still too expensive. The reason is that hemoglobin could be a synthetic blood and natural, donated blood is relatively inexpensive per gram of hemoglobin. The reason for the need for synthetic blood is that EPO cannot treat. Somebody who just lost three to five units of

blood; EPO would work over several months, but the patient would be at too high risk. There is a need for immediate hemoglobin replacement. Synthetic blood could be free of infection risk. So the Somatogen equation was very simple: we're going to use *E. coli* and we're going to make synthetic hemoglobin. They could, and it was beautiful, and it worked. But the dose to do any good is about 50 grams. The dose of EPO is 50 mcg. So you have a one million times larger dose, and with the fact that you're competing with blood means that you can't charge more than a few hundred dollars for a "transfusion." Otherwise, people would just continue to use blood. So, a look at the economics means that if you're going to have a hundred million-dollar business, you're going to make thousands of kilos of recombinant protein. No way out of it, thousands of kilos. The problem with making thousands of kilos is you've got to build your plant before you know you've got a business. If you build your plant before you have a business, you've put in three hundred million dollars for what might be useless material. So that's why Somatogen has failed so far.

But anyway, you had a good point there. That's an awful long answer, but to get the yields up was a challenge that industry faced more than the academic world, but there were leads in the academic world, as always, that were very helpful like plasmid replication and some of the other things to get the yields up.

SLATER: You seem sort of varying in your attitude towards the academic interactions.

RATHMANN: Oh, it's all one way. It's all good. It's just that—don't count on them for things they don't do because they're not interested. You don't go to an academic and say, "I want you to get interested in this." They won't do it. I went to Bob [Robert A.] Weinberg, who got the Nobel Prize a few years later, and I said, "What you're doing is so exciting, we'd like you to be a consultant for us." Bob Weinberg at MIT said, "No." I said, "You won't be a consultant for us? Is there something wrong with us?" He said, "No. I don't want to take a chance." I said, "You don't want to take a chance? There's no chance involved here. We'll pay you, and if you don't do anything, it's still okay." He said, "I don't want to take a chance, I have a feeling I've got the right instincts. If somebody comes by and tells me that this is what's important, or that's important, I think I'm going to mess up my instincts. I think I'm on the right track for something really good, and I like you guys. I mean, it would be great, you know. Read my papers. Talk to me any time. But I don't want to be a consultant, and I don't want to find myself directed along lines that might be of significance commercially, because I think my instincts are getting me where I want to be." He was right. I mean, it was a beautiful thing because he got the Nobel Prize three years later. He's a remarkable man. He did it his way. He was intrigued by certain things and that was what motivated him.

So if you wonder if the scientific community made contributions, they did, and they were <u>infinitely</u> precious, and what scientists have done for this industry is absolutely the most essential part. So, I'm sorry to give that other impression, because it would be very inaccurate if I don't correct it. On the other hand, there are certain things scientists aren't interested in, and in fact, consciously, they're sometimes not interested in the commercial direction. In that case,

there was a good explanation. The academic scientist is uncovering astonishing things every day, and to say to him, "Here, this is the thing you really should be doing;" he doesn't know if that's going to lead him to astonishing things. There may be a practical result, but it may not be as astonishing and as important as where his instincts were taking him. So, no, I have no fault with them at all. It's just that you've got to face the reality; you're in charge of your destiny in that plant, in that company. If that company needs something, you'd better be prepared to do it from the ground up with your own staff, because it might not drop in your lap from an academic lab. But there's probably some help out there somewhere if you look around.

SLATER: At Abbott, I assume you had academic connections?

RATHMANN: What do you mean?

SLATER: You had consultants on the outside? I'm thinking back to what you were saying about how 3M was very insular as a research organization. I imagine by being in a different business at a slightly different time.

RATHMANN: Abbott was in between. I think the dependency on the academic world in biotech is far greater than anything I've seen. I mean 3M is one extreme and Amgen is the other. That's a very interesting observation. Yes, I'd say that even today, I think biotech has swung back. They've swung back away from the idea that the external consultants are that important. We use them in a very different way from the early biotech companies, and not surprisingly. The earliest biotech company, Cetus for example, started in 1971. The first thing they did was put three Nobel Prize winners on their Scientific Advisory Board. That was a different purpose from making sure you had the most fruitful ideas in the world. Biogen put a whole group of scientific advisors together. They would meet by themselves and they had great stature and half of them were on the Board of Directors. Again, I'm not sure how extraordinarily useful it was. There's a purpose. You can decide. There are different purposes to having consultants. The purpose that we put them to at ICOS today is partly the result of the experiences at Amgen. At Amgen, golly, they were really great. They helped us think about our first programs. They helped us in recruiting the first scientists. They were brilliant, brilliant people. Yet, after a while, when they'd show up for reviews with the scientific staff, the scientific staff said, "This isn't useful. These guys don't think about this stuff but once every three months. Not only that, they're consulting with three other companies, and we don't really want to tell them what we're doing anymore." They just stopped it. The scientists themselves just brought it to a screeching halt, and the Scientific Advisory Board ceased to meet. The people that started ICOS, the two scientific guys—we were all business guys, but the guys that were really going to run the science, Bob [Robert C.] Nowinski and Chris [Christopher S.] Henney said, "I don't want a Scientific Advisory Board. I don't want them telling our scientists what to do."

Well, that isn't necessary either. You can have them as consultants. They don't have to tell your scientists what to do. But they were very skeptical about the use. So what do you end up doing when you do it? It's almost back to basics, which is not a lot different from what 3M did. That is, if you are in a field where there's a renowned individual, like Paul Flory, for example, you have Paul Flory come in and talk to you about your polymer program. Herman Mark was a renowned polymer scientist. Herman Mark would come in. He gave the same speech to every company he went to. He'd charge you fifteen hundred dollars and he'd give you this canned speech of the latest gossip from the industry. It was worth hearing, but it wasn't like Paul Flory who would look at one of your scientific programs, as he did with me, and say, "You seem to be happy that that number came out that way. I don't think that that's right. That number looks too low." He's right! You know. So that was a different order of magnitude of scientific quality than Herman Mark. But we used both. We had others that we'd come by, and that's more like what we do at ICOS. There's a Richard [J.] Ulevitch down at Scripps [Research Institute], he's got some science that relates to ours. We started out by finding a scientist at the University of Utah, and actually they had prepared an animal form of a protein that we thought might be interesting if there was a human form. We prepared the human form and have used Dr. Prescott as a consultant ever since, because he was an authority on lipases that are involved here. So we do it on a selective basis. We certainly have a lot of consultants in the medical field and some are difficult to work with. You may suddenly find that you're dealing with a guy who says, "I don't think you should proceed that fast with that experiment. I think you're taking risks." He may talk your scientists into reducing the dose, and you carry out a two-year study that you never get to the dose level where you see anything. The advisor thinks he knows everything in the world, and it's really pretty painful. So consultants are something to be very careful and chary about. I think you have to be cautious. But I think you'd be making a terrible mistake if you said that there's nobody out there that can help me. Well, I'll build a Chinese wall and be sorry for it later on.

SLATER: Back in the late 1970s, early 1980s, there seemed to be a certain range of molecules that people, for one reason or another, thought would be good targets for this technology. Were they floating out there? Did one person come up to it, as you were suggesting earlier, and then learn about it? Interferon, and IL-2 [Interleukin-2] were molecules that were studied by a range of companies. If you think of all the possible therapeutic areas and all the possible proteins, isn't it strange that a few were studied by many? I mean, what was the *Zeitgeist* of the moment?

RATHMANN: That's a very interesting question. I am not sure I have an answer. I do know that by 1987—I have a chart on this—there were fourteen proteins that were in the clinic. There were several interferons, either in the clinic or on the market. There were three alpha interferons: one by Schering, one by Biogen and by Genentech, and the third one was Amgen's. There were also two other interferons. There was beta interferon and gamma interferon. But gamma was not in the clinic, and it lagged way behind. It was in the clinic but it did not get on the market for a long time. So of the fourteen, you had five interferons. So there were nine others. What were they? Insulin, TPA, erythropoietin, tumor necrosis factor [TNF], platelet-derived growth factor, epidermal growth factor, and maybe two others, something like that. So

you had fourteen of these things—no, epidermal growth factor wasn't on the list because it turned out that everything on the list, except TNF—I guess platelet-derived growth factor wasn't on the list either, and fibroblast growth factor. Those came on a little later. They were not on the list at the time. But of all the ones on the list, they all went on the market except TNF, and the TNF receptor that's the decoy for TNF that is going to be a billion-dollar business by thwarting the actions of TNF. But we put TNF in the clinic at Amgen. We didn't have our own TNF. It was Asahi's [Chemical Industry]. Oh, the other one is IL-2. You mentioned it. IL-2 did go on the market, but it was a relatively small market.

Now, how did I become aware of each one of those, or how did people become aware of them? There were two colony-stimulating factors: G-CSF [granulocyte-colony stimulating factor] and GM-CSF [granulocyte macrophage colony stimulating factor]. First of all I think in every case it was an academic group, and usually more than one. Sometimes there were companies involved. Morinaga Mill of Japan came by more than once to see if we would work with them on M-CSF, microphage colony stimulating factor. How they got theirs, I don't know, but they got it from an academic group in Japan, I think. So what was the original basis of getting things going? A lot of times it was tissue culture, where you'd have a specimen of some sort or other that yielded an unusual protein or a protein that you might have heard about, or thought about, but didn't know where to get hold of it and all of a sudden one of these tissue cultures was producing an interesting factor. An example of this is the Mo cell line that was picked up by [David W.] Golde at UCLA, a surgeon who had a patient [John Moore] with hairy-cell leukemia, and then raised this tissue and found out that he made gamma interferon. That was the billion-dollar tissue that everybody was accusing everyone of stealing away from him, and they made the deal. He made the deal with Genetics Institute to collaborate it. What they got instead of interferon was GM-CSF. Immunex got it from another source.

So I guess the thing is that there was awareness that a new protein was interesting, and by its very nature, the ones that people were able to look at were the most interesting ones. The ones that are most likely to be useful therapeutically are what you might call secreted proteins, or soluble proteins. If secreted proteins are the most likely to be commercially interesting because they're going to transmit themselves through the body through the bloodstream, then it's quite interesting that the first proteins that you're likely to be able to isolate with rather primitive techniques would be secreted proteins. I never thought about it this way, and this is probably a sweeping generalization, but it suddenly strikes me as being very right. So in other words, if I've got the universe of proteins that can be prepared, and we know roughly how many that is; for humans it's about a hundred thousand. I've got this universe. Now, if the techniques that I have for finding a new protein are all over here and they all find secreted proteins, now I have, for the first time in my mind, the real explanation as to why, when I listed those fourteen proteins that people were working on, every one but one went into the marketplace, and the next five hundred proteins that people found generally did not. We found fifteen cadherins, we found fifteen phosphodiesterases [PDEs], we found six or seven ICAMs [intercellular adhesion molecules], and we found two leukointegrins. Just ICOS alone found forty-five of these, and one PAF [platelet-activating factor]-acetylhydrolase—Pafase, we called it. This is a secreted protein.

With my simple-minded approach, looking at thirteen out of fourteen that went on the market, I thought we were in clover when we got fifteen cadherins. I thought we were absolutely swimming in opportunities when we got six or seven more ICAMs. Amgen signed up Regeneron because they could make various brain growth factors, some of which are only going to be useful if you inject them into the brain. Trying to get into cells with proteins usually doesn't work. These extra-cellular proteins or secreted proteins are the ones that are going to be the most interesting and those are the first ones you're able to find. So it's not surprising that guys like me made the wrong calculation. Namely, this is a simple business. All I have to do is, one by one, hit the rest of the hundred thousand, and when I do, I'm going to have a goldmine in every case. Then I find no goldmines in cadherins. In PDEs, what's my goldmine? It's using it as a target and shutting off the enzyme, and we have an anti-impotence drug, which is very exciting. But it isn't offering anybody a phosphodiesterase. In the ICAMs, we know that our best hope is to shut them off in cases where the ICAM is in excess and causes a pathology. Leukointegrins function the same way. So you shut off alpha-D because maybe alpha-D enhances your ability to get athrosclerosis. But that's a very different thing from administering proteins. So what was it? It was the means of preparing the proteins that was spreading through the academic world. When they'd find one, because they're looking at secreted proteins, the probability was that they had something very exciting. So let's see what happened when I was at Abbott. What were we working on? We were working on urokinase because there'd been a background in urokinase in the company. The proposals for the recombinant DNA program at Abbott were interferon, but not very seriously because they thought it would be too hard to do; erythropoietin because they'd talked with Gene Goldwasser, they had that on the list; and tissue plasminogen activator, because they'd read the papers of Desiree Collen. By the time that they got into gear and said, "Let's go do something," Desiree Collen was signed with Genentech. Two years later Genentech cloned it and they owned the product.

So these are not coincidences. In other words, you really had a good question there. I don't know that anybody in the world cares about the answer, but I think you do. [laughter] I think it's a profound truth and interestingly enough, the reverse of that truth is coming before us right now. Human Genome Sciences can say, "We can prove to you that we have sequenced 95 percent of the genome because 95 percent of the genes we find are, in fact, in our gene bank." Well, is EPO there? Oh, shoot! It's not there. Oh, well, that's too bad. "Well, that's one of the 5 percent that we missed." Then it turns out that the ones that are missed are rare ones. So the method by which you're doing this is picking out those genes for which the material is produced in abundance, where there's an abundance of message. As a result, some of the most exciting things, which are also the secreted ones, are not picked up in your gene-sequencing work that you're doing. So now you have other people that are saying, "We get the rare ones, and we're going to have a much higher hit rate because we hit the rare ones." That may well be true, but there may be an awful big overlap, too. If you've already got all the rare ones out there like TPA and erythropoietin and G-CSF, how valuable is what you've found? Well, the market value of two of them, namely EPO and G-CSF, is sixty-five billion dollars. So if two things can give you sixty-five billion, you have a huge incentive to look for one more. You've got a lot of money to spend to look for one more.

I'm sure it's there, but I was the first person to assume that our hit rate was going to be 95 percent. I really was. It was just stupid because I just wasn't thinking about the real nature of proteins. I mean, the thing that makes you feel like it's got to be a high hit rate is that you will not preserve in your body a gene that doesn't do something critical for your life. It's not just that you use it. It's got to be critical, or it's gone. As a result of that, it's easy to argue that every single gene in your body is worth exploring from the standpoint of commercial potential because it's critical to your life. But after you've found about fifty of these, like the cadherins and the PDEs and nobody is administering cadherins or PDEs to anybody. What difference does it make that you happen to have a way of finding a lot of proteins that are membrane-bound and all the rest of that? As a matter of fact, in Pafase, the one that ICOS has, that's the soluble platelet-activating factor-acetylhydrolase, there's a second, insoluble version that to date is worthless. You can't get it into anything. You can't do anything with it. The only way you could possibly use it is to cleave it and hope that the part that you ended up with is biologically active and enzymatically going to degrade platelet activating factor.

So that's probably the explanation. I hadn't thought of it quite that way, but I have been kind of surprised in my own mind that we all started talking about the same things. The place that I'm offended sometimes is that there's a lot of sentiment today that the good things were easy things and they've all been done. So, "You poor guys that are trying to start a biotechnology company, you don't realize how hard it's going to be. You don't realize how easy it was back in the old days. They were picking, as they put it, 'low hanging fruit.' Erythropoietin was low-hanging fruit!" You say, "Wait a minute! Now there's something wrong here. If it was low-hanging, that implies it was very easy to get and put in your pocket, and yet all these companies that you know full well didn't find erythropoietin shows it wasn't hanging so low that anybody could reach, because they couldn't reach it." That's point number one. So it bothers me that they're discrediting some really great work that was done. Point number two also concerns me and that is, you're discouraging people today from thinking that there's anything good out there to be discovered. The way you're doing that is—and this happens all the time in science—you compare the status of a program in 1999 that started in 1998 with the status of a program that started in 1980 and you're looking at it in 1999. Now, if you truly looked at erythropoietin in 1981-1982, it would not look one whit better than a lot of the programs of today. I'll take PAF-acetylhydrolase every time. But if you make this other comparison, and you wait until it's mature and it's got all the potential and so on, and then you compare it to a program of today, you will talk a lot of people out of starting companies if they listen to this kind of logic. I think it's too bad because I think these companies are achieving wonderful things and they're going to be doing just as many great things in the future. I'm sure that in the year 2010 they're going to be talking about the "low-hanging fruit" of 1999, and I really believe that. By the way, 3M had a counterpart to that. At one time people started to measure whether a product could be afforded, because after all, they got Scotch Tape for about twenty thousand dollars, and that's a multi-hundred-million-dollar business. Why are we spending hundreds of thousands initially, later on millions—on fluorochemicals? It's never going to be as profitable as Scotch Tape, and that's right. It never would be. But we weren't going to get there for ten thousand dollars with fluorochemicals. We absolutely weren't. Yet, very profitable businesses were generated but the formula changes and it changes with time, and

it also changes in making comparisons. You really have to compare it to the same time in the development of the idea.

