Annual Reviews Conversations Presents

A Conversation with P. Roy Vagelos

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Andy Marks: Good morning. My name is Andy Marks. I'm chairman of the Department of Physiology and Cellular Biophysics at Columbia University, College of Physicians and Surgeons. I'm delighted to be here this morning for a conversation with Dr. Roy Vagelos, retired chairman and CEO of Merck & Co., Inc. Good morning, Roy.

Roy Vagelos: Hi, Andy. How are you?

Andy Marks: I'm going to ask you some questions—this is very informal—and we'll go from there. Unfortunately, the first question has three parts, so please feel free to ask me to repeat any of the parts as we go through it.

Like so many in your generation, Roy, as a highly accomplished scientist, you grew up in a poor immigrant family with no role models as scientists. How did this affect your drive to succeed, and what drew you into an academic career, which was so far from culture of your nuclear family? And, ultimately, how do you think your family origin influenced the scientific questions that you chose to pursue?

Roy Vagelos: That's a complicated question.

Andy Marks: Yes, it is.

Roy Vagelos: I'll take it one at a time. First, my family was made up of immigrants. Both my mom and dad were born as Greeks, but both were born in Turkey. My grandfather on my father's side was a physician, and it's quite amazing that he was born on the island of Lesbos; Lesbos is very close to Turkey, so his children were born in Turkey. My grandfather was trained at the University of Athens as a physician and practiced medicine during his early life, but he died very young.

When he died, he left a rather large family—five children, four boys and a girl. Then slowly, the boys, one after another, immigrated to the United States. None had been educated, at the time [my grandfather] had died, to a higher degree.

When they arrived in the United States—starting with the oldest of the brothers: He did what all good Greek immigrant families did. He started a small restaurant and little luncheonette in Westfield, New Jersey. All the other brothers subsequently followed and came and set up with him initially, and then [they started] different little luncheonettes around Westfield, Woodbridge, and Rahway. They started these small businesses and then went back, each of them, for an arranged marriage.

My dad went back and married my mother, and therefore, we were all brought up in the United States. My two sisters and I were born in the United States. We were born into a family who had known a father who was highly educated, but who were not themselves educated. They had the notion that education was very important, and the last thing they wanted was for me to end up running the restaurant, but that's not to say that I was shielded from it, because it was a family restaurant.

My sisters and I always worked with my parents in our restaurant, and my dad, among the brothers, was the person who made things. He made ice cream and candies and supplied the other brothers in the other stores. He was a doer, but he was someone with a very high spirit and someone who felt that education was primary, and that you would succeed if you got into college. I heard that from the early days, and of course, I worked pretty hard.

I started out as a very poor student. When I was young, I was not at all serious and somehow got the notion, through repeated discussions at home, that going to college was important and getting a scholarship was important. Once I got to high school—that was in Rahway, New Jersey—I really turned it on and worked hard, which was different from my earlier years, and I was quite successful.

In our luncheonette, our major customers were people who worked at Merck, so I was in contact early on with people who were chemists, microbiologists, and engineers, and [their discussions were] what I heard as I was doing the usual waiting on tables and cleaning up and sweeping the floors. I was in contact with these people almost continuously.

My early ideas, as I went through high school, were to be like them: Not only were they tremendously interested in their work, but they were very happy people, and I liked their lifestyle. As I finished high school, my choices were few. I didn't know that much about universities, and there was much less known about other universities in a small high school. I applied to three places: the University of Pennsylvania, Johns Hopkins (by chance), and Rutgers.

I was not accepted at John Hopkins, which was interesting because I was not accepted during an interview in which they asked me whether my parents had attended Johns Hopkins and I said, "No." They said, "Well, where did they go to college?" and I said, "They didn't go to college."

Then they said, "Do you have any questions?" That was the end of my interview, but I was accepted at Penn and at Rutgers.

I went to Penn on a scholarship and immediately got involved in chemistry because I wanted to be like the Merck chemists; that really caught on with me. I loved it. I took all the chemistry courses that were available and, in fact, a course that was taught for the first time—an advanced course on the mechanisms of organic reactions taught by a man by the name of Allan Day. I loved that.

I was heading into a career of chemistry or, possibly, to be like my granddad, a physician. At the last minute—I was to graduate in three years, as it turned out, because I took so many courses so quickly. At the end of my second year, I was faced with the decision of graduate school or medicine. A lot of the bright kids at Penn at that time were going into medicine.

That influenced me. My grandfather, of course—the story of his life influenced me as well. I applied to medical school and went to Columbia's College of Physicians and Surgeons, where I initially had a very tough time because I have a terrible memory. Anatomy almost wiped me out because that was all memory. Fortunately, there was also biochemistry in the first year and a few other things I could do, so I survived the first year. Then I had the notion that I could use my knowledge of chemistry as applied to medicine.

From early on, my ideas were: How do you understand a disease, or how do you understand the mechanism of action of a drug? At the end of Columbia medical school, I went to Mass General [Massachusetts General Hospital], where I was in internal medicine. I loved it, and I wanted to be a practicing doctor. That's what I wanted to be at the end of two years, but at that time the doctor draft was still ongoing.

This was 1954, and I owed Uncle Sam two years of service time. I signed up for the Army, but the head nurse in one of my services had a boyfriend at the NIH [National Institutes of Health], and she said, "You ought to go visit the NIH." The person who was already there was Dan Federman, and his future wife was the head nurse.

I agreed to go to the NIH, and I flew from Boston. That was the first time I had been on a plane. It cost $25, and I took out insurance. I was worried about it because I had already been married—I should mention that I got married between my internship and assistant residency, after one year. I married a woman who was just graduating from Barnard College and whom I had met while I was a medical student. We had already been seeing each other for three or four years before we got married.

Anyway, I visited the NIH and met Earl Stadtman. That was the changing point in my life because Earl was a young guy; he was 10 years old than I. At that time, I was 26 or 27, so he was about 37, and he was one of the top biochemists at the NIH. He was at the National Heart Institute. Meeting him was a real experience because he was so excited about what he was doing, but he spoke very softly.

He told me about what he was involved in: microbial fermentations and understanding how fatty acids were broken down. He talked about esters of coenzyme A (CoA), and CoA had barely been discovered when I was in medical school. The fact that he was working with acetyl-CoA at that time was, to me, startling. He told me about the reactions that the CoA esters were involved in, and he we so excited that, by the time I left, I was also excited, although I didn't follow much of what he said. All that was transmitted to me was this intensity of interest and excitement based on his own research. I asked to work in his lab, and he agreed. It was an interesting relationship because he was a PhD. He had never worked with an MD and was very suspicious. Why would an MD be interested in this sort of work?

Every few weeks he would ask me if whether I thought I had made a mistake, and I wondered if he was trying to give me a message, but we worked together. By the way, the clinical work that I was assigned was something that I already had been thinking about, and that was cardiology. I was at the National Heart Institute. All my patients were heart patients. The deal was that I would spend half my time taking care of patients and the other half doing research.

By the end of two years, I had been called by Walter Bauer at Mass General and offered a position on the junior faculty; I went to Earl and said, "Earl, I think it's time for me to go back," and he said, "Why would you do that?" I said, "Because I'm very good at clinical work, and I've been offered a position back at Mass General, which is where I started." He said, "You can be an even better biochemist." He had never said that to me. This was a revelation. He said, "If you stay, I'll give you a new space and you can start your independent career."

I didn't quite know what that meant, other than the fact that we were just finishing some papers together. What it meant was from then on, instead of discussing everything, which we did otherwise, we didn't discuss anything. He walked away and left me on my own, but he had also given me a technician and a position where I could recruit someone who wanted to come to the lab.

Soon thereafter, Al [Alfred W.] Alberts, who had been a graduate student at the University of Maryland and hadn't finished his degree, but needed a job, came to work with Earl Stadtman. Earl said, "I'll give you a job if you'll work with Roy." Al Alberts and I started working together. That was in about 1958 or 1959. Thus started our collaboration, and we started working on fatty acid metabolism. Ultimately, we got into the biosynthesis of fatty acids, which became my major work for the next 10 years.

I worked very closely with Al. Al was my assistant initially, but he quickly became a colleague because he was very smart and very capable in the lab. We worked together on the synthesis of fatty acids. Soon thereafter, we were joined by Phil Majerus. Phil got into it also, and we discovered the acyl carrier protein, which was the central carrier of all of the metabolites during fatty acid biosynthesis.

We discovered that almost simultaneously with Salih Wakil's laboratory at Duke. We were competing with them. It was interesting, though, that the competitors at that time were, in addition to Salih Wakil, Feodor Lynen in Munich, and Konrad Bloch at Harvard.

Andy Marks: Pretty heavy hitters.