I think it is sort of an explanation of how the field has developed. It's developed along the lines of those things which turn out to be most useful therapeutically, and a lot of them were discovered prior to the time that this industry got going with recombinant DNA. Now, some were simultaneous. The colony-stimulating factor that Amgen came up with was in a cell line that was at Sloan Kettering [Memorial Sloan-Kettering Cancer Center]. There was a linkage in many cases—the tissue that came from cadavers or came from sick people, or whatever, like the Mo cell line. So they had a cell line and that produced what they thought was a pluri-potent stem-cell factor that would cause stem cells to reproduce. When they put it into a culture, it would stimulate the formation of a lot of different cells. Yet when contacted only briefly it would produce only one type of cell. It would cause the precursor to neutrophils to make neutrophils (granulocytes), and that's all it did. So you might have thought you were producing a lot of different cells with long exposure but there were feedback loops and so it appeared to stimulate a lot of different cells even though the first direct effect was strictly making neutrophils. That was very disappointing, but then it became exciting when we learned that the cells we were making were the ones that are consumed most readily in chemotherapy. So there was a good commercial payoff. The sources of a lot of these things were observations from surgical specimens and some interesting science going on in the academic world to study these tissues and then isolate the products from them.

[END OF TAPE, SIDE 5]

SLATER: This begins our second session with George Rathmann.

BROCK: Well, some questions I'd like to ask you about have to do with your involvement with BIO [Biotechnology Industry Organization]. I understand from my reading that you became involved with that organization in 1982 or thereabouts? Is that right?

RATHMANN: It was not my idea. It was Ron Cape's, who was one of the pioneers in the business, Cetus being one of the first biotechnology companies. He was the Chairman. He felt it was appropriate to start to organize an association. I wasn't sure what the association should be doing. I was very busy. It was the first years of Amgen. So I selected one of the people on our staff to participate on the Board. It was not very active there for the first couple of years when that person was representing us. But he left us I think in 1983 or 1984. That's when I became involved with the Board. After a few years, when they were looking for a sequence of potential heads of the association, I got in line, so to speak. I served my two years, I believe in 1987 and 1988 as Chairman, and continued to be on the Board most of the time since that date; although, right now I'm not on the Board. There's always kind of a cooling-off time after you've been on for a long stretch. Right now I'm on one of those "vacations," but I have been

associated with BIO since the beginning. During the two years that I was Chairman, I was really very active. The main opportunity for someone to do this is that they help the industry and get themselves exposed to things that otherwise they'd never have access to. I was meeting with Congressmen and staffers, and understanding the whole political process by necessity as the Chairman of what at that time was called IBA. That was a real opportunity, and I certainly was grateful. In turn, you really can carry some weight. I mean, you really carry the mail for the industry because meeting with those people is essential for them to understand. As I mentioned in the talk today, for example, John Dingle and Ted Kennedy would not support drug price controls after a lot of people contributed good thoughts and good ideas and lobbying, which is basically what we did. Lobbying, of course, has a bad name. Everybody assumes that you put money into the hands of congressman and you get them to do wrong things. Well, the lobbying that we were doing was what it should be. We gave an education about biotechnology to these people, so they fully understood the consequences of a new piece of legislation that could be very damaging to the industry and if it's damaging to society, they should be careful about it. That's what we did with Dingle, Kennedy and many others.

There were times that we interacted very strongly with Washington and it became a major activity particularly in connection with the FDA [Food and Drug Administration]. Some significant advances were made during, and since that time, by interacting and trying to show the FDA where some of the problems were. Commissioner Kessler was quite amazing because he'd say, "Well, I don't believe that's a problem." We'd say, "Well, come on, let's go through the facts." Ten years ago there weren't products being put on clinical hold. There weren't any disasters. Why do we now have products going on clinical hold all the time? It's because super conservatism has been allowed to creep in and people just decide not to take any risks, instead of weighing risk/benefit ratio. As soon as he became really fully aware of the FDA's history, he could realize that things had gotten a lot worse without his knowing. So it was an opportunity to share information with the people that were determining the destiny of biotechnology. It was very satisfying when they seemed to re-orient themselves, as he did to some degree. But unfortunately, after a few changes and he began to feel that all had been done, and the job was over.

BROCK: Do you think that the experience of you and your colleagues in BIO was as much an education for people in the biotechnology industry about government bureaucracies and political process, as it was for the powers that existed?

RATHMANN: I think it was, yes. One reason that's important is that it takes an inordinate amount of patience to present information to people that you feel are antagonistic. If you begin to understand their antagonism, you have an incentive to say, "Let's share information. Maybe we can talk them out of it." But your first reaction is: I don't want to waste my time with those people. They're wrong-headed; they've got wrong views. That doesn't accomplish anything. So I think we were all educated; we saw the need for understanding the viewpoint of government people, and the need for patience because they truly were not very well informed. You could see some progress when you did inform them. So you set about the rather difficult

task of making sure. You listened to them when they had views. I think they were actually right. I think when they said, "You can't have national health care without price controls," I think they were partially right, because I think if you're going to pass the money out to cover every possible cost, and people then can run the costs up because there's somebody there to pay for it, that's a really serious problem. But it would be paying too much of a price if you put in price controls because then you've destroyed any element of the free-enterprise system that relates to health care, and the free-enterprise system works. So you have to think about it the other way. How do we preserve the free-enterprise system? Rather than, how do we reduce health care costs? Because you want to do the two together, not one and not the other. So I think we recognized the problem more than we ever had before, but we still weren't sympathetic with the idea that a ready solution is to just put in price controls. You can control the prices any way you want. Matter of fact, you can completely eliminate the costs of any new drugs because there aren't going to be any. You're going to run the companies out of business. In most cases, I think we can show them that new drugs save money. The drug component in the health care package was 7 percent, which was a shocker to most Congressmen when you tell them, "You're looking at 7 percent of the problem. If health care costs are too big, you're looking at 7 percent. You know what percentage of the problem you're looking at when you look at biotech product costs? You're looking at about 8 percent of the 7 percent. You're down there under half a percent. You think you're solving the problem by putting in price controls on biotech products. It's absurd. It's just plain absurd. So it isn't going to solve the problem. But not only that, I can show you the direct relationship between the opportunity to make money in the biotech industry and the support of the industry by investors. It's questionable sometimes as to whether—with a large pharmaceutical company—there's a direct relationship between their profits and what research programs they're able to initiate. But in a biotech company, there is a direct relationship between the money they can raise in financing, and what they can accomplish. If they cannot finance, they cannot do anything. They're out of business because they don't make money until they've got a product on the market."

So there was a lot of education. I think we also began to understand the other views. I certainly understand the views of the FDA a lot better because I can see the pressures that are on them from all different sources. That's why I often feel—and it's a role for Chemical Heritage [Foundation] among others—there's a role to keep public education in mind all the time, because if the public moves off in the direction of a risk-free society, the FDA has no choice, they have to go toward risk-free behavior. Risk-free behavior, which does not weigh benefits, will always lead them to the same thing. You would not inject a patient with anything—saline, for heaven's sake—if there isn't an upside. So if you don't look at benefit, you will do nothing. You'll just stand absolutely still. The medical equation is particularly serious because you can picture almost anything going wrong with almost anything you do, and you have to be weighing the benefits carefully. Our job in starting a clinical study is to show the FDA that the probability of a benefit is pretty high. Then when we begin to see those benefits, then we expect them to weigh the risks to continue with the program in which we've got very good evidence we're going to see a benefit.

So once you accept the fact that they're constrained by those kinds of parameters, you can still try to attack the idea that risk-free doesn't work, and at the same time, be sensitive to

the fact that they've got a lot of pressure on them. So I think we learned a lot, and I think BIO has been very effective. I sure hope they can do something about the current threat of price controls because I think it's not a pleasant experience to wake up this morning and find out your stock has dropped 20 percent while you were out of town for one day. That's a big hit. There are a lot of investors. I'm going to be hearing from them. They're going to say, "What's wrong with the company?" In almost every case that our stock has taken a hit, it's been an industry issue, not a single company issue. But we're just as susceptible as any other biotech company. If you have really bad news, you're going to take a hit. But it's particularly painful to keep taking hits that have nothing to do with the performance of your company, and it's what happened in 1994. As I showed today, it's a steady downward trend in stock price for everybody, so that you're almost unfinanceable by the time you get to the end of the year.

BROCK: That covers the regulation component of the world that the industry operates in. Well, during your time with BIO, were you involved in any activities on the public perception side of things?

RATHMANN: Well, we had several ventures, and some of them were successful and some of them weren't. At that time, it was clear that we had a mission—a good mission, but maybe an almost impossible one—to educate people about biotechnology. One of the approaches to that was provided by some of the PR people from Monsanto [Company] and DuPont. They were very sophisticated PR people. They said the thing to do is to put together videos that would be professionally done, that would tell the biotech story, and make it clear how benign it was as a technology. People were afraid of it. So let's put together these videos and let's inform the public about how wonderful it is. We'll make these videos available to schools, and this must be a problem you people encounter all the time because it sounded very attractive. So we had a budget at that time. I hate to speculate, but I know it was infinitesimal compared to the budget at BIO today. It was several hundred thousand dollars a year, which covered everything we did or something like that. It was a really modest budget. So we were going to allocate a few hundred thousand dollars for public relations.

Well, you can't do much with that beyond just having some publicity. But what you can do is say, "Well, let's tax each of the participants at BIO to produce these videos that we think will be educationally important." There was no doubt about it that one of the reasons to support it, if you were Monsanto, was you were going to get a little message in there about some of Monsanto's products. There'd be a trailer at the end to say, "Generously supported by Monsanto, et cetera." It was reasonable that you could collect special funds in this way.

It was very tough for us at Amgen. We were losing money every month. We didn't have a bankroll of any kind. We didn't have a cash flow that was positive. The idea that we should help participate in funding these public relations documents or videos was very difficult for us, but we tried to do our share. Let's say it's going to cost you two hundred thousand dollars to put on one of these videos and it couldn't come out of our standard budget because it wasn't big enough. So each company tried to find ten thousand dollars. I was simultaneously

attending PHARMA meetings, [Pharmaceutical Manufacturers Association], PMA it was called at the time, and they were saying, "If you want to do a public relations job, be careful. That's expensive. What does it cost to impact the habits of a housewife? Fifty million dollars. How much money do you have for your public relations if you're going to reach John Q. Public or Mrs. Q. Public? You've got a few hundred thousand dollars. You aren't going to reach them. It is not possible." We didn't happen to have fifty million dollars to have a massive PR campaign. They said, "Well, then, don't try it." Well, I thought, that's a defeatist attitude. Here we want to affect public opinion and you're telling me give up, don't even try. They said, "No, but there are opinions you can affect. You can go after the key decision makers in Congress. You can go after the key targets in various types of activities such as the FDA. You can start an information campaign to affect those people that are very important to you. You can also develop coalitions or consortia or some types of alliances so that you don't try to do it alone. You take the Pharmaceutical Manufacturers Association along with BIO, along with maybe Chemical Manufacturers [Association] or somebody else, and if these are fairly well represented in the mission you have and they all have similar problems, you can get at least four or five organizations. You're leveraging what you're going to put in. You're going to be careful to address the most significant populations, not just John Q. himself, and you're hoping that this is going to rub off in benefits to society that then the average person will get an awareness that biotech can go great things."

So we learned a lot about that, and have evolved into an organization that I'm not that close to anymore. It fully recognizes the realities as well as the opportunities, and the realities are pretty tough. In fact, a generalization in my mind was the most effective PR that we can put together is getting companies to be successful in launching products to treat patients, because it is so dramatic when they can have a friend or a relative who's going to gain the benefit. I mean these things, it's like a word-of-mouth publicity campaign, but it works. I get people walking up to me today when they recognize who I am or they know where I came from, and they'll tell me, I saved their life, or I saved their mother's life. We impacted their quality of life to the point where it's changed everything about how they live. It's very effective, and you don't have to spend all that money, because you're trying to put products on the market anyway. The fact that good things are happening will take care of reaching the public in many ways. So I've felt for a while that it's probably the single most important type of information exchange that relates to our success. In other words, when we started addressing these things back in 1984 and 1985, I gave a speech at the Brookings Institute. I thought it was a good speech, it was on the promise of biotechnology. We were saying, "Here's what it's going to do." I think because I was careful in how I did it, and I took information for all the existing biotech companies so I could talk about the potential of tissue plasminogen activator, about plant genetics, and about a dozen or more different potential products that were getting close, it was effective. But when you're able to talk about results, it's much better. If you can talk about results, I think it's a terrible waste of time to have a lot of publicity about what biotech's going to look like fifty years from now when the intersection of biotechnology and computer science gives us a brand new dimension in medicine—I think that's really very ineffective. I think to tell somebody we've cured a lot of people of anemia or that we've made big advances in cancer, it has a message that everybody relates to. So I think one of the other things we learned is that maybe our very successes were a better way to impact a cross-section of society. If by taking your PR program

and addressing Congress, opinion leaders, and decision-makers in the government, that would facilitate the approval of the products that are pending if we did it right, and that in turn would impact the society by an indirect way. I think we came up with more or less that conclusion.

We did put those videos together. They were very good videos. I still have them. They're very impressive. They were well done. They kind of proved to you that genetics is an old thing and we're not doing something new and horrible. We're doing just a little more of what we did before, and in a more controlled way than used in conventional genetics. They were really well done. But I suspect that their impact was very minimal. The number of videos that were distributed and how they got people to buy them, and if they didn't buy them, how they financed the distribution. We thought we had a liquidating program in which somebody would take on the job of getting them distributed for a modest amount of money. It never worked. It just cost a lot of money to get them out there into the schools and so on. The schools didn't exactly know what to do with them. That whole program was more educational than it was useful. Educational for us rather than the people we were trying to persuade.

So that's still a big issue and I sympathize with the mission of the Chemical Heritage Foundation in trying to say, "Let's help people really understand and get good feelings about science, and every little thing that can be done is important. The younger the people are when they get that message, the better off we'd be." But it's really a difficult job. Hopefully, biotechnology helps and the sort of science that's going on helps, because we do have this other thing going in parallel where people are so impressed by the fact that there's a drug to treat a problem that previously has been totally untreated. That's compelling, that what's going on in science is a good thing, and bioscience is certainly a great way to move ahead as far as things that are good for society, good ideas for kids to think about, and the whole thing leads to a positive result. But the direct effect on the entire population is something that's just about impossible to implement.

BROCK: I have just one other question about BIO: were there sorts of questions that you and your colleagues were addressing about the industry itself? About maybe rules or standards, things like that? Industry practices, or forming a real cohesive sense of industry community?

RATHMANN: There are some internal education programs along those lines. Because of the different status of different members of the association, some of them have had many products that have gone into clinical testing, some have many that have been on the market. It's relatively easy, and the Pharmaceutical Manufacturers Association has done it for years, to set up workshops and you kind of bootstrap yourself. You have some formal individuals invited because they're very knowledgeable, but you also have participation by the haves to talk to the have-nots. That's constant. So how to make sure that you dialed in enough good manufacturing practices, but didn't have the overkill that might be disabling. What are the common practices, what are the best practices, what sort of safety precautions are desirable and necessary and should be endorsed? So there's lots of internal guidance for associations like that.