Roy Vagelos: Heavy hitters, and a group that we had fun competing with because it was friendly competition.

Instead of staying at the NIH for 2 years, which was the original plan, I stayed for 10. We started a family, and I had a very productive time, at the end of which I was offered a position at Washington University in St. Louis, which I had never visited. So that was an interesting change.

Andy Marks: Was Phil Majerus already there at that time?

Roy Vagelos: No, we moved together. Phil had started out at Washington University Medical School and was the top student in his class. Then he worked with me as a postdoc for several years. Then, when both he and I moved simultaneously, he moved to the Department of Medicine with a joint appointment in Biochemistry, and I moved in as head of Biochemistry, succeeding Carl Cori.

We picked up the family and moved to St. Louis. I was then back at a medical school teaching medical students and graduate students and continuing my research. The research was going great. We continued research in fatty acid metabolism and branched out into complex lipids and ultimately cholesterol.

All of that knit together to build a career that was all science. It was getting back toward medicine; we had come back to medical school. That was something that I didn't think a lot about when I was at the NIH, but when I was at the medical school, I started relating more of our work to what was happening in medicine.

Andy Marks: Did you continue seeing patients in Washington?

Roy Vagelos: No, the patient work covered only about five years at the National Heart Institute because, after my two years, I could see them as often as I wanted. I slowly geared down my clinical work over a five-year period. At the end of that period I was doing pure research, and that was giving me a message: You tend to do the things that you're most interested in and that come most easily to you. Research just sucked me in.

I had terrific feedback from the work that was going on at the time. At the time I moved to Washington University, I was a biochemist. Teaching medical students was as close as I was going to be to medicine, but it was closer than I had been. At the end of my time at the NIH, I was a researcher and a teacher.

Andy Marks: We'll get to more of the science and the rest of your career in a moment, but I have another question that's philosophical in nature. You have identified music—violin and singing—as something that you love, and it has been a part of your life from very early on, even before science. We've heard how you got sucked into science, and the influence of your grandfather in your decision to get into medicine, but can you talk about the role of music in your life and what parallels, if any, you see between music and science?

Roy Vagelos: Music has always been something that I loved. I stated playing violin when I was in about the first grade, and I played it right through high school. Then, when I went to the university, I rowed. I forgot to mention that. I rowed on the lightweight crew, which was hard on the hands.

You cannot [row] without getting callused hands and fingers and play the violin [at the same time], so I did not play that much while I was at the university. By the way, the only thing I did seriously, other than chemistry, was row on the lightweight crew, which was fun because it also modified my life.

Andy Marks: What do you mean by "modified my life"?

Roy Vagelos: It got me into the idea that part of each day should be dedicated to doing something athletic. That's something I picked up then and have never quit. It allows me to not get obese, because I eat a lot.

Andy Marks: Today it's tennis.

Roy Vagelos: Tennis, and I work out. I have an elliptical runner and a Concept2 rower, which I use almost every day; that is the way I control my weight. It keeps you limbered up.

Back to the music: It has always been something that I have gone back to. I went back to music when I was on the house staff at Mass General. We had a quartet. Later on, whenever I've had time, I've gone back because I love music. Now, it's mostly passive. I love all the performing and music events that go around the city where we live. We love the Metropolitan Opera. We love the symphony orchestra. We have been involved in the New Jersey Performing Arts Center. Music is something that requires dedication, practice, and focus. Those are the things that really relate to science as well.

Andy Marks: It seems that so many scientists are either musicians themselves or are music lovers, and there must be some connection in the brain, I would imagine.

Roy Vagelos: I think there is. I think it's certainly something we all love.

Andy Marks: Getting back to the clinical period of your career, earlier on: You write about a Munchausen patient whom you saw earlier in your career seemed to make a lasting impression. Is that true, or did I get that wrong? If so, what lessons were learned? Maybe you can describe what the patient had—many of the listeners may not know what Munchausen is.

Roy Vagelos: Munchausen syndrome is a condition in which people fake a clinical syndrome, a clinical disease. While I was a young clinician at the National Heart Institute, a patient was admitted who was said to have a heart problem that was causing him to have seizures. He was admitted over a weekend; I had come in after the weekend, on Monday, and suddenly I was the doctor for this person who was having seizures. I examined him and found nothing wrong with his heart. I had some skull films done and the usual cursory neurological examination, where I found nothing, but I was not sure until I invited the head of the neurology clinical group to come and to examine him as a consultant. This person came and he said that clearly I had missed a lesion in the brain because I did not interpret the skull films properly.

I could not believe that. When he pointed out what he was talking about, I couldn't see what he was talking about. Nevertheless, he walked away and told me I had really flubbed it, but I could not believe what this man was saying because I could not see any kind of defect in the skull X-ray.

When he left, I continued to watch the patient. I realized by observation that when he had a seizure he would call for medication, and the medication was always morphine. After watching this pattern, I realized that this guy was faking it. I called the city hospital and described the patient, and they said, "Oh, so-and-so is up at your place now." He had Munchausen. He was faking the whole thing.

The impact that had on me was that the senior neurologist of the Neurology Institute at that time was so dogmatic that he was not willing to take the opinion of a junior person; he just put that person down—that was me—so I never got over that. I have always been careful to listen to anyone, at any level, because people have good ideas and have opinions that are very valuable. I've been pretty darn sensitive to that.

Andy Marks: An important lesson. I was laughing because I had a very similar experience during my training with a Munchausen patient.

You mentioned Stadtman earlier, and how he influenced you. What would you say was the most important thing that you learned from him?

Roy Vagelos: First of all, he was incredibly smart, and he was wonderful in dealing with young people. You may know that Mike [Michael S.] Brown was trained in his laboratory and went on to get a Nobel Prize. Stanley Prusiner was trained by Earl Stadtman. Earl had a whole number of people go through the lab after I did (I am much older they are). The beauty of Earl was that he would start you on a project and then allow you to become independent as soon as he thought you were capable.

There was never any feeling that you were being controlled or slowed because of Earl's involvement. After the first two years I worked with him, all the work I did from then on, which clearly was derived from his early ideas—he never put his name on any of those publications.

Andy Marks: That's unusual.

Roy Vagelos: He was loyal to me throughout my career. If you were to talk to Mike Brown or Stanley Prusiner—all these people—they will tell you about how supportive and loyal [he was] and how quickly he released people from any kind of commitment to him. He was a wonderful developer of young people, and people loved this guy. He was the best.

Andy Marks: Obviously, you're in great shape for a person of any age, and yet you talk about being obsessed with fat. You studied fatty acid metabolism, and very early on in your research you were already thinking about making new drugs, in this case, targeting fatty acid metabolism. Where did that interest come from, and how do you explain that obsession with fat?

Roy Vagelos: The ideas about fat came about from our research in fatty acid biosynthesis, and the idea of working on drugs was very peripheral. It was never serious while I was doing basic research, either at the NIH or at Washington University. In fact, after I had been at Washington University for nine years, something happened that was very important in my career.

I was called by the University of Chicago and then later by the University of Pennsylvania, and in each instance I was told that I was a top choice of the committee to become dean. That was very troublesome because I never pictured myself as a dean.

I thought I was a researcher, someone who was going to do research my entire career. I did not think deans did research. In fact, the deans I saw did anything but research. That was a rather depressing thought: that people who were observing me would think of me as a dean. Not long after that, I was called by a friend at Merck. He was a friend because I had worked one summer in a Merck research laboratory, between my first and second years of medical school, so I knew a few people there. I was called by this person who had, by that time, become a vice president in research. I was asked whether I would consider becoming head of Merck Research Laboratories.

I said, "No, I have no interest." I hadn't thought about drug discovery. He said, "Why don't you come and visit?" I agreed to visit Merck Research Labs—and got to visit my parents, who lived in Rahway at the time—and what I saw was that pharmaceutical research for drug discovery was based on pharmacology.

[Merck conducted] live-animal research, where animals were given syndromes or conditions that were akin to human diseases—high blood pressure, heart failure, infections, and so on. Very little biochemistry was being used as the basis for drug discovery. I went away from that original visit thinking it was odd that they weren't doing it. Would it be possible to get into serious drug discovery by understanding the mechanisms of action of drugs and targeting on single molecules?

The more I thought about it, and contrasted it with the idea of becoming a dean, I thought that going to a place where I would be responsible for basic research, drug discovery, would take

advantage of my background and was something that I wanted to do. It would also put me in the position of doing something closer to clinical medicine because I would be potentially impacting the health of people.

I then thought about the transition and decided it was worth the risk on my part. It was a huge risk on the part of the people at Merck. Henry Gadsden, who was the CEO of Merck at that time, offered me the job, and I said, "Henry, if I were to take this job, I would completely change the approach to drug discovery. Would that be okay with you?" He said, "If we did not want a major change, we wouldn't be talking with you."