The only thing that's not shared is anything to do with pricing. Of course, if you have to take on the government that's going to put in price controls, that you can do. But what becomes a very difficult subject once in a while is how a biotech company decides it's pricing, and there's always great concern about potential antitrust. Of course, it seems like an absurdity. You have a group of companies who collectively lose money, and you would think it's a strange quirk indeed to think antitrust. It's really kind of unfortunate. But it really is not necessary for an association to go ahead and discuss pricing, and I can see why there's a great sensitivity. So that's forbidden territory. But helping another biotech company in any other way is absolutely appropriate and it happens. In fact, we actually have a lot of relationships with PHARMA, pharmaceutical people, because we have many common members, and there'll be information exchanges across that interface all the time. So there's huge value in these associations. Of course, it has the very desirable purpose that if you're going to argue with the FDA; a single company rarely ever wants to take that chance. They're just afraid that if they start to let the FDA know that they've got serious objections to the way they're doing things, it just sort of sounds as though what's going to happen is you're going to get on a blacklist and that somebody in that FDA is going to make a decision against you for the sole reason that you've given them a big pain in the neck. It's much better, if you're going to have a confrontation or a discussion, that it be done by the association and they can just simply say, "There is an area here that needs your attention. There seem to be some concerns." That's a pretty good system, although I say it isn't impossible to do it on an individual company basis. So there are lots of benefits. I think what I find is the biggest benefit is that when you're confronted with a lot of arbitrary decisions and price changes in your stock that you have nothing to say about, and you get to feeling like you have no control over your destiny and so on, the natural instinct at that point is to complain. But complain to whom and what does it do? It doesn't really accomplish anything. Much more fruitful then is: what are we going to do about it? An association can help you focus on the solution to the problem rather than crabbing about the problem, and I think it's wonderful. When I hear people complain I say to them right away, "Are you a member of the association? Why don't you get active in that association? Why don't you use that association to approach who it is? Is it FDA? Is it HCFA [Health Care Financing Administration] in reimbursement? Is it Congress? Just use the association and share your time and effort with them, and it will be multiplied manifold because there are others that could do it, and third parties speaking on your behalf is very, very effective." The lobbying, in other words, that was done—and I mean proper lobbying—in connection with the patent system, the regulatory issues with the FDA, the finance issues and how to maybe get better consideration of these companies. In one of those testimonies that I gave to Senator Pryor's committee, he asked, "Just how much have you gotten from the government in financing your R&D anyway?" I said, "Nothing." He said, "Would you answer that question again carefully? I've asked you how much you've gotten? Don't forget about tax breaks." I said, "We lose money. We don't get any benefit from a tax break. We don't pay any taxes. As far as the other things, we've raised all our money from private investment. The government hasn't funded our programs. We don't have NIH [National Institutes of Health] grants in our company. The government has not put money into Amgen"—in those days—ICOS to this day. It's still true.

Well, that was a big revelation. I mean, it just had to be. But there are certain tax considerations that are worth talking about. There are indeed tax credits, which ultimately will

affect you in the future, when the time comes that you're going to make some money, and so it isn't like there aren't some benefits there. Actually, the tax issue that probably is the most significant for biotech is that they keep toying with the idea of a capital gains tax reduction, and want to do it in this way or that way that's going to be just right. It's so simple in my mind that if you ask somebody to make an investment in a biotech company and if they hold it for five years, and it's a high risk investment on a small company, where's the harm in giving them a break in terms of capital gains? It can't help but stimulate more investment in biotech, and the actual amount of dollars is proven to be a very small number. As a matter of fact, because there will be eventually a capital gains anyway, even if you delay it and you reduce it, if there were more investment in very successful businesses, there's more taxes. The businesses pay taxes on their profits, and the individual investors pay taxes on their gains to some degree, no matter what. So it seems like it's a pretty obvious place to expand the horizons of a biotech industry.

But my own feeling is, if I had to ask for something from the government, the first thing I'd ask for is reduced barriers and not necessarily tax breaks, because I think tax breaks give a wrong message to society that they're subsidizing businesses and businesses therefore are manipulating the government. So just take away the barriers. Take away the barriers to international trade. Very important. Take away the barriers in regulatory situations. For a while there was a possibility that there would be dual regulation of biotech, and it still occurs once in a while. You've got the FDA, which is a mighty force, and you've got EPA [Environmental Protection Agency], and all of a sudden someone's trying to say, "Well, you've got to get your product approved by the FDA, but you've got to have your process examined by the EPA to see that you're not environmentally hazardous." Well, it was clearly overkill in many ways, far beyond what anybody might have imagined. That has so far not happened, again, by sharing information and recognizing that the FDA knows full well what's safe and unsafe in what you do. Good manufacturing practices are, in fact, safe practices. So it's taken care of. We don't need an overlap of regulatory agencies. Those kinds of issues are extremely well addressed by associations.

BROCK: I just had one follow-up question: has the relationship between PHARMA and BIO moved closer? Has that relationship increased over time?

RATHMANN: It's basically a strong, positive relationship. There are times that kind of shake you up, when you have the feeling that your ally, PHARMA, is not your ally. The only thing is, you have this concern as to where that might emerge some time when you least expect it. So you're trying to streamline the FDA. You sometimes have the feeling that the biotech companies that are have-nots are far more dedicated toward letting new products come out faster than the organizations that have all the products. There are times when individual decisions do smack of being in conflict with the way BIO would like to do it. But that's a small price to pay for a relationship that overall does an awful lot of good. One of the reasons is PHARMA is so much more sophisticated in having struggled with many of these issues for twenty, thirty, or forty years. I know I've been associated with PHARMA for thirty-five years. So I know that they've been around a long time, previously the PMA. They are very savvy

about when the government is putting its nose under the tent, so to speak. So it would be tempting to say, "Oh, that's not really a problem yet. They're only doing this and this. Now they're only doing this and this and this. But that's still not really a problem. It's not impacting us." And PHARMA's very quick to say, "Now, wait a second there. If we ignore the steps that are being taken, we could be leading to a very serious problem, and we'd better take action now." They're good at anticipating where some of these problems could go and be very serious. They were the first to indicate that the so-called innocuous prescription drug benefit—the government's going to pay for prescription drugs—they could see that one coming right away because they've been there a few times, and that is, "Hey, guys, there's a certain sequence of events that are going to occur here. Number one, they're going to offer prescription drug benefits to everybody so they have all their drugs paid for. Then once they have all their drugs paid for, the way they're going to get that through is, they're going to say, It won't cost that much. Then they're going to do it, then they're going to measure how much it does cost, and we can estimate it's going to be tens of billions of dollars. This idea that it's not going to cost much is absurd. So now what happened was, you went ahead because it isn't going to cost much. You found out it cost a lot. There's only one thing left to do and that is have price controls to keep the price from going up. It's all going to follow like night follows day."

You go through that a few times, and you watch what the history tells you, and you say, "Watch out for that one because as much as we'd like to see everybody get a drug benefit, and certainly we hate to see that people can't afford a particular drug, but the solution that says let's have our health care bill go up by a factor of ten and no one's going to fuss over it, that's a terrible solution. It's not going to happen." So that's where the PHARMA people help the BIO. BIO, on the other hand, is much more dedicated toward change than PHARMA is, and it's something you've got to watch out for. So sometimes, the status quo is too acceptable for BIO's taste, and then we take slightly different views.

But I think for the most part, both sides are very sensitive to their obligation to keep the other party informed. That exchange of information is very important so you aren't zigging and zagging, and then getting them pitted against each other. I think it's been very successful the last five years.

BROCK: I think, then, I would like to move back to some questions about the early days at Amgen. The first question that I had was in the 1981-1982 period when staffing is starting, the organization is being set up. What was your individual role in designing how the company would be organized and structured, and what was it like trying to staff this new organization?

RATHMANN: Well, first of all, in general, I followed the precepts of 3M: that the smartest people in the business are not necessarily the guys at the top. So if you analyze what's needed in the way of knowledge, you find out that in the case of Amgen, your Scientific Advisory Board was a reservoir of incredibly insightful science, so you'd better listen closely to what they can tell you about the scientific approach and where the opportunities are and whether things are right or to move ahead into something else. In terms of structuring the departments, hey, these

are academics who have put together a large number of different departments around the country. So if you're going to do something practical—and they didn't know how to do that necessarily—they were quick to suggest that you don't just want molecular biologists. Those are the people that splice genes. You're going to need a combination of biological backgrounds. You're going to need some biochemistry, diagnostics, immunology, monoclonal antibody capability and you're going to need this and that. Well, of course, it's very easy to list a lot of the things you need. It's harder to do it, but at least you're aware. My first idea was I'm going to hire a bunch of molecular biologists, because when I was at Abbott, they didn't have a strong enough team in molecular biology. So that's what I wanted, recombinant DNA. But when you're setting up a separate company, it's actually different from doing it in Abbott. In Abbott, you had the biochemistry, organic chemistry, and analytical chemistry. Here you have to be careful. You can't have these poor lone rangers in there, molecular biologists that can't go to anyone to get the things they need. They advised me right away, "Now wait a minute. It's not going to be all molecular biologists." And they were right.

We had quite a cross section that was sort of laid out by semi-formalized planning, saying, "Well, let's start with a plant for forty scientists, three of these, six of these, five of those, et cetera. and then we'll see what we can do." We set about right away to use the scientific advisory Board in recruiting, because we figured it makes a difference if you get top-notch people, reasonably top-notch people or average people. So we went after the very best that we could, and we had the scientific advisors screen our candidates in the best way you can, which is: they pick up the phone and they call their colleague at Harvard or at Princeton or somewhere else and say, "What do you really think of this guy?" I don't want the, "He's better than average, like everybody else you turn out. I want to know." We got the right answer, so that we had a very careful screening process for putting these people together.

Then I'd run them by the scientific advisors and have them meet them personally, and the reason for that was to say to these young people, "Yes, you're scared to death that this company's going to go out of business. I think worse things could happen to someone than finding out that you've impressed Lee [Leroy] Hood or Marvin Caruthers or Arnie Berk, these people that you've met in the last twenty-four hours. If you do a job, and we happen to have a tough time, you're still going to be intact all the way with respect to your professional career, because you're going to be impressing these people that are on our Board and they're terribly interested in what's going on in the science of Amgen." As far as I was concerned, it was a rare day when we got turned down by somebody that we thought was first-rate. Yes, I remember the disappointment about the second month, the guy that I thought was very good, said, "No, I want to go to DuPont." "Why do you want to go to DuPont?" "Because it's safer. DuPont's going to be around for another fifty years. I don't know that about you." I gave him the pitch about the scientific advisors, the whole bit. He went to DuPont. Then I, of course, have to say to myself, "Well, maybe he's not the right kind of person for biotech, although he could have been a great guy. I don't know." But we went after them really hard when we knew their records were very strong. Rarely did we get that problem.

I had some others that cropped up. There were times when they were worried about who they'd report to, and you didn't know who they were going to report to, and you have many

uncertainties, but eventually you develop a cadre of people that are very, very good, and the people that are coming in and interviewing realize, "Hey, those are good people, and I'm going to be part of a great team." So, we had a very high success ratio. Thousand Oaks is a good place to recruit, too. It's a wonderful community, and so is Seattle, by the way. The crime level in Thousand Oaks is about the smallest in the country for its size. It's got incredible climate. There were a couple of people who turned me down because they were sure we were close to the smog belt. I wasn't able to get people from northern California. They hate southern Californians. [laughter] I was quite astonished at that. I found out that it was hard to get people out of Boston and some places on the East Coast because they didn't like the culture. We did very well, but these are all issues. In the Midwest—a fellow would come out and you'd say, "Well, this is really wonderful. How would you like to live in California instead of Kankakee, Illinois or something?" They'd say, "Well, how about housing?" Whereas I had enormous difficulties recruiting Californians for Abbott. I found out that recruiting people from the mid-West into California was almost as hard, because the person would say, "Well, I've got two acres, and I've got a four-bedroom house, and it cost me forty-eight thousand dollars; I look around here and it's three hundred thousand for anything that I could possibly live in. What am I going to do?" Well I gave them front-end bonuses once in a while, but I had to keep things pretty well in line. I couldn't just go off the deep end. So we missed a few like that, but I'd say we got at least nine out of ten of the people we looked at. We had the combination of the Board and the things we were doing, and a good track record. If they checked me out back to Abbott or back to 3M, I had a pretty neat reputation, so that was helpful.

Then as we built strong members of the staff, they were lightning rods for getting more and more good people. The way you actually allocate resources has always been an interesting issue among people, because everybody wants to know. They think there's some magic secret, and I suspect there's a lot of magic here because you can do it wrong. But there are a few things that are terribly important in my mind and one is that you make sure that the people that have an assignment like their assignment. So you're very reluctant to start shifting people around. You're far better off to recognize that you shouldn't take that responsibility, you shouldn't take that authority; you shouldn't take that power. You should get him or her to tell you how great it is to go over there, and that program is very exciting, and you pull him rather than push him. The push just doesn't work. They're bent out of shape. They feel pushed around. We practically never did that.

Another question is: how do you terminate a program? Well, pretty carefully, because sometimes persistence can be the way you get there, and if somebody has persistence, you'd better be a little careful about derailing him because he's in a bad program. He might be right; it might be a good one if he thinks he's about to get some daylight. So you've got to be careful about that. But you also have to be aware that it's far better off to attract him into something than to push him out of something. It's not that hard because most of the people are alert enough to see that program is moving ahead very rapidly and this one hasn't made that much progress. In fact, we've had a couple of setbacks, and there's no obvious way around these setbacks. So you do it somewhat more cautiously than might sound appropriate, but I think it's not a difficult job to allocate resources. You have to do it with a certain amount of consistency, and you have to do it with a thoroughness and attention to the individual attitudes of people. If

you err once in a while, when someone stays on a program that does fail, or a little too long, I don't think it's worth the pain of trying to hit everyone at the very first moment you know it's in trouble to try to pull somebody out because some of those do recover, and you're better off to give a little slack in the system. That's really one of the keys that I learned at 3M, that intentional slack in the system means that the scientist is not held to every second of every day that he's going to be working on his program. He or she has this latitude. 3M called it 15 percent of our time. That's a lot of time. We don't have a formalized 15 percent, but let there be slack in the system so that you can try something that you're intrigued by, you can even do parallel studies once in a while because you don't know which one's going to work. You allow a lot of that stuff because, fundamentally, there's a divergent or creative dimension to science that you just can't predict precisely the right single path to be on. To allow for that, you allow people some latitude and some slack so they can do lateral exploration once in a while, divergent thinking, and so on. It's really not a difficult job once you get used to the idea that you're not a genius and that you can't dictate precisely what people should be doing, that you're going to have some inefficiencies, and mostly you're going to hope that people are so excited about their program that they're going to generate their self-pressure. You're not going to put pressure on them. Pressure has a very negative consequence. In order to really make pressure stick, you almost need a punitive step at the end of the line. "I'm telling you, I want that by July 1. I'm telling you I want that by July 1—oh, it's July 10." Slap! Once that happens, you decide the next time, you're not buying into it. The next September 1 date, you're going to say, "It can't be done by that time." All the forecasts are slower than needed. They all get slop in them to the point where you can't get on top of everything. So you have to say, "I want you to work as hard as you possibly can to get that July 1 date. Remember this: others are depending upon that date because when you get that molecule, they are going to start their studies. They are depending on you, so it's really important to try to hit that date." But, you tell me what went wrong when it goes wrong, and you tell me how you learned what you've learned, then we're not going to go back and beat up on you. We're going to just give you some more time. I've even gone to the point of saying, "You hit your goal last year. Your goal was to have that before the end of the year. By golly, you got it on December 41, or December 52. That's pretty darned good." [laughter]

We even pay off some of our incentive programs to say, "Hey, that's good enough." [Robert] Swanson, the CEO of Genentech, didn't do that. I understood. He refused to make allowances for any kind of slack. He ran a great company. So there are other ways to do it. He felt that dates were dates and you've got to hit them. He was also trying to make a profit every quarter. A company that has no products, the way you do that is you have to hit milestones that you're going to get payoffs on, and if you're going to make a profit in a quarter when you're in that early embryonic stage, that means that you've got a way of getting a collection in December, you're not going to hit that quarter if that collection comes in January. So Swanson would say, "You don't have a choice. You've got to hit that December date, and I don't want anything later than December 31. That's as late as I can go." So he differed from me. I didn't care that much whether I made a profit every quarter. I had the feeling, if I wanted to do the right thing, I had to make a bit of an adjustment over that idea that I could predict my income stream or cost stream so perfectly that I'd know exactly what's going to happen every quarter. So we didn't make a profit every quarter. He did. He was very successful. His was by far the

most successful company until Amgen came along. Now, whether that was partly because Amgen had a little more flexibility, I don't know. We were lucky, too. I'm sure that's all part of it. A very careful thing is to avoid fear. That was in one of the things that we heard all the time at 3M. We don't want to have people afraid to do things. They'll never take risks if they're fearful. Fear is a lousy motivator anyway. I mean, it's a tremendous motivator, but it usually channels you in the wrong directions and gives you a terrible outlook. So it's a terrible way to run a company. We don't want to be that demanding that we end up with fear. We do want to set a very high standard of excellence, and there are lots of ways of doing that. At ICOS we did it in a way that was different from Amgen in the sense that suddenly we had a Board of Directors that were just pre-eminent in their background. We didn't have a pre-eminent Board at Amgen. We just put various people, mostly venture capitalists on our Board. But at ICOS we ended up, by virtue of a different philosophy, getting a really pre-eminent Board.

[END OF TAPE, SIDE 6]

RATHMANN: On the surface, the Board may have looked like it was just window dressing but they are marvelous, marvelous people. They're still there. Walter [B.] Wriston, the ex-Chairman of Citicorp; Frank [T.] Cary, Ex-Chairman of IBM [International Business Machines]; Jim [James L.] Ferguson, Ex-Chairman of General Foods; Bill [William H.] Gates [III], current Chairman of Microsoft; and a number of others that had excellent reputations in the business world. When you realize that they're supporting your company, they're buying stock along with other things that they're doing, I think that that sets a standard of excellence for the entire organization. It's a wonderful way to start. Our scientists are very well aware that they're expected to be performing at a very high level. They're going to disappoint some really wonderful people if they don't hit their goals as well as they possibly can. Still we don't have punitive steps that are taken if there's a miss. So I think there's a lot of pretty obvious things to do that are not always done correctly, and it's not hard to do them right.

BROCK: Has it been your experience with Amgen, and I guess ICOS too, that the organization has to change as you near the—I don't know what you properly call it—"the commercialization phase?" Or when you're nearing the end of FDA approval and clinical trials, does the nature of the organization change? Do you have to reduce the amount of slack time you have in things? I'm just wondering.

RATHMANN: What you have is a metamorphosis in any program, and people are aware of this. They know that there is more slack, more uncertainty, more willingness to concede that there might be a problem, and hope it's going to go away in the early stages. So there's kind of a ratchet that works as you go through the programs. It could in fact be that a given individual who moves along this progression is beginning to experience a different level of pain from the fact that some of the freedoms are gone. But actually, it turns out that what really happens is that certain individuals are more susceptible, have a strong appetite for being very exploratory

and continue to be that way, and others are more interested in being more focused. So, yes, a successful product depends upon early days, divergent thinking, and slack. Later days: focus, execution. It's still a balance, because sometimes in the later stage, if you run into an obstacle, there are two ways of dealing with it. One is to knock it down, and the other is to think about maybe the best way to get around it is a whole new approach, something that sort of backs up a little before you start going ahead along another channel. So you always have to consider divergent thinking even at the very late stage. Conversely at the beginning, once in a while some focus is really desirable. The balance does move in the direction of less slack, as you said.

It's not always the same person that ends up making those adjustments. Sometimes there's a pass-off, but you've got to be very careful about pass-off. If you pass off responsibility from a number of people on the research side or the exploratory side to a number of people on the development side, that is fraught with great risk. There's a right way to do it. I think I know how to do it. But there's a necessary set of circumstances that you make sure hold. So if you're the inventor and it's pretty obvious that you kind of like a scatter approach to things and it looks unlikely that you're going to be the driver for getting this thing to go all the way, the first person that's going to tell me about that is you. You're going to say, "You know, I'm getting to the phase where I'm in love with this molecule, but I don't really think that I'm going to enjoy the next four years of this thing." "Well, that's very interesting. If that's the case, we'll have to find somebody that does have that interest and capability. But there are some prerequisites we'll put on you. Number one, you personally get involved in selecting that person with us, and you will say that your confidence is that that person will do the job. Then, I'm going to have to be convinced that he likes what you've done up to this point. If I find a guy somewhere who thinks he's the greatest guy for carrying this ball the rest of the way, and he tells me how many mistakes have been made by the research group; I am not interested. I'm not interested in starting over again because he wants to have a fresh start. I'm interested in the guy that's going to follow it the way you would do it if you had the interest, and who has a lot of respect for you and whom you have a lot of respect for. No matter how much you're going to go back and do something else, you're on call. For the rest of your life, you're on call for this molecule. [laughter] This is your molecule. You know more about it than anybody. You're never going to turn your back on this molecule, and we're not going to turn our back on what you know about it. But, we got the message; you'd like to start doing a new exploratory program. The one you have in mind sounds pretty exciting. That's all okay. But before you go, you're going to find that guy or woman who's got the same kind of motivation that you've had up 'til now, but wants to take the next step, who absolutely has confidence in what you've done, so their main goal is to sustain what you've done, not show how dumb you were. You give me some of those prerequisites and by gosh, you're off the hook. But you're going to be called on occasionally to make sure that we don't lose your institutional memory when we embark on this program. So the thing turns yellow under a certain circumstance, they should be back to you and say, "Have you ever seen it turn yellow?" "Oh, yes. I know what that is. That's an impurity that came in on the hexane that we were using." "Okay. Let's get that fixed. In minutes instead of months." Some people can do both. Some people are absolutely incapable of doing much of the down stream stuff. You have to decide whom that is, and hopefully they will agree, "Well, that's not for me." It was a very difficult decision and I didn't make it alone. It was almost pushed on me when Dr. Fu-Kuen Lin, the scientist who discovered

erythropoietin—and he had done it by guts, courage, and tremendous effort; a brilliant guy—was running the program at the time when it began to get to a much different magnitude. He ran it when there were two or three people on it for the couple of years until he got to the gene. Then all of a sudden we wanted twenty and thirty people. He was a Taiwanese; he was brilliant; but he had a little language difficulty, and it was difficult for him to really lead an organization and effectively even chair a meeting because he didn't have that facility with the language. So there was immediate resentment that he could not handle the job. Well, that's a really painful thing. You're going to take the job away from him? No, you're going to have him serve as one of two leaders, and the other leader's going to take on the second burden. After a little while, Fu-Kuen was phased out into another new program. But that's a very painful process and it's one you pay a lot of attention to because the last thing you need is to take the guy that's just created a billion dollars for the company and kick him in the head. You know, that's really too terrible to even imagine. So it takes a lot of care. If I hadn't been pressured by the rest of the organization, I would have been tempted to let him stay with it longer than I should have. I think they actually made a wonderful call, and the organization sort of said, "Hey, this has gone on long enough. This is not the guy that should be doing this." There were some concerns, and I explained to him that this is going to be a change, and we tried to phase it a little bit, but it was painful for him. But it was, without a doubt, timely, and if we had done it much later, we might have paid a huge price.

When you finally come down to it, a molecule like erythropoietin, during the last year, before it goes on the market, you have almost the same cost as when you're on the market. There's a small manufacturing differential because you're making more stuff when you're on the market. But mostly, the financial equation is: you're going to bring two hundred million dollars into the top line the first year you sell erythropoietin. It's going to drop down to two hundred million dollars in the bottom line. You think, "Oh, it can't be. There are costs." Yes, but all those costs you already have. You put your sales force together, you put your manufacturing together, you've got your sciences together; you've got everything in place, and all you do is change your operating statement, by putting two hundred million dollars on the top line, and it just goes boom, right down to the bottom line.

So it's pretty painful if you miss a day or a year or a month in the approval, because if you're making twenty million dollars a month, it's almost a million dollars a day. How many times do you look at a decision and say, "It's worth a million dollars if I could save one day." But we did that. We said to people, it's probably worth close to a million dollars if you can save a day. So you tell me you're going to go and make this chemical yourself instead of going and buying it for twenty thousand dollars? You're crazy! It's going to take you two months to get that, and you're on the critical path. Go buy it! Twenty thousand dollars, five thousand dollars—sometimes three hundred dollars. People would foolishly think about saving a relatively small amount of money. The same way with the pace at which we're running this program. If there's somebody who's not efficient in how he's running it, and he gives away a week or two every two months, whoa! Is that a cost! I mean, millions and millions of dollars. So you have to get that mind set in the whole organization that time is the most precious thing we had in the company. That's partly because we also had the pressure on us of losing money all the time, and the fact that this takes us into a profit position. If we don't get in a profit

position, it's not like you make less money. It's you lose money, and you continue to lose it while you're in the clinic with these programs, and that's building up a real problem for yourself in trying to get your next financing.

BROCK: As the organization is growing, as Amgen's growing, as ICOS is growing, how do you educate the people who are coming into the organization, who may be coming from a background just in university-based scientific research? What's the internal education like?

RATHMANN: Well, probably, as you're maybe suggesting, the right solution would be recognizing all the needs of such people and put together a series of—we don't do this, I'm warning you—put together a series of programs that are designed to have them understand the product development process, the economics, the equation of how your payoffs will justify the investors with what he's looking for in the way of his investment and all the rest. There are a zillion things that such a person would benefit from if they were given it almost in formal training. They're coming from an academic environment. They can handle formal training just fine. You give them two afternoons a week in which you go ahead and do this. But you don't do it, and mostly it's carelessness and a shortage of time. So you're depending a lot on osmosis. The osmosis works best when the number of people coming in is a percentage, but not a dominant number compared to the number that are there. So the osmosis process actually works pretty well if you're hiring 10 to 15 percent additional people per year. Maybe even 30 percent per year. But it's a disaster when you start hiring 100 percent per year. You know, if you're looking ahead and saying, "Oh, boy, we're going to need a lot of people in this company." We had five hundred people when erythropoietin was approved. You're going to have a two hundred million-dollar business with five hundred people? Nobody has a two hundred million-dollar business with five hundred people. You've got to have a lot more than that. So let's have a thousand. Well, I resisted that. Then after I left, they multiplied the number of people at Amgen pretty fast. But I resisted because I was afraid of this very thing. You bring five hundred people into an organization of five hundred people—how in the heck do you train those people? You're going to have to have an analysis of everything that people really know that they didn't know when they were in academic life, and you've got to get them at information in a formalized and efficient way. But if you bring in a hundred people when you've got five hundred people, you've got five hundred people training a hundred people, and they're very conscientious about it. There's a climate in a biotech company that's very positive and very clear, and that is, "You don't have a job if we fail. So if you can help somebody in this company, it doesn't take me to have to educate you of how important it is to help them. You're already educated. You want to keep your job and you want to keep this company successful." So if there's something someone doesn't know, you're all over him. I mean, you're helping them learn it, you're taking your time and effort. So the internal staff that are there will make darn sure that wherever they can help somebody, they'll go and do it. Then you'll also tell the new people, "Look, you've got a question, go ask a question. Ask anybody. Remember also that there are skills in this place that'll cover almost every part of the science, so you don't have to run off and study textbooks to learn about those words that I had on the chart today—apoptosis or signal transduction or something. Just go down the hall and find out who's the best

person in the field to instruct you in those scientific areas. Very likely they will run some of the experiments that you'll have to learn carefully how to do because they are already doing it once in a while in their lab, or has done it before. There's a great deal of synergy possible, and you don't have to do everything from scratch. We're going to be concerned if you go off and start learning how to sequence genes when we've got someone down the hall who's sequencing genes. In fact, that's your job, to make sure that you don't do redundant things to what we already have in place. It's also your job to ask questions and expect people are going to give you answers. It's very unlikely that you're going to get on somebody's case and ask them so many questions that you pester them to death and then they finally come in and say, 'Get that guy off my back.' It's never happened to me, so I know that people are willing to try to help and train and so on."

So, a lot of those things are taken care of that way. Now, there still is a need to do more things and we always regret not doing enough. At the end of the year, we get with the Human Resources Department and say, "Do we have enough training programs? Gosh, there are people who've been asking about stress management; there's a lot of stress in the organization. How do we handle that?" Then there have been some "time management" questions. So you try to stick a course together, one or two a year, that rather haphazardly deal with some of the things that people have raised as areas where they haven't had training.

Now, there's a much more critical, philosophical problem that you have to address. That is what happened maybe after about one year at ICOS, and ICOS had more academic people than Amgen did. We had a few industrial people at Amgen that helped quite a lot in giving us the right orientation. But ICOS was almost pure academic, and we also started with sixty-five at one time. We hired sixty-five people on day one. Not surprising they were academics, because we pre-hired them before we started our lab, so you can only hire academics nine months in advance, whereas if you started to do that with someone in a company, you'd be compromising his relationship with his company. He's committed for nine months, he's going to join your company. What's he doing in his company? He shouldn't be getting paid, maybe. So we had almost pure academics because of the way we started, and we also had this big surge of them. So we had sixty-five people there and every quarter after our Board meeting I would fill them in on what the Board did. There are some things we don't share completely, but certainly most of what we do is something that belongs to our staff. "You're doing the job, so here's the story." After one of those meetings, my scientific director came up and said, "We've got a problem." "What's the problem?" "Well, George, you have the problem?" "Well, what did I do?" "You used the 'P' word." I said, "I used the 'P' word? [laughter] I don't know what that means." He said, "Well, you used the word 'product.'" I thought he might be saying "profit," but I couldn't recall using the "P" word "profit," because we weren't close. But the "P" word product, I had used. He said, "You used the 'P' word." I said, "Well, and that caused a problem?" He said, "Yeah, that caused a big problem. Mary was so disturbed she almost resigned." "She was so disturbed she almost resigned because I used the word product?" He said, "Yeah. She came here to do science. She didn't come here to make products and do poor science. She wants to do good science and she's a great scientist. She's very concerned that we're not going to be doing that. We're going to be cutting corners to get products. She thinks that's inevitable. That's the only way we can get products is to cut corners and we shouldn't talk about products.

I don't think we should talk about products anymore." This is the Vice President of Research. I thought, "Well, that's interesting." Of course, he came out of an academic place, too. So I said, "Well, I've got to think about this a while because I don't think I'm going to be able to eliminate the 'P' word."

Well, it completely corrected itself four months later when she resigned, and by that time he was beginning to realize that she was at the extreme end of the spectrum, and if you wanted to retain people like that, you had to make special allowances, and you can do it. You can say, "We're going to talk product, but you don't have to think about products. You can think about basic science. You can do spectroscopy; you can do this and that. You sometimes do that. But if it's an average situation and she's an average individual, and she's got an average type of assignment in a company like ours, she's going to have to think about products. It's always painful when you lose a talented scientist, but I didn't think that was a huge loss. I think it was necessary. We couldn't cater to that many people saying, "We're not going to talk about products." What we actually did not too long after that, and that was the second wave of concern, was that I realized that we had been moving now for two or three years, and we weren't very close to getting into clinical testing because a lot of times, the people were almost too thorough in looking in an area. So you have a new protein and you're making antibodies to it, and you realize that you'll learn from every additional antibody that you make, because some of them will react this way and some will react that way. So you start making antibodies and suddenly you've got a scientist's paradise. There are an infinite number of antibodies that you can make and you've got a secure job, and this is great. About that time I heard, "We had dozens of antibodies," I had to step in, "Now, why do we have dozens?" "Well, we still think there's one that will do the job a little better than the ones we have." Okay, I've got a problem. So what am I to do about that?