I then said, "What would happen if the business got weak and sales were not going well?" I didn't know what I was talking about, of course, with regard to sales. He said, "If things went poorly, we would cut back on all parts of the company. We would cut back on marketing and selling. We'd cut back on the corporate groups." But, he said, "The last thing we would ever do is cut back on research because that's the future of this company."

On that basis, I thought about it for another month and then accepted the job, with another major transition for my family. We left St. Louis and moved to New Jersey.

Andy Marks: You've talked about the time that you were in medical school and, through the early part or your career, seeing patients. You were a physician, and then you became a scientist, and then you went on to eventually head up Merck. Can you talk a little bit about that transition from early in your career, where you clearly saw yourself as one kind of a person, to when you became something quite different? Do you have any words of advice for any people coming along that path?

Roy Vagelos: I see it as a sort of continuum. I left Mass General—as you know, people leaving there think they're the best practitioners of clinical medicine possible—and I loved it. By the time I left the National Heart Institute, I realized that I had strengths in biochemistry and I wanted to do that, but the deeper I got into biochemistry, which was pure basic research, the further I got from clinical work.

The transition to Washington University was a transition back toward medicine because I was teaching medical students. That was getting back to my original goal of being a doctor. When I then transitioned to Merck, this was an opportunity to really close the circle: If we were able to discover drugs that were important for human health, then we could impact the lives of millions of patients.

Andy Marks: Do you think that without an MD you would have been able to make those connections between your basic research and the needs of patients?

Roy Vagelos: That's an interesting question. The transition to Merck and medicine was far easier for me because of my background in medicine. There's no question about that.

I worry about people who take on jobs heading organizations with no background at all because by simply understanding disease and understanding the impact of other medicines, you can immediately start making connections between what you know from science and how that could impact a disease or improve a drug class. You could see how to make improvements.

Andy Marks: Turning the clock back to a very exciting time in your career before Merck: What was the central problem that you were trying to solve, vis-a-vis acetyl-CoA and the enzymes controlling fatty acid synthesis? Try to put us back in that time and describe what the challenges

were scientifically and how you approached them.

Roy Vagelos: The knowledge of fatty acid metabolism started with A.J. Barker at Berkeley, who was a teacher of Earl Stadtman. Earl Stadtman was carrying on, looking at fatty acid metabolism and how it was broken down. β-Oxidation had been discovered along the way. CoA had been discovered by Fritz Lipmann. The structure of acetyl-CoA—that is, an activated acetate—was discovered by Feodor Lynen in Munich at the Max Planck Institute.

When I got into it, it was hot stuff; it was as hot as you can get in a given era. I fell right into the middle of it because of my association with Earl Stadtman. What was then being discussed was β-oxidation, the way fatty acids were broken down; fatty acid biosynthesis was the reverse of that. That was the general understanding of everyone.

By the way, my ability to get into that field was very much based on my ability in chemistry because all the intermediates of fatty acid metabolism are thioesters, and they're very hard to make. With a chemistry background, I was making things that other people could not make, so I could move much more rapidly. The whole thing boiled down to what happens to acetyl-CoA between a 2-carbon chain and a 16- or 18-carbon chain.

Was it just a reversal of β-oxidation? We discovered acetyl-CoA as a metabolite early on—unrelated to fatty acid biosynthesis. We found this 3-carbon-activated group, and when we put that together with acetyl-CoA in a microbial enzyme system that we had made, we were whipping out fatty acids. We suddenly had a new intermediate in what appeared to be the pathway between acetyl-CoA and the long-chain fatty acid.

That was exciting. Then we discovered that, for this series of enzymes to do anything, we needed a heat-stable factor, which turned out to be a protein. This was ultimately characterized as the acetyl-CoA carrier protein, which was an amazing thing at the time and was the key to understanding fatty acid biosynthesis. As I mentioned earlier, we discovered it and Salih Wakil at Duke came up with it independently, but we were ahead.

We won the race, and it was very exciting to be able to understand how you could build this 16- or 18-carbon chain, do it rapidly and efficiently at room temperature, and characterize all those enzymes. That was heaven from the point of view of an enzymologist, and understanding the enzymes and all these reactions was what drug discovery for me was ultimately all about.

Andy Marks: Can you describe the importance of Jacques Monod and François Jacob in your science?