Well, we're going to have to have some people that are going to do long range stuff, but I just arbitrarily, out of pure instinct, said, "We're going to be checking our actual allocation of resources in such a way as to decide that we're moving toward 80 percent—moving toward, not there yet—our R&D will be directed toward products that are in—and we had nothing in the clinic yet—or will be in the clinic within eighteen months." Eighty percent—just arbitrarily, because I had a sense that that was about right. "Eighty percent we'll try to get in the clinic within eighteen months. So you have a program, you want to work it, then you're going to tell me how long it's going to take to get it to the clinic. If you say fifteen months, you can be part of the 80 percent. If you say twenty-four months, you've got to be one of those 20 percent guys, and if there's too many of you, we're going to revisit what you guys are doing." We're going to say, "One of you is going to have to get either a little more optimistic about what you're doing, or we're going to have to realign what you're doing." [laughter]

Actually, that went over quite well. A lot of people said, "You know, it suddenly made it clear to us what our job was. We suddenly fully realized. No one had presented it to us because—scientist talking to scientist—are you doing good work? 'Yeah, I've got exciting things. I'm making antibodies.' Suddenly somebody made it clear what we had to do to be a company and we want to be a company." They all have stock options. They all want to be a company. They all want to get wealthy or famous or both and have a place for their families

and the whole bit. So it turned out to be a relatively successful proposal, and it turned out to be a really good guideline. It turned out that we started getting things to the clinic and to just massively attack the clinic. When we go to companies—it's quite interesting—there are a lot of biotech companies that don't do that. For example, there's another way to become renown, famous, popular, look great. That is to develop a partnership with somebody. Have another company endorse your science by saying they want to have a collaboration with you. So you can get your mind a little distorted at the time. You say, "Which do I really want? Do I want to put a product in the clinic, or do I want to attract a company to be my partner?"

Well, partnership tends to be played up very heavily in the articles about biotech companies. Now if I get a partnership in which a company says they want to put in twenty-two million dollars, that'll be in *Bio World* tomorrow. My stock will look good and people in the company will be proud. Then there are other things that can tempt you to do the wrong thing. You can find out that a buyer comes along and says, "I'll offer you a hundred million dollars if you can do some gene sequencing for me and give me a hundred new targets because those are going to be interesting to me some day." That doesn't put you in the clinic if you're the guy that's doing the sequencing. It puts the buyer in the clinic with something. But they're paying you a lot of money for it. They'll pay you a hundred, two hundred, three hundred, up to four hundred million dollars for a bunch of targets? You forget about going in the clinic. You just start making targets for somebody. So you've got an artificial economy that's misdirected you away from what I think is the only thing to do: get products in the clinic. Recognize your job is to treat patients, and stop thinking that you can be a supplier to the guys that do the hard work and go into the clinic and you're just going to supply them with stuff and be rich. Because first of all, you have to have an awfully powerful franchise if they're going to keep buying. The franchise that Genex had, when they were supplying the raw material for Aspartame in the early 1980s, served fabulous at the time and it just disappeared. They were supplying aspartic acid and phenylalanine, which were the two components, and they had done it by recombinant DNA and they had a great franchise, except they had no patent position. They thought they had a contract, but they knew full well the contract had rubber terms in it so that the people could actually get out of it if they had to. And they obviously did. The ballgame was over. You got thirty or forty million dollars in sales and then you went to zero.

So, you begin to appreciate, when you've gone through some of these things that there's nothing quite as secure as product that's going to be sold to patients, doctors, healthcare, or any part of the customer package you might be in, but where you're actually going to be supplying molecules to treat disease. That's the business we're in. There may be some people that can be supports to that business and they can have platform technologies that they'll sell parts to people in various ways and various times. But I'm a skeptic. That's not a permanent franchise, and you'd better be evolving into something else, most of which will have to do with supplying something to patients someday. So that's my view of the simplified version of how to be a successful biotech company and it's not always accepted. But this is really a long answer to your question about how do you orient these people correctly. In theory you do an educating job, and we're doing that. But a little bit too much of it is on-the-job education, and there probably should be more formal efforts. But you're moving pretty fast, and you're also finding that things that are important to teach people in the beginning of 1999 may no longer be the top

thing to teaching them by the middle of 1999. There's a combination of technologies that exist, and there's strategies that exist, and there's horizons that you're barely thinking about, and as you move, you have different demands. But I think the common demand, the one that's really important is: we're going to get to treat patients as soon as we can and we're going to have a product that's going to be sold for patients. That, I'm pretty steadfast about. Whether there are other techniques for skinning the cat, you consider them, but that's the one. Your organization begins to feel that right down in its very roots, and when we talk to these companies that have different mindsets, it's quite clear. Our own people say, "My heavens! You know, they're not even trying to get something in the clinic." And I think, okay, that's what they're doing, but that's not what we're doing.

BROCK: I'm going to be revealing a little bit of my ignorance here, but did you ever, with either ICOS or Amgen—partner with another pharmaceutical company to do any particular aspect, like marketing?

RATHMANN: We've done all things. When we were at Amgen we didn't partner very fast because we had nineteen million dollars. Other biotech companies starting with a few hundreds of dollars or maybe ten thousand or maybe more like half a million needed to partner pretty quickly because they wanted to sustain their R&D with the partner paying the bill. So we didn't partner very fast. We didn't have to. Let me think. Our first partnership did not occur until 1983. So we started operations in 1981, and up until 1983 we had no partners of any kind. In 1983 we decided to do a partnership in diagnostics because it wasn't in our main thrust. We'd do a partnership in diagnostics and I was going to do it with Allied [Chemical], and then Abbott came back and said, "Hey, we put money into your company. We didn't do it for the purpose of helping Allied get a product. We want a shot at your diagnostics." I said, "Well, you're going to pay for it." They said, "Yes. We'll offer you forty thousand dollars a month." I said, "Well, you're not going to be competitive. We'll go with Allied." They said, "How much would you like?" I said, "I want fifteen million." They said, "Fifteen million for a diagnostic job?" Well, I was at Abbott for five years and ended up having products that totaled four hundred million dollars in sales within a couple of years after I left. It was not out of the realm of reason that we could develop a lot of pretty good diagnostic products. So I said, "Yeah, that's the story. I would like fifteen million. In fact, we've got something pending with another company and it probably would net us about twenty-five million. But since you people have already put in five million in the early days, I can't hold you up for the same number that I'd get from somebody else. But, I'd want fifteen million." We debated that for a while, and they finally went ahead in 1983 and gave us the contract for what turned out to be a nineteen million-dollar contract covering five years.

So that was our first deal. It never led to anything particular. It may have accomplished their objective to keep Amgen out of the diagnostics business, but it didn't do much else. The way they ran the program partly ensured that. They made sure we didn't get our hands anywhere near a finished product. We had to feed them the raw materials and they controlled trying to make it into product. So we didn't get into the business. It was kind of obvious. But it

was okay. We got our nineteen million, and we got well paid for our staff, and we learned a lot of things. But that was our first one.

The next one was probably within six months or so, and we ended up, about four years after that, with a total of seven or eight partnerships. In all cases, we tried to design them that we had a few prerequisites that we insisted on. We didn't get that out of the diagnostic thing because that one was designed to settle a deal with Abbott that we owed them something because they put money in. But in all the rest, we tried to have participation in the marketplace with the product. So we weren't concentrating on raising money. We were concentrating on types of collaboration where we could enter the market and have a business if we were successful. The problem with these collaborations, otherwise, is that if they fail, your partner's out of there before you know it. As soon as he knows it's not a successful deal, whatever numbers that had been written up in *Bio World* are ridiculously misleading because he'll put in his million and a half and the first year it looks bad he's out of there. Whereas, if he's successful, he'll continue to put the money in, you'll keep getting the money, and milestones and all the rest, but when the day comes that it's a two hundred million-dollar business, which by the way in the case of Amgen's two businesses—G-CSF and EPO—that's all they have is two businesses, the market value is forty-four billion dollars. So each of those businesses is worth twenty billion dollars. Now, there's a certain amount of value for the Amgen infrastructure and all the rest, but there's no question that those businesses are worth between fifteen and twenty billion dollars each. Now, how often would you imagine if you've got a partner, that he's going to be willing to give you the value of fifteen to twenty billion dollars because he's put in two or three or five or ten million into your company. He'd be crazy to do that. And he doesn't. So what he does is, he offers you a royalty. You get about 10 or 15 percent, maybe at the most 20 percent, of the payoff and very little of the infrastructure that's going to be there too.

When we run a program at Amgen, we've got about a 60 percent pre-tax, putting the money to the bottom line—60 percent. You're funding about 20 percent additional R&D out of every hundred dollars of sales, and you've got your sales cost and other things that are being underwritten out of the cost part of the equation. So you've got all those people paid for. Now, you have a royalty and you get a raw number that's a nice number, maybe ten million dollars for every hundred million in sales. But, of that ten million, some of it is going to be spent on research that you kind of want to use to say that you can be around when the second-generation products come along. So some of it gets consumed that way. Other dollars get consumed in other parts of your R&D, and in any case, it does not have an asset value in the billions of dollars. You can't push that into billions of dollars of asset value.

So partnerships are dealt with some caution. About a dozen relationships have all gone south, and they include great companies: Johnson & Johnson, Eli Lilly, Eastman Kodak, Hoechst, et cetera. Of those dozen that are there, about six of them had lawsuits and the other six were just bloody disasters. So partnerships are not an automatic road to success. But you have to consider them. So what we've done is, we've had about two or three prerequisites. One is that the partnership gives us downstream value if at all possible. If we can possibly make a claim for downstream value, namely that we would share in the marketing of the product, then

we do that. In the first instance, we had a situation with Glaxo [SmithKline] in which we would be able to share as co-promotion, but we couldn't be a joint-venture partner—they wouldn't do a joint venture—but we could at least share in the selling of the product in co-promotion, and we got that worldwide, but we did not have a joint venture. That turned out to be a disadvantage, but eventually the program was dissolved after they did discover a very fine molecule. They decided it wasn't good enough to pursue, so they gave it back to us, and we've since pursued it and we've made a relationship with Eli Lilly to go ahead. Now, you say, why did you make the relationship with Eli Lilly? Well, we wouldn't have if it hadn't been for Viagra. We were in the field of erectile dysfunction when Pfizer came along with an enormously successful drug and we realized that we're going to be up against a frontrunner that's out there ahead of us, so we needed all the marketing power we could possibly have. Otherwise, I would have been happy to do what Amgen did: our own marketing. But we had plenty of time. Nobody else could get erythropoietin. It was a unique franchise. Whereas in the erectile dysfunction area, somebody's already got a better franchise than we're going to have for quite a while. So we thought we needed a marketing partner.

In the case of Glaxo in the first instance, even though we couldn't get a joint venture, we did get the co-promotion that we felt we absolutely had to have with the chemistry. We had all these targets. What we needed were small molecules that inhibited those enzymes very selectively. They had the chemistry. We didn't have it. We would have had to start hiring people. It would have taken us five years to get it. If we'd have been absolutely efficient, hiring as fast as we could hire, the best people we could hire, and put them together in the best possible cohesive group, it would have taken us at least five years to do what Glaxo did in two. Well, that would have been a terrible blunder to say, "Let's do it ourselves." But the consequence was that they had control of our destiny and we worried about it a lot. They put the product into the clinic without telling us. They took the product out of the clinic without telling us. You feel pretty much abused when you're a small company and you're getting this kind of information. Oh, you know, everything's after the fact. When they took it out of the clinic, we said, "Well, let's try and do something about that. Why don't we take a look and see what it looks like? If it's good enough, maybe we'll take it off your hands." That's what we ended up doing and it was good. We thought they had over reacted to some animal data. The same thing happened to the FDA when we tried to enter the FDA with that product, they over reacted to the animal data and said, "You can't go into the clinic." We finally showed the FDA that the animal data was misleading and did not reflect any risk with the product. So the product got into the clinic. We were lucky to get it back because it was a miscalculation by Glaxo that it wasn't worth much.

But the key point was, we needed their chemistry. We couldn't have run the program without it. That's the basis for doing partnership. We've done a lot of them. Between Amgen and ICOS, now, we've probably a dozen, maybe a few more. They're all done on an individual basis. We did one with Suntory where they got Japanese rights to one of our molecules. It paralleled very closely with one that Amgen with Kirin [Brewery Company] on erythropoietin. We kept the rights to the U.S. market for erythropoietin, and yet got a lot of funding from Kirin, so we had the best of all worlds. We had the downstream values that we wanted, but we got a lot of funding out of the partner. That's what ICOS is doing with Suntory. They put thirty

million dollars into the joint venture and they retained the Japanese rights, but ICOS retained the U.S. rights.

So there are lots of ways of doing a partnership and it's a pretty important part of the business, but it's not quite as important as many people believe. They think it's the essential thing. Make partners early; make partners often. You can't miss. I've listened to that lecture, and I sort of say, "Well, I hope you never live to regret what you just told me, but I'm not going to do it."

BROCK: Let's see, what do you think, Leo? Do you have any thoughts about where we should go next? I know you and Leo talked about EPO yesterday.

SLATER: Do you want to move to some of the last of the Amgen questions on here? You covered a lot of it. You wanted to ask about Neupogen?

BROCK: Yes. Being the second biggest of Amgen's businesses, as you said. Then I think that we can move on to some other questions. So, like I was saying, I know you and Leo talked a bit about the story of EPO yesterday. I was wondering if there were big similarities or differences that stand out in your mind about the story leading to the development of Neupogen?

RATHMANN: That's a very good question. What you keep looking for is some generalizations; then you find out there doesn't seem to be any. Epogen was in our original outline of what Amgen would do—to this degree. We're going to work with Gene Goldwasser to get some of this material. He'd reported he could purify EPO from a urinary source from patients that have aplastic anemia. He had some small amounts of material that he purified. He'd make them available to us and be our consultant. We'd take those materials to Lee Hood's lab; he would sequence them. From the sequence, we might be able to deduce enough of the peptide sequence that we could take a shot at finding a gene, and then we'd find the gene. That was all in our original plan of twelve projects that would be starting Amgen.

We took a big setback within the first few months because finding a gene in those days usually meant finding some tissue that produced a message, and then from the message you made CDNA. So it was the accepted way of cloning, which was not suitable for EPO as no one had tissue producing the EPO message. So we were suddenly aware that one of our nice programs did not have a clear track to run on. But the thing that was going to distinguish it from G-CSF was there was a top-down decision. We would work on EPO. We would do it by this approach from this scientist, and that approach from that laboratory. That was determined by the Scientific Advisory Board before the company ever had a single person on the staff. As soon as we got the first person, we said, "Get some EPO and do some sequencing." So that was an interesting way to do it.

In contrast, G-CSF was discovered by the scientist that had done chicken growth hormone and had looked around and found another molecule that he was interested in, bottom-up, all the way, he said, "I'm interested in IL-2." I'd been interested in IL-2, which was called T-cell growth factor at the time, because I'd been reading and seeing things. So I also was interested in T-cell growth factor, and so kind of endorsed the idea that we should possibly try to make T-cell growth factor. Immunex was trying to do it. They called it IL-2 by that time. Other people were trying to do it, so we thought we'd try to do it and we missed. The other teams both got it before we did. So our scientist was good, but he couldn't reverse time. He came in with this one kind of late, and they had the molecule.

So they had IL-2, but he made some anyway, because as soon as it was published, we didn't have to find the gene anymore. We could copy what they told us, and we made the gene and made IL-2. Sure enough, we found out that a lot of people were having some difficulty. We had heard that there was difficulty in purification, but we had a super team—two scientists, actually—who were very good and they made pure IL-2. This same team that did chicken growth hormone heard from some friends of theirs at Sloan Kettering that if they could only get their hands on IL-2, they had a lot of need for it. Well, what was going to be the need for IL-2? As we look back, it was a very inappropriate need. But it was to treat AIDS [Acquired Immune Deficiency Syndrome] patients, which by that time was recognized to be immunodeficiency. IL-2 would both bolster the immune system and that would be great; it would make more T-cells. The T-cells would fight the disease. It just so happens that T-cells harbor the disease, and the odds of being able to solve that problem with a T-cell growth factor is like trying to solve malaria with EPO. The malaria parasite infects your red cells so how are we going to beat that? We'll just give you more red cells! But you could also replace the ones that are lost, but it's kind of a losing way to go about doing it, and that became rather clear pretty soon.

Well, anyway, they wanted some IL-2 and our scientist Larry Souza and Tom Boone said, "Well, I've got some IL-2 for you," and so they sent it off to Sloan Kettering. They said, "You guys really know how to make proteins. That's the purest stuff we've ever seen! We've got other people. Talk to them. You know, you guys are the kind of people we'd like to work with." I didn't consider it all that important a program at that moment. But then as soon as they came back to us and said, "We've got a cell line that produces something we call pluripoietin." They had our attention. Our scientists stated, "We'll do a collaboration." They accepted that that was a fair thing to do. You do a collaboration in which you share information and they send us some stuff. We send them the information, and eventually we'll figure out what kind of a contract we're going to have. This would be interesting to do. We regretted part of it later on, but that's what we did.

But again, the key point here is: this is really the scientist that's the innovator, not the scientific Board or the executive. Now they're working together, and sure enough, our team, as you might expect, was good enough at purifying that they could purify better stuff out of it than anybody had ever expected. From the good stuff they figured out the gene, they cloned the gene, they started producing it in cells, and much to their surprise, it was not pluripoietin at all. It did not affect the beginning of the stem cell hierarchy that I showed you today. It went way down toward the other end and produced neutrophils, and it was basically granulocyte-colony

stimulating factor. So when they discovered that that's what this molecule did, there was first of all huge disappointment, and then euphoria. The disappointment was, "We had one that we thought would make all the molecules that we'd ever want to make, all the cell types that we ever wanted to make. Here we made only one cell type. But on the other hand, it's not so bad because it's the cell type that disappears the fastest in chemotherapy and the one you'd really like to restore for many diseases. You might also have fewer side effects from playing around with this stuff, and so this sounds like a great little molecule." So we put it into high gear and fully recognized—this is now a company-wide program—but until a certain point it was literally one or two people from our company on an almost independent basis, keeping us informed but not necessarily being guided by anybody at the top.

So that's very different. In one part, it was the same—it was very, very hard work on the part of a couple of people working very hard to get the gene and do it right, and that part was common. But the very source of it was much more grassroots in the case of G-CSF.

All right, what did it do? Well, it produced neutrophils; and did it produce neutrophils! It would take a normal person and double his neutrophil count in eight hours. That's the first clinical study that was done. We said, "This has got to work!" Of course, it did. Much like EPO, however, it was not obvious how you'd get approval. People don't know this, and it's probably a sideline, but it's interesting to hear. With EPO, what we could do was we could change your red blood cell count within one month to a number that would put you right in the normal range, where you might have had three years in which you weren't in the normal range. So there was no question it was working. Could you get approval for that? No. The FDA said, "We will not approve that product for that reason alone." "Are you telling us that it's <u>desirable</u> to have a very low red blood cell count and we're messing somebody up by getting their red blood cells up?" [laughter] "No. No, we're just telling you that's not enough of an improvement." "We've got people that have hematocrits of 20 and they're going to 40, and there are no side effects, and 98 percent of the people are responding, and this is not approvable on that basis alone?" "No, it's not. This is only a biochemical constant. You're affecting hematocrit level. You're not affecting physical status. You're not affecting his quality of life. So why don't you do a quality-of-life study?" My scientist said, "Well, that's pretty easy. Why don't we do a quality-of-life study?" I must say I did intervene at that point because I happened to look up quality-of-life studies on patients on dialysis. I found out quite remarkably that a quality-of-life study had been done on dialysis patients, and found out that the quality of life of dialysis patients was indistinguishable from normal patients. You tell me how that happened, because they had a miserable existence. But if you picked the right parameters and you say, "Quality of life—can you breathe? Is your pulse okay? Can you stand up?" Then of course there's a spread of patients in the dialysis population—they're up and down. Some are very, very weak, and some are not that weak. It depends upon the hematocrit, as a matter of fact, more than their uremia.

So I said, "I don't want to do a quality-of-life study that could backfire on us. We could find out that the patients that aren't on EPO are doing just fine, and we can't do it from here. So I don't want to do that." So we went back and visited with the FDA over and over again, and they said, "Well, you just have to show patient benefit." We said we could go for eliminating

transfusions, but that was dangerous, because we'd only be able to treat the people that were on transfusions, and that would limit our market, so we didn't like that very much. So we worked with them and said, "How about the phrase: 'reduce the need for transfusions.'" So even a patient that was not having transfusions might have a reduced need now that he had the drug. They said they'd go for that. So then we found an interesting cycle that they never objected to and that was: how does a physician decide to make a transfusion for a dialysis patient? He does it based on hematocrit.

[END OF TAPE, SIDE 7]

RATHMANN: So with G-CSF we were prepared for resistance by the FDA. We said, "Well, what we can do is take a patient and we can double his white cell count in eight hours, if he's normal." "Well, the normal doesn't get any benefit, so that's no basis for approval." "So who's the guy that needs it?" "Well, he's the guy that's deficient in neutrophils." "Well, what does it do for him?" "Well, if you take a look at his chemotherapy cycle, and if you give him G-CSF at the very beginning of the cycle, he will not dip down as low in white-cell count. He will still dip down, but he won't dip down as low for as long, and you've obviously given him a huge patient benefit." The FDA countered, "His white cell count—that's a biochemical constant and does not constitute a patient benefit." "Okay, well, what could be a patient benefit?" We worked with the FDA about that one. They said, "Well, if he doesn't get infections." "Oh, I see. So if we can show that we've both treated and untreated (Placebo) patients and they were comparable populations, and the placebo group got more infections." So we defined these infections as febrile neutropenia. So you would get a fever from any source, but it usually was because of an infection, but we would count the number of febrile neutropenia patients that were on the drug and those that were not on the drug, and we'd compare.

The first study, which often happens, was surprisingly perfect. In other words, we had something like thirty patients receiving placebo, many had a fever, and we had thirty that were on the drug and none of them got a fever or neutropenia. We said, "This is too good to be true." It turned out that later studies were not quite that clean. The ratios would ordinarily be two-to-one, but they wouldn't be infinite, that was one of those funny things that happen. It's a good thing when it happens early sometimes because it gives you tremendous momentum. It's a bad thing because you might be misled. But it always tracked that we reduced febrile neutropenia by a very significant percent, and the product was approved for that.

But it's funny because people don't always realize the extra complications that are involved here in doing the job and getting it through. But the stories, in some sense, were parallels, and it's like that you had to do an extra few steps to get through the FDA. They were both very fast. One was three and a half years, and one was four and a half years in the FDA, which is truly fast. It's as fast as practically any AIDS drug has ever been. They were extremely important products. As soon as they hit the market they picked up sales right away. We sold fifty million dollars worth of G-CSF the first week! But we're different from our predecessor, Genentech, in the sense that what we did was, start warning people months in

advance because Genentech took a terrible hit when they put TPA on the market, and it wasn't an instant billion-dollar product. So what had happened was, we knew the history, studied it, and understood it very well. They had promised a billion-dollar business. They put the product on the market. They had pipeline filling the first week or so, which computed out to be a billion-dollar business, and their stock went soaring up, and then it started to go down and it just kept going down. They lost about two-thirds of their market value after launching a successful product, because the expectations had driven the price up much too high.

So we avoided all that. I warned people that I didn't want them speculating about the company, "We will keep you informed, but we don't want you thinking that we're hiding something; that we've got this product already approved, and it's already doing this or already doing that. So just wait until you hear the announcements and don't jump the gun too much. We're probably going to report—if things go well—that we're on the market. We'll even report our sales, but be careful because those could be misleading. We could be pipeline filling." So we reported our fifty million dollars in the first week and it didn't blip our stock because we said, "You have to understand, this is pipeline filling, and no one would know. Is that fifty million going to last those cancer centers until the end of the year? Is it going to last them a month?" Well, it lasted about a month. Then we had to start renewing that, and it turned out that would have corresponded to a six-hundred-million-dollar business. It wasn't that big, but it was a big business. It was about two hundred seventy to three hundred million the first year, and it kept growing to a billion and so on.

But Amgen never underwent this surge, because we spent a lot of time convincing people they shouldn't let their euphoria take over and speculate about the company. Even with the fifty million in sales. "We're going to tell you we've had some pipeline filling sales." "Well, how much were they?" "Well, they were fifty million dollars in the first week, but we're filling the pipeline. We don't know how long it's going to last." So that didn't drive the stock up, and it was a steady gain for quite a while. Amgen stock doubled every year for about five years, or something like that, which is thirty-two fold. That's a very nice uptake over a five-year period. So it was much steadier and better than some of the things that happened before. But we also benefited from the disappointment with TPA. So people were ready to be cautious. I mean, if TPA had gone through the roof, we couldn't have held it back. We'd have been the basis of speculation. So theirs goes through the roof and we come second and we're a disappointment. We wouldn't have been able to deal with that. But because of their disappointment, we could work off of that.

So the two products had a lot in common and there were certain clear differences in how they were discovered, and how they affected the marketplace, and how they were approved. But there were a lot of parallels, too, and they were remarkably good. What would be my prediction? It would be that within two years, Amgen would have another product, and it would be based on making platelets or something in the hematopoietic family, but they also had a capability to do almost anything. It could be a cancer product. It could be any kind of a product. I figured we're just going to see enormous numbers of products very soon. I didn't make projections to blow our stock price up, but if anybody asked me about the outlook for the biotech industry, I would have been more optimistic in those days than I am today because I just

thought you can hardly miss. Well, there are ways to miss. But I think that the promise of today is still wonderful because the science has moved along a great deal, and there are plenty of opportunities. But you have an incredible psychological dimension in this business that, for reasons you can hardly understand, people get colder than ice, and then for reasons you can barely put together, they'll go higher than a kite. There are certain common denominators to the euphoria and the pain. Euphoria comes when there's a reported very good scientific or medical result, and the pain comes when there's something negative like pricing or product failures. But there's still a lot of factors that you can hardly quantify that are very, very powerful affecters of our stock price and the attitude of the investment world, possibly the whole world, with respect to how good biotech is. So when *Business Week* says, "Biotechnology: Why it hasn't paid off," that's really an indictment. You've got all these people betting their lives with your company, and they're all committed to making biotech pay off, and the pronouncement is there: "Biotech: Why it hasn't paid off."

There are two images from that issue of *Business Week*. One pictures an analyst saying, "It hasn't lived up to expectations, so it just doesn't look very promising." The other one is an analyst and investor, saying, "The only solution would be if about 70 percent of these companies went out of business." That was the recommendation from one of the experts in analyzing biotechnology companies. All we needed to do to solve our problems is have 70 percent of the companies go out of business. That certainly would solve the problem for 70 percent of them, I guess. But those kinds of levels of pain are really quite remarkable. You feel like you've lost complete control of your destiny and the destiny of several hundred that are betting on the company and you're thinking, "How are we going to salvage this thing?"

But then you go into the lab and have somebody tell you what they've just done this week, and it's very exciting and very positive, and they've learned something they never would have dreamed of, and they've got a way of sensitizing cancer cells to radiation, and you're blowing them out of the water at levels of radiation that no one would ever imagine. And you say, "We can sure make something out of that!" "Well, it's cancer. We're not really in cancer." "Well, we don't care. If it's based on something that we've discovered already, we'll push it as hard as we can." Or you find out that you're seeing some real progress in cutting down pancreatitis or some other disease state that you're beginning to realize is very serious and very, very difficult to deal with. And you get all charged up again.

Now, these things all go up and down. The next piece of information can be the other way around. But it keeps things going and it keeps everybody in the organization going that you have these areas of progress to offset some of these doldrums you get into just because of psychological reasons that we don't understand very well.

BROCK: Actually, that issue of these psychological and other sort of nebulous factors with these crazy cycles is a nice segue into what I wanted to talk about next, which was about the importance of venture capital to the biotech industry to a sort of tolerance of financial risk amongst American investors. So let me start asking you about it this way. Do you think there's a difference between the tolerance of risk of venture capitalists, than maybe Wall Street as

represented by the analysts who make these prognostications, et cetera? Maybe that's not a very well-formed question.

RATHMANN: Yes, I think the venture capitalists understand the high-risk equation. But their tolerance is very limited and proscribed. In other words, when we set up Amgen, we wanted to raise fifteen million dollars, and the question is: what would the venture capitalist expect as a payoff? He expected a tenfold return in five to seven years. He knew he wouldn't get it from every investment, but he wanted you to put forth a plan as to whether you get a tenfold return in five to seven years. Then he could measure your plan against other plans and he'll support the ones that have the highest probability of giving that return. It turns out if you sustain a tenfold return over a five- to seven-fold period, he only has to have one winner out of every three that he finances. If you can sustain that same rate of growth, which is 42 percent compounded every year for ten years, he only has to have one winner out of ten.

So he's not exactly risk tolerant because he recognizes that nine out of ten of these are going to fail if he has one success. He's not very tolerant if you don't give him a promise of a tenfold return. He'll turn you down. So he's well aware of your risk, but if you can't offer him the reward, he won't have any part of it. So he's got this ability to manage a high-risk situation as long as you can promise him a high return.

The risk and return relationship for Wall Street isn't that equation. They're not trying to go to a customer and say, "How would you like to risk your capital but maybe quadruple it? Or tenfold?" The average investor doesn't want to be confronted with that purchase decision because he's going to say, "I don't want to take a chance on losing it all. I want preservation of capital." Wall Street has got to deal with investors that want preservation of capital, and therefore they usually can't operate on that end of the risk equation. So they pass up the big rewards in many cases because they say, "I'm not going to take that kind of risk."

So I'd say that, yes, venture capitalists are comfortable with risk, but they're just as demanding as Wall Street. They demand the return commensurate with the risk. Now, did venture capitalists play a critical role in the development of the biotech industry? Absolutely! It's not even close. The best way to see that is to take a look at a map of the United States and ask yourself where the academic centers are. There they are all over the country. They're in the Midwest, they're on the East Coast, and they're on the West Coast. Then ask yourself where the biotech companies are. They are all at academic centers, but they're <u>not</u> in the Midwest. The prevalence of biotech companies is on the West Coast and the East Coast. So you say, "Wait a minute! The secret for a biotech company is to be near an academic center. Why aren't they in the Midwest where there are great academic centers in Wisconsin and Chicago and so on? What's gone wrong here?" Well, I presented stories to the venture capitalist community in the Midwest. The venture capitalist community in the Midwest makes a banker in California look like a risk taker. It's just absolutely ridiculous. They'll have a crowd there and they'll be talking to all these so-called aspiring entrepreneurs, and they'll give them the story as to how they can become an entrepreneur. "You know how you become an entrepreneur? You put together your business plan. Now be sure you have a good analysis of the costs of the product

and what it's market projections are, year by year into the coming years, and when you've got that business plan with all your costs laid out and all the "ifs, ands, and buts," then go get somebody who's running a company, or the head of your school, or somebody else, to help you submit that plan to us, because we don't have time for just any old plan from anybody."

That's the Midwestern mentality. At least that's what it was about 1985. What's the mentality in California? The venture capitalist goes into the university and says to the professors, "I just read your paper. That's a great paper. Would you like to be a millionaire?" [laughter] Now, that's different from saying, "Put your plan together, have your costs worked out, and I'll get you a company." In the Midwest discussion, we asked, "How many of you would like to be an entrepreneur? Well, here's how to do it." And then they tell him that. Boy, they're all turned off. They'll never get anywhere. And they didn't. There weren't any biotech companies to speak of, even today, of note, that are in the Midwest. Yet, Wisconsin has a fabulous molecular biology department, and the University of Chicago, Illinois, and Northwestern—they're all great. They've got great science. It's absolutely essential to be near a science center, no question about that. You don't start a biotech company down in the middle of Kansas or somewhere. You don't do it. You just have to have those big academic centers.

So, venture capitalists are the difference here. You've got the fuel with the talented science, but you've got to have the ignition from the venture capitalist. But they are not in the game that involves Wall Street. Now, they play their shots very carefully. At the time when we started, the venture capitalists focused on start-ups, and the start-up absolutely had to have a venture capitalist. There wasn't anybody else—no banker is going to finance them. So the venture capitalist was essential. But as time has evolved, a lot of them have become much more conservative. Not to the point of being like a typical Wall-Street banker, but a lot of them will put their money into a small, publicly held company before they'll put it into a start-up. They'll just look at the publicly held company and say, "Gee, you know, he went out on the market as a publicly held company at eight dollars a share and now he's one dollar a share. He's got to be a better bargain than this guy over here that can't possibly launch an initial public offering. First of all, when he's public, I've got an exit strategy. With this start-up, I have the possibility that he's never going to go public, and I'm never going to get out. So I've learned my lesson from guys like you. I'm going to steer clear. I'm going with bigger outfits. I'll buy public stock, and I'll start looking at public companies a lot more than I ever have before." And that's true. So you have a funny situation. You have the really young start-ups that were never able to move into Wall Street right away. Now, they're finding out they can't even move to venture capitalists, and then they find out something even worse, and that is that if they struggle along with angel financing and other sources of money, that they <u>still</u> can't get into the public market, and practically like they're never going to get venture money one way or the other because they can't enter the public market because the public market is saying, "We're waiting for companies that are further along than you are. We don't like this very primitive stage. You're too primitive. If you don't get enough money, you'll never stop being primitive because you don't have enough money to really blow it out of there and get advanced clinical data or something else that you're going to apparently need to meet the requirements for going public."