Roy Vagelos: As was habit at the NIH, the seventh year on the job meant that, if you wished, you could have a sabbatical; I heard the scientists Monod and Jacob talk in New York City. Specifically, Jacques Monod gave a lecture, which was electrifying, about allostery and messenger RNA.

That was just the beginning. That was in about 1962. I asked to work in his lab, and I went to work with Jacques and was exposed to an entirely different kind of guy than Earl Stadtman. Jacques Monod was someone who had a tremendous imagination. He was so imaginative that many people thought he moved too fast and that he moved without enough facts, but in fact, most of what he explained turned out to be fact in the end.

The messenger RNA turned out to be accurate, and allostery became accepted by everybody. He was just terrific. I worked a year in the laboratory and largely picked up microbial mutants as tools of the work that I was going to do back in the United States.

I looked for a suppressor mutation. I never found one, but that was part of the work I did. Then I did some allostery and enzymology with him. We became fast friends and he tried to convince us

to stay in Paris, but I was drawn back to the work I was doing in the United States.

Andy Marks: Can you talk about your move to the head of research at Merck from the prospective of its impact on your science?

Roy Vagelos: That's interesting. When we moved to Merck—I initially moved with a very small group from Washington University. Al Alberts, who had been with me at the NIH, then came to Washington University.

Andy Marks: Didn't he eventually get his doctorate?

Roy Vagelos: He never did. Al never finished his doctorate, which was something I pushed for very hard. In fact, at one time I told him he had to take off for a summer and could not come back to work until he finished his degree. He did not finish, but I needed him and he wanted to come back. When I moved to Merck, Al had by then gone up the faculty ladder and was an associate professor with tenure at Washington University on the basis of his accomplishments.

Andy Marks: Right.

Roy Vagelos: The faculty members were the ones who wanted to have him promoted. I didn't hold him back, but when I was to move to Merck, I told Al that I was going to leave and that it was a risky thing and he should remain where he had tenure and where he had done so well. But he said that we had been working together for so many years that he would like to come. He came with a small number of postdocs.

My initial idea was that we would slowly learn about drug discovery and then get into discovery ourselves, but I would retain a research group myself. For the first year, I did retain one, but during that year I recognized that the research group that I was now in charge of was large. It was so much bigger than I was used to that it was taking all my efforts to understand what they were doing and to try to reorganize the research to bring in the biochemical approach. By the end of the year, I had arranged for all my postdocs to take jobs, and they all got excellent jobs, but Al, of course, stayed. We quickly adopted what was going on at Merck as our entire work.

Two things happened. One was that I felt it was my responsibility that everybody succeed. I spent time with every research group, and where I thought their research was not very productive, I waited until I had an idea of something that they could do that involved their expertise, then swung toward biochemistry to get them onto a new project.

The other thing I realized was that I could not continue to be a primary researcher. I could not do that as well as oversee the large number of projects that I had to be involved in. I decided early on that I was going to be an advisor, someone who would give ideas. I set the pattern very early on, then I never put my name on the papers.

No paper that was ever published from Merck—and, of course, there were thousands over the 19.5 years I was there—had my name on it. I made that decision so that people would feel free to talk with me and not feel that they would lose leadership of a project. I wanted them to feel ownership, but I would stew and worry and think and call them at night if I had an idea about their project. I felt very much a part of every project that went on at Merck. It was a tremendously steep learning curve for me as I learned about all the different areas of research, including vaccines. We had experts in different kinds of research all over the place. I wanted to be able to help them and to succeed, and we did.

Andy Marks: Can you tell us about the development of the HMG-CoA reductase [3-hydroxy-3-methyl-glutaryl-CoA reductase] inhibitor at Merck and your role in this project? In particular, can you comment on the highs and lows of this project?

Roy Vagelos: The HMG-CoA reductase project was one that was very dear to me. Early on, when Al and I moved to Merck, we looked around to see what might be a project for drug discovery. We knew about the cholesterol hypothesis, and that was based on several things: the fact that in people who died of coronary heart disease or heart attacks, their arteries were filled with cholesterol; the animal models of hypercholesterolemia [that was] then causing coronary heart disease; the epidemiology around the world where the Japanese, with very low blood cholesterol, almost never died of heart attacks; people in Finland who had an incidence of death from heart attack that was 14 times higher than that of the Japanese and had extremely high—sky high—blood cholesterol.