Particularly in those periods in the last few years—and we're certainly in one right now where there's just not a great deal of unusual enthusiasm coming out of nowhere—there isn't the ability to finance a small company, yet there's still financings of companies that are fairly prosperous. Of course, ICOS has had a special situation. If we could get Bill [Gates] to invest, we can finance any time in the world. But even companies that are not in our shape, are able to finance much better than the very small companies. As a matter of fact, a number of people looking at this have said, "If you have a market capital of half a billion, you're really in trouble, because a lot of these institutions are not willing to come in and buy your stock because you haven't got a broad enough market base." Of course we did a very funny thing at ICOS. We went to the public market in the form of individual investors, so we didn't try to get institutions. We were a one year-old company and we had twenty-five thousand investors, and Amgen had about the same. So we were already very well spread over the retail market, and very poorly represented in the institutional market. Everybody was very sad about that, except it turns out to be that we did it at a very good time because the retail market was relatively stable, and the institutional market was looking for bargains. So when they suddenly think they can buy your stock as cheap as it's getting to be, they'll dump his stock to buy your stock, and all of a sudden, they all leave him because a lot of them are momentum players, and they like to buy when the stock's going up. That's a great thing. So you get this lovely surge when they all come in, and you go from 15 percent ownership to 40 percent ownership, and then one of them is out, and your stock starts to go down. They say, "Gee, I bought the stock because it was going up. I didn't buy it because it was going down!" Whoa! Exit, exit, exit! You go down to your 15 percent again, and in the process you take one terrible ride.

So the financing in biotech is still very difficult. The venture capitalists have absolutely had a pivotal role. The academic institutions, by the way, as I said, had absolutely a pivotal role. Wall Street, in the form of public market, has a pivotal role as well because if you're going to sustain a healthy balance of the venture capitalists investing in early-stage companies, they will not do it if there's no public market for these stocks. So it's just as important as it's ever been that you be able to hit the public market in a timely way, and have, hopefully, solid progress in the public market. So what happened for a while was, you could still get into the public market, but you squeezed so hard that within two or three months after you hit the public market, your stock was down. Companies like Hyseq—they would come out at ten, go up to twenty, and they're down to three, you know. Well, that's almost as bad as people not able to get there. After a while they say, "I'm not going to take another risk on going into the public market with this kind of stuff because I see that it doesn't last. I, the broker, am going to be selling this stock to my favorite customers, and they're going to be unhappy with me if three months after I've sold them a nice big IPO that they're in love with, it has got one third the price of its offering." So that makes it harder and harder to get public, it makes it even less attractive for the venture capitalist then to go into the private realm, where they have a wonderful mission, but where they aren't crazy. They don't have to give their money away.

But venture capitalist—the main message I'd want to be sure anybody gets is that I believe that it's a critical part of the success of this country in a lot of ways. The venture capital, risk-capital system is what makes this company different and a lot better than any other country in the world, and the fact that people get rich and all the rest of this has distressed

people quite a lot. How much wealth do you want some guy working for Microsoft to have? Do you really want to have billionaires at Microsoft in Seattle? As far as I'm concerned, yes, you do. If that guy's working the way I know they're working, which is mighty hard and mighty fast, and trying to do great things and very sensitive to what the world's looking for, as far as I'm concerned, that whole equation is a very good one. As far as I'm concerned also, I'm terribly biased—the technology—and this is why I like Chemical Heritage—science and technology is what's made our civilization, even more clearly in the past few years, a more prosperous civilization than ever before. If people think it's because we've got [President William Jefferson] Clinton in there, or because of something else is why we're prosperous, I feel that that's just terribly misleading. The reason we're prosperous is we've allowed a system to continue to work that features high tech, high risk, and dynamic businesses that are rewarded if they are risk-takers that produce really good stuff. A lot of wealth has been created, and this has made a lot of things possible, including reducing our present national debt and all the rest of it. This is all addressable by this power, and the power is so clear. I mean, these kinds of companies cannot form in Japan. They barely survive in Germany. In Japan they can't survive because the big companies dominate everything in kind of coalition with the government. I know that's an oversimplification. But in Germany they can't survive in our business because they've got these very strong environmental groups that are just impacting their capability to do these things. So suddenly, the U.S. is all by itself in the world markets for biotechnology products. I think you've got to give credit where credit is due, and some of it is a *laissez-faire* time in our government's actions with businesses, although they're not quite so *laissez-faire* with Microsoft as I'd like to see. But mostly, we haven't had escalating tax structures, which is what kills a small effort.

We've also had the benefit of literally, letting technology move as fast as it can possibly move, and it's been good, and the venture capital system has been effective. The academic thing, I worry about it, that the university pleads with us by telling us that they're not getting as much out of the legislature; can we help them? And we testify, and we write letters, and we say, "Why are you letting some of these tax-control measures cut back on your support of the university?" That's a terrible thing. You should realize that when you adversely affect the university, you're affecting the economics of this whole community. You're certainly affecting the ability to make companies like ICOS, because we wouldn't be there without the seeds from the university. Absolutely not possible.

BROCK: I was interested to hear you talking earlier today, because I have these questions about venture capital that you of course mentioned. Another question that I had written down that you also talked about was intellectual property law and the patent system. So I was glad to see that it's sort of on the right track. But I was wondering if you could talk a little bit more about the importance of that change to being able to patent living organisms for just the growth of the biotech industry in general?

RATHMANN: This was caught right away by Bob Swanson as a key point for getting to go public, and why would that be? Because the power of biotechnology was to be able to duplicate

a human protein in another organism. Think about it. If I duplicated a human protein in another organism, what do I patent? Can I patent the protein? Initially, you'd have to admit that it would be very unlikely I could patent the protein because I'm duplicating a human protein. I didn't invent it. Nature invented it. So, there's going to be a challenge there. It turns out there's ways to do it. But there's going to be a challenge in getting conventional patents for the field of biotechnology. A conventional patent—if I invent a new chemical is—I get a patent on the chemical. I make this biochemical and I can't get a patent because nature did it first. As I say, there's a loophole that I can get through, but it's clear that it was an enormous breakthrough to recognize the possibility and the reality that what I'm doing is something that is unique. I've created an organism, it's man-made, it's a living thing, but it does something that no organism has ever previously done. If I give business a right to that which it has created, it's not taking anything away from anybody. Now, Jeremy Rifkin and other critics of biotechnology will say, "It won't be long before companies will own every part of us. They'll own our genes, they'll own our proteins, and they'll own us. It's terrible appropriation by business of what really belongs to us as human beings." It's a very appealing story and it surely can scare people.

But the fact is that erythropoietin, as I mentioned, was named back in 1907. No patient had ever benefited from erythropoietin until we put the drug into patients in January of 1986. So you had eighty years that it was known by nature, but it wasn't doing anything for patients. The only time it was doing something for patients is after someone could make it by recombinant DNA. Was it an invention? Well, Biogen couldn't do it, and tried. Genetics Institute couldn't do it, Genentech couldn't do it, and Integrated Genetics couldn't do it and Suntory and all. That's an invention when everybody tries and they fail and you do it. That's an invention. So how are we going to protect this invention? Well, it turned out the Supreme Court decision, in June of 1980, was a perfect decision.

We had cells that produced erythropoietin. We claimed cells that produced erythropoietin. We can claim them very broadly because no one had ever had any kind of a cell that they could tailor to produce high levels of erythropoietin. So that was a very natural thing for us. It was natural for Genentech when they had cells that would produce human growth hormone, and natural when they had cells that could produce tissue plasminogen activator—you claim the cells.

Now, you also have a chance in trying to claim the protein, and the basis for that is: you have made the protein <u>pure</u> for the first time. Nature did not provide this protein to you in a pure form. It was therefore unsuitable for therapeutic use the way nature provided it. So you didn't invent the protein, but you invented pure protein. So you claim pure protein. You can get that, but not always. It depends on what's been known. If somebody had isolated some pure protein from natural sources, as Gene Goldwasser had done, that puts a crimp into that plan because he made tiny, infinitesimal quantities that are unsuitable for human testing, but he made it. So it was done. You can't say I've invented it for the first time. Quantity is not an argument for invention. You either claim quantities if you want, but you can't claim the material itself. You have to claim something else. It's pretty tricky to try to get around when nature has already invented it and then somebody has made it pure.

Now, it just happens that the stuff that was made by Gene Goldwasser had been processed by the body and it was therefore no longer fully active biologically. So what Amgen was finally, eventually, able to claim was a fully active protein, more active than anything Gene Goldwasser had, and somewhat different in structure from what Gene Goldwasser had. So they were able to get a product claim. But without it, you could be right out in the cold. You have this patent that you've done wonderful things, and someone copies it, and in fact, that's what happened to us in Japan. They decided that they could copy our way of making these proteins, and because our patent was slow to issue in Japan, they went ahead and did it. Then of course, they finally did issue a patent in Japan after carefully looking at what the Japanese companies were doing, and the Japanese companies had decided by that time that you could make EPO from CDNA clones rather than genomic clones, and so they gerrymandered the patent that we were awarded to suggest that it was limited to the genomic clones only. So that the Japanese could continue to make the stuff with the CDNA, which was absolutely anticipated in our application. There's no doubt about it. The other thing is, they didn't issue the claims on the gene until the companies had put their genes into organisms, so they were not infringing our purified gene claims.

That's another way to do it. You claim the purified gene, because nature never provided the purified gene to anybody. So that's a clear winner. But it's only good up until the time that they've put the purified genes into something, and once they've done that, then they're outside the scope of that claim. So the patent system is very important. It's important that the U.S. system was as enlightened as it was. I had just started to think about recombinant DNA in 1980, but I sure wasn't aware of the enormous significance of that decision. Enormous for the United States biotech industry and for the world. It certainly was clear that they made the right call, in my opinion. There's a whole industry, there's a huge amount of value that's been created, and the possibility of putting five hundred million dollars into a product and people can sit back and wait until you've done it, and then say, "You haven't got anything to protect. I'll just move in like Searle did on the Aspartame and I'll start making the stuff. I don't have to make everything you guys have made, because some have failed in the clinic. So I can sit there and just make the winners if there's no patent protection. I'm going to be the best company around." So I think the intellectual property protection is a wonderful thing, and yet we had a judge who was looking at our case at one time and said, "I'm going to make sure I do the thing that's in the public interest. I'm going to have as many suppliers of erythropoietin as I can possibly have." So he's really, literally, saying the patent system is a terrible system because it limits us to one supplier. Once you've made the discovery, it looks like it's in the public interest to force the person who made the discovery to license it to everybody else, because it looks like, well, now it's made; the best thing for the public would be to make it cheap for everybody by having everybody produce it.

But the part of that equation that's faulty, and I feel very strongly, though it's hard to sell some people, is that without the inducement that I'm going to have control of this business, I will not make the five hundred million-dollar investment to produce that product. We'll wait for others to do it, and it won't be done, because I think they have to have some protection. Otherwise, it's foolish to spend the money in that way. Now, you can do the next thing, and that is you can have the government step in and say, "This is so important. <u>We'll</u> spend the money

to make sure we make erythropoietin." Now, you have the government in every element of our business that's important, because they're going to do it so much better and because they have the money that nobody else does, and the free-enterprise system has just failed. Well, the free enterprise system is not a bad system, and betting on it has never bothered me. But there are people that keep thinking there's an improvement available in some way in which the government gets involved in a very deep way. I'm opposed to it.

But anyway, I think that the story on the patent side has been a good one. They speeded up the patent system. They got rid of the Patent Commissioner at the time when Senator Ron Widen got into the act. He nailed him, and drove him out, and the new people are very, very good. I've met with them and they've made a bunch of very good calls. So the only thing that has happened is sometimes in the GATT [General Agreement on Tariffs & Trade], we have been so imbued with worldwide vision and enthusiasm for worldwide coordination and cooperation that I think we've just about sold out the U.S. once in a while. The whole idea of going over from the system that we had, which was clearly to our advantage, which was seventeen years from the date of issue to twenty years from the date of filing, and falling in line with the rest of the world in many things, was definitely not to the benefit of U.S. companies. Was it fair? Well, I think probably the new system is more fair in that sense, but there's a lot of compensating things that we do not do in this country and that other countries do, that are very punitive to trade and fair trade. I didn't think that that one place in which we had a slight advantage was something that we had to give away without any benefit. That's what we did. We just gave it away. We were just imbued with this idea we have to do the right thing by the world. I'm sorry about that, because there were some intrinsic advantages for us. It was almost necessary because you're still at the mercy of the other country when they decide not to issue the patent. We should have lily-white behavior on everything, and yet treat every country with free trade even when they're being very unfair. Maybe "fair trade" would be all right. If they're being unfair, then we become unfair. But trying to concentrate on free trade under all circumstances when it's not reciprocal is not very smart. We're a very powerful country, but we're not so powerful that you can give away every advantage and still come out economically ahead.

So I think the patent system is one that has to have constant vigilance. My own preference is to be concerned primarily about the developed countries. I feel it's kind of strange to concentrate on beating up on Thailand or India or somebody that's a very undeveloped country and saying, "They've got to issue those pharmaceutical patents, because we want that market, and we don't want them to be able to even serve their own market with a pharmaceutical that infringes our patents." I guess that's true. We're entitled to the world market if we've done the work. If we're a pharmaceutical company, we're entitled to monopolize India and Thailand. But if you've covered the United States, Europe, and Japan, and they have enlightened patent systems—Japan's been improved but not enlightened—then at least Thailand isn't going to be importing into the United States. They're not going to be importing into Japan and Europe, because you knock them out at the borders, and so they use a nice development from the U.S. to help their own economies. I can't feel too bad about that. That's not the worst thing that ever happens, but I think it's terribly unfair when they start cutting into the markets that are viable for us and where we should have the kind of patent

protection that would make it exclusively our market. Then that's unfortunate. Anyway, there's a lot that has been accomplished, and lobbying was a factor there, and Congressional oversight was a factor in making it work right.

SLATER: Do you want to tell us a little about your transition between Amgen and ICOS?

RATHMANN: What part are you interested in?

SLATER: Oh. Why? How? Your feelings about it.

RATHMANN: Okay. What actually happened was, there was really no relationship between what I did at Amgen in resigning as CEO and ICOS. I'd never heard of ICOS when I resigned as CEO and retained the Chairmanship. That was simply a matter of feeling that it was appropriate at my age, which was a lot less then than it is now, that there were people there that were capable of running the company. We were about to launch erythropoietin. I figured that would be a great thing if they got a running start by launching erythropoietin as the new management team. I was worried that I was getting too old to really carry the burden of a company that size and magnitude. I felt there were lots of good reasons like that, so that I should face up to the fact that I should no longer stay as CEO. I presented it at the Board; the Board said, well, they don't like that idea, but they said, "What do you propose to do?" I said, "Well, I propose that Gordon [M.] Binder become CEO and Harry [F.] Hixson [Jr.] become President." ICOS was not even close to being around. It had never been thought of. There was no such thing. Some people say why did I do this? It had nothing to do with ICOS. It was just a matter of saying I'd reached that stage where that probably was a good thing to do. I knew that these two people were very eager to have that responsibility and I knew that it would be great. They didn't like each other very much, unfortunately, and I worried about that, but I knew they'd work together, and I told them they had to work together, because I'm still around, and I'm a heavy stockholder, so they'd better figure out how to resolve their differences. [laughter] And they did a great job.

So they launched the product six months later, in the summer of 1989, as you saw. Late that year, ICOS was formed by two venture capitalists and Bob Nowinski, and they approached me right away and said, would I like to be Chairman of the Board? Well, I was still Chairman of the Board of Amgen. It certainly was an acceptable idea to me that I be Chairman of the Board of a couple of companies. I didn't think the Chairman of the Board had to be a full-time job, though I was a full-time Chairman when I was at Amgen. So I talked to Amgen about being Chairman of the Board of ICOS, and I said, "It's kind of a tempting Board. I thought it would be a lot of fun with Walter Wriston and Frank Cary and the rest of this. It's kind of a nice interesting company, and I would like to do that. I'll stay on as Chairman of Amgen as long as it's appropriate." I thought I'd probably stay as Chairman of both companies, though I was already toying with the idea that I might move to Seattle, and be Chairman of both

companies from Seattle rather than from Thousand Oaks, because I really didn't have that big a job in Thousand Oaks. The better they did, the CEO and the President we'd put in, the less job I really would have. So I thought I'd still enjoy being Chairman.

So, they approached me to join ICOS as Chairman and I said, "Okay. I checked it out with Amgen and they had no concerns." So I joined and became the Chairman as of about the first of February, 1990. The object of ICOS, then, was to raise some money and then start a lab and we already had pre-recruited these sixty-five people, or were in the process of doing that. I visited with the scientists and I got charmed all over again with the starting point. I have to say, in may ways it was more interesting to me and I felt more vital as a member of a brand new group getting started. They hung on every word I said. I was worried. I thought I can't help them as much as they think I'm going to help them, but I knew I could play a very pivotal role because I'd been there, and you know, I can help them get to Mars. I've been to Mars. So that ought to work. I was seeing some changes in Amgen, which were very difficult for me to get excited about, namely, the new building was going to have more floors, more offices, be bigger, and have more expenditure than ever before. I just kind of shied away. For me, when I go through the buildings at Amgen, people ask me, they say, "How do you have the courage to take the risk of starting a company from scratch?" I'd say, "It takes a lot less courage for me than authorizing a building like this." You know, you can hardly see to the end of the building. Those are really hard decisions for me. But starting a company, that's pretty easy! [laughter] I really feel that way. So, I have to say my comfort level, as soon as I started dealing with the scientists at ICOS was all over on that side. That's fun. They're just getting started. They need help. I was redundant in many ways back in Amgen. But I really did intend to stay on both Boards.

We then had a financing and the financing was one of those rather stimulating experiences because as we went around the country, the founders of ICOS had decided that that's why they wanted me, to help the financing. I didn't realize that, but that was true. The deal would be that we'd go the Paine Webber system that had been used by Amgen, and go to their "sophisticated" investors: read "rich." [laughter] Their rich investors would probably buy the stock because they had a good association with me because the Amgen investment had paid off so famously. And it worked exactly according to the scenario. These guys are smart guys, you know—probably smarter than I was. So I just went along with this, [laughter] going up and down the streets of the U.S. and talking about buying the stock of ICOS, and it went like hot cakes. So we thought we'd raise twenty-five million, which was an awful lot. It was more than Amgen had raised. Instead, we raised thirty-three million. Bill Gates came in for five, so we raised twenty-eight on the regular market, and five from Bill. It was a smashing success.

I knew that there was a key role being played, because I'd get to these meetings and people would come up to me and say, "Oh, my whole family is indebted to you." I said, "It's not me. Amgen was a great company." They'd say, "Oh, we'd buy anything that you're associated with." Then they bought ICOS. So I suddenly realized that this had a downside, which was that very shortly the people would come back to the Paine Webber brokers and say, "Is Rathmann going to stay with Amgen?" They'd come to me and say, "Are you going to stay as Chairman of Amgen?" We're just looking at the transition there between Amgen and ICOS.

I said, "Well, yes. I'm going to stay as Chairman of Amgen." "Oh, well, that's really a disappointment for the entire Paine Webber organization." "Why is that?" "Well, we went out and sold the idea of ICOS stock because you're Chairman." I said, "Well, yes, I am Chairman." They said, "Well, but now people are asking us if you're still Chairman of Amgen, how much time are you really going to spend at ICOS?" I said, "I'm going to spend more time at ICOS because that's where I'm needed. Amgen's got a management staff." "Well, that's not acceptable. We're really having trouble. Some people are really very cynical and they've heard that you're going to stay on as Chairman of Amgen." I said, "Well, I don't know what to do about that. I'll go talk to Amgen, but I told Amgen that I'd stay on as Chairman." I went there and I talked to the Board and the Board said, "George, you said you were going to stay on as Chairman." I said, "Yes, I know I said that." I said, "But, please, I really think I have to resign. I'll stay on the Board, but I have to resign."

[END OF TAPE, SIDE 8]

RATHMANN: So what I did was, I had to say that I'd like to resign, and they said that they really didn't think it was a good idea. I said, "I think it's a good idea. I think Gordon will relish the job of Chairman, and Harry would love to be continuing and so on. They've done a good job, they've worked together very well." And the Board had some more misgivings, and then said, "Well, we won't make the call." They said, "We want you to make the call, as the guy that knows this company better than anybody. You decide whether this is the right call to make." I had so much personal involvement, I couldn't make an objective call. "I'll make the call that I will resign and you will put them in." They said, "Okay. If you say it's going to work, it's going to work." Harry Hixson lost his job three months later, and that was really tragic. He was a big asset to the company, but he had a conflict. So I knew I was the glue and the glue was gone. There was nothing I could do about it at that point.

So that was the downside of the whole thing. The people at Paine Webber were euphoric. It was so successful that when we went back to the Paine Webber brokers again the next year for a public offering, we had great success. When we went back again two years ago, in 1997, with a limited R&D partnership, which is one of the things we'd done at Amgen, a limited R&D partnership for eighty-seven million dollars, that sold out like hot cakes. That's already paid off. Those investors after two years have all their money back by a factor of two. So the role for me at ICOS was very well established, and it was an essential role, and it was one I felt I really ought to play. It's been an easy thing to say I really like that.

Now I'm in pain all over again as of two months ago because we've spent about two years trying to find a CEO at ICOS, and we just hired the guy for CEO, and I once again see the situation where you don't really have a job when you're Chairman. You do it for a while because you want to be sure the transition is solid. Then you just have to face up to reality. This time I did it for a totally different reason. I was seventy-one years old and had told the Board a couple of years ago that I'm going to have to face the reality that I'm not going to live forever and I'd better not be there in the saddle when something bad happens. So we have to

get a replacement. There's been kind of a mixed feeling on the Board as to whether it's the smartest idea in the world or not, or whether I should stay and continue to serve. From a personal standpoint, I would prefer to be President, Chairman and CEO of ICOS than a retired, independent chairman, or any other job in the world. I think this is the most fun job there is. So I, with some reluctance, realized I couldn't keep doing that. So now I'm Chairman and I'll probably have to decide over the next year exactly what that role should be and exactly whether that's a role that should again be ceded to the new CEO at the right time.

Then the question is, what do you do? This goes back to father. Somebody was asking about my father the other day. I guess that's the standard question; you've got to know what your father was like. My father was working on the day he died when he was eighty years old. My brother was working on the day he died when he was seventy-five years old. There's something in the genes that I really think is there. But it's also a role-model situation where there's a lot of excitement in having a job that you feel like you're doing pretty well, and that people seem to appreciate. It's a nice ego trip and it's fun to be on it and I've been on it for a long time. So I don't really look forward to saying I won't do that. However, with ICOS I assume that that will happen, in which case then, if anybody wants an old, used-up brain and body, why I probably would entertain some other kinds of responsibilities that would be very helpful to some start-up or something else. I certainly have no appetite to be involved—I mean, the bigger the company, the less interest I would have, because I think the part that's really fun is getting your hands around the science and the people and the dynamics of getting things going. So I would probably be involved with things like that. But maybe not. I might not find that it's too bad to spend more time with my families and grandchildren and so on. That's always possible, but I strongly suspect I'd rather not make that a full-time deal.

So that's the transition all the way beyond to the end now of the ICOS story, because that's where I am on the Chairmanship. I'm no longer CEO. They had it right in the introduction but they didn't have it right in the book because they had me still as Chairman, President, and CEO.

SLATER: In looking through your resume here, I think you'd be a very qualified consultant. You'd probably find work somewhere! [laughter]

RATHMANN: I might! Yes.

SLATER: Even if you're out of a job.

RATHMANN: I do need it to sustain the livelihood that I've gotten used to!

SLATER: You could always come here, and I'll give you an office upstairs you could use.

RATHMANN: Oh, is that right? Well, this is the best deal I've had this week! [laughter] Okay. Is there anything else you want to hear?

SLATER: I don't want to duplicate what you've given us today in your talk, but you were talking about when you're trying to market the industry. You don't want to just, you know, throw the company out there. There's going to be this intersection between information science and biotechnology somewhere, you know, fifty years down the road. Look at eight years at Amgen, eight years at ICOS, the industry has changed. What do you think the next eight years of biotech will be?

RATHMANN: Yes, that's an interesting question. I can put on my visionary hat once in a while. I really don't like the word even of being visions. Visions relate to me something not very real, and if you get carried away with how good something sounds instead of being able to weigh its probability, I find that to be—a typical example is how many people want to do the study of what programs to fund. So they move in the direction of which is the biggest payoff, instead of which is the direction of the highest probability of success. You have to have something in between, but if you totally ignore probabilities, and gravitate toward where the big payoff is, you don't get there very often, because you've got a very big number times an unknown which approaches zero, and the product is well established as zero. Zero times anything still comes out zero—except if it's infinite, and then it's an indeterminate. But every other time it's zero. [laughter] So you'd better think twice about the fact that this is so attractive because it's so big. It's attractive if it's feasible, if it's viable and if you can do it.

The first thing to prove is that it is truly viable or feasible. I think the same thing should be a measure of where the world is going. Do I really accomplish something by imagining a world that has everything I could ever want? I have computerization and biotechnology and everything's solving all the problems in the world, and yet if the probability of that in my lifetime is zero, I don't think it has much meaning. So that's all I was trying to say. There are so many tangible things that I can be almost certain what will happen, and they're actually very wonderful also. I'm saying those things are going to happen. Words and concepts like check prints and apoptosis will be real therapies in a few years. They're going to even be paying off in the next ten or twenty years. So the payoffs are very tangible and understandable.

But they're <u>not</u> as dramatic as the concept that I'm going to have a chip around me and it's going to automatically program drugs into my body that are going to solve all my problems based on my genes, and things that are possible but <u>remotely</u> possible, and so unlikely in the next twenty years, that I really don't care about them. So I don't really like to sell that level of future where the probability has gotten so low that it's almost trivial to talk about it because it probably isn't going to happen.

So what I feel is that the clear picture of the future is very promising because, I can see that we understand cancer better today than we did a few years ago, just a few years ago. We have much more information in the last three years. The whole story is very similar to what we had about three years ago with AIDS. About three years ago people were wondering, "How can you know so much about the AIDS virus, more than you ever knew about polio or smallpox, and yet you haven't solved the problem?" The answer is: "Hey look, this is real progress. We know so much about the AIDS virus, we will solve the problem. It's going to take some more time. It's an insidious virus. It does terrible things to exactly the kinds of systems that in the past, we've enhanced to try to beat a disease, and we can't use it, because it dismantles that part of our immune system. But we're going to solve the problem because we've got this incredible level of understanding of that molecule." The problem is not solved today. But now I think it's pretty clear that the progress was almost inevitable because of the knowledge that we have. I feel that we're getting to that point with cancer, where the knowledge is now so great that we're going to solve that problem and it's going to be now in a very finite period of time and it's going to be very important.

I think some of the other things, the aging question that I've hinted at is a little more problematic but I think there's going to be some real important things that come out of that work, but there it might not be what people would ask for.

I tend to be pretty conservative. When I see that the feasibilities are low, I think those things deserve to be in our minds and, in the vernacular of 3M, "on the back burner," so you aren't shoving it up to the front and putting coals to it. If I had a little more time in the speech today, I might have thrown in some slides that are very interesting. One was that the number of people we had on EPO in 1982 was two. The number of people we had on EPO in 1983 was three. In 1983 they cloned the gene. The number of people we had on EPO the next years was twenty and thirty and so on. So it's not so hard for me to decide to control my enthusiasm until I really see feasibility. Yet, it means that you don't ignore those things that have very high payoff. It's just that you keep them in balance and don't get carried away in proportion to the potential payoff, if in fact the probabilities are very low.

So in looking at these things that are coming along, I've been unimpressed with the idea of grabbing hold of gene therapy, for example. Gene therapy, by careful analysis, looked like it was fraught with enormous risks and probabilities much lower than would be true for just finding an exciting protein and putting it on the market. I have been relatively cool on antisense because it had the same situation. I am very glad that progress has been made. I think it's wonderful. I certainly wouldn't be opposed to finding a company like ICOS watching a technology like that begin to develop, and pay the full price for it when it's feasible. Somebody said, "You can get it so much cheaper when it's not feasible." I think, "Yes, is that cheap?" That's got a very expensive price tag. [laughter] So I tend to be a bit more conservative than you might think of someone that's so willing to start new things. I feel like it's more fun for me to have kind of a track to run on than just totally random experimentation. The track to run on still might mean a tremendous amount of divergent thinking and a lot of approaches that people might have to think about and discover that they haven't even thought about yet in order to

make it successful. But I have a feeling I've got my hands around it, and that's a lot more comfortable for me.

So we don't have any gene therapy going on in ICOS. Yet I put it in there because I think there's no question about it, with a certain amount of time, it is a solution to many, many problems. So there's going to be huge advances. All the sciences move so fast, that I'm very optimistic. But I think there's a surplus of things to work on already, so I might as well pick the ones that have pretty good high probability that they're going to work. A very important part of that is the patent system, because if you're doing something novel enough to be patentable, it doesn't matter if you're chasing after something that five other guys are chasing after, because if you get the patent you'll have exclusivity. Whereas sometimes in these popular fields, you automatically know you're going to have an awful lot of company and that's not so easy to decide, "I'm going to do the thing that really looks good, because I'm going to have everybody else in there with me." But if I see a way to get a patent or some other kind of intellectual property protection or other kinds of protection, then that combination—knowing what I might be able to protect, and the fact that I might get there first, therefore, and get that protection—it's worth racing to do some things that are, in a sense, kind of popular things. Solving cancer is certainly one. But every approach is different, and there's a very good chance that the ones we're working on are going to offer us some real significant protection if they happen to work. So even though we're an inflammation company, we've found ourselves with some technology that fits into cancer, just as we found ourselves with an approach to male erectile dysfunction, and we're happy to pursue those things when we think there's feasibility. Name any disease and I'll bet there's going to be enormous progress on it in the next five or ten years. Is it going to be solved? Is it going to look more like AIDS at that point where it's partially solved? Or is it going to look, well, more like multiple sclerosis, which is partially solved today? Or is it going to just continue to elude us and perhaps be viewed as almost an inevitable consequence that we can't solve the problem. I just don't accept very many of those. I'll accept death as a consequence we aren't going to solve very quickly, but the rest of them I think we're going to be able to deal with in time. I mean, when you finally have a molecular description of every part of the body, and know every phenomenon that's going on right down at the molecular level, there's an awfully good chance you're going to be able to do the right things to prevent negative consequences and not introduce problems that are more serious than the thing you're trying to cure.

SLATER: Okay. You want to let him enjoy his family for a little while?

[END OF TAPE, SIDE 9]

[END OF INTERVIEW]

NOTES

1. Paul De Kruif. *Microbe Hunters* (New York, Chicago: Harcourt, Brace and Company, 1939).

2. Robert L. Burwell, Axel H. Peterson, and George B. Rathmann, "A Temperature Control Device Employing Thermistors and a Saturable Reactor." *Review of Scientific Instruments* 19, no. 9 (September 1948) 608-609.

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4. See for example:

   A. J. Curtis, P. L. McGeer, G. B. Rathmann, and C. P. Smyth, "Microwave Absorption and Molecular Structures in Liquids. (VII). Effects of Viscosity and Dipole-Dipole Forces." *Journal of the American Chemical Society* 74 (1952) 644-648.

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5. Marshall R. Hatfield and George B. Rathmann, "Constant Stress Elongation of Soft Polymers," *Journal of Applied Physics* 25, no. 9 (September 1954) 1082-1085.

6. George B. Rathmann, "Fluorine-Containing Polymers. V. Light Scattering and Viscosity Study of poly-1,1-dihydroperfluorobutyl acrylate," *Journal of Polymer Science* 15 (1955): 544-552.

7. See for example:

   Allan R. Shultz, Paul I. Roth, and George B. Rathmann, "Light-Scattering and Viscosity Study of Electron-Irradiated Polystyrene and Poly(methacrylates)," *Journal of Polymer Science* 22 (1956): 495-507.

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