All that information was available, and the biosynthetic sequence—24 sequential enzymes for biosynthesis of cholesterol—had just been unraveled largely by Lynen in Munich and Bloch at Harvard, for which they got the Nobel Prize. Lynen's laboratory also indicated the rate-limiting enzyme as HMG-CoA reductase.

That information was stuff that I knew and that I thought we could apply, but so did everybody else. It came at a time when it was an obvious target for drug discovery. That was brought to a head by the Mike Brown and Joe [Joseph L.] Goldstein experiments, which also indicated that HMG-CoA reductase was a "choke point" in the biosynthesis and a regulatory enzyme, [and by] the initial discovery of the first statin by [Akira] Endo in Japan.

That was a startling discovery: He found a metabolite from microbial fermentation, which was compactin. Another name was mevastatin, which was the first inhibitor of the HMG-CoA reductase. Many organizations had focused on that enzyme, including Merck, but the discovery of the first statin was made in Japan.

That, of course, focused us even more—we had to get going. Al's group quickly came up with lovastatin, which was, again, a fermentation product that was isolated. It was structurally related to but different from mevastatin, which came from Japan.

It was very clear that we were behind in the race, but we were number two. We were racing along and did all the animal studies to support the clinical studies. Then lovastatin went into the clinic. It was well behind the Japanese group's work, which was probably months ahead of us, when we heard that all the clinical studies in Japan had been stopped. It was a shock because it was an open competition.

I immediately got on the phone and talked with people at Sankyo Company, the Japanese company where the drug was being developed, and asked them to explain to me exactly what was found. My concern was that it was an enigma. Was it possible that all inhibitors of HMG-CoA reductase would be a problem? That problem they would not give any information about, but the rumor was that compactin or mevastatin was causing tumors in animals.

The enigma was: Do all inhibitors of HMG-CoA reductase cause tumors in animals, if that is what is being seen, or is it possible that our lovastatin, although related to their compound, would not cause a problem? We couldn't tell; they said it was an industrial secret and would give us no information. We stopped immediately, that day. We stopped all clinical studies with the notion that if there was a problem we could not put any patients at risk.

Lovastatin was stopped in the clinic for two years while we finished all our long-term animal carcinogenicity studies. Also, during that period, chemists were hard at work trying to come up with another structure that would be chemically different enough to possibly not have the

problem of lovastatin, if lovastatin did have a problem. Also, [the new drug] may be superior in some other aspect. They came up with simvastatin.

That was exciting because it was more potent, had a longer duration of action, and was different in structure. But at the end of the two years, physicians on both the East Coast and the West Coast, come to Merck and said, "Look, we've got patients with hypercholesterolemia who are going to die unless there is some way to reduce their cholesterol." The US Food and Drug Administration agreed that we should go back to lovastatin, but only in high-risk patients.

We went back into the clinic, after having been out of it for two years, and started experiments in patients who already had coronary heart disease and high blood cholesterol. What we found—I should say that all the studies were clean at Merck. We found that we safely reduced total cholesterol and low-density lipid protein (LDL) cholesterol.

The drug was approved. The first statin in the world was approved in 1987. The project started in 1975—12 years, which is about average. Some physicians thought it was a good idea and were going to use it to lower blood cholesterol. Others said, "You're lowering blood cholesterol; so what?" That was an issue, and we needed to have an outcome study.

This was new in those days. This was the late 1980s. We started what was called the—instead of using lovastatin, we went to what we thought was a slightly better drug, simvastatin. We did the Simvastatin Scandinavian Survival Study (4S). The 4S gathered some fame because it was based on the study of 4,400 patients who had coronary heart disease, high blood cholesterol, and high LDL cholesterol. Half of them were put on simvastatin, and the other half were put on a placebo, for 5.5 years.

This was a double-blind study. At the end of that time, they broke the blind, and the result was just amazing. There was a reduction in death, from any cause, of 30%—this is comparing the drug versus the placebo. The reduction in death from heart attack was 43%; the reduction of strokes was 30%. That one experiment changed hypothesis to fact and essentially revolutionized the treatment of cardiovascular disease.

Andy Marks: You've said you don't have a good memory, but you remember those numbers, obviously.

You transformed Merck from a traditional pharma approach to drug discovery to one based on mechanisms of action and inhibition of specific enzymes. Can you comment on why and how you achieved this transformation? Has this model caught on at other major pharmaceutical companies?

Roy Vagelos: The focus on enzymes or ion channels or receptors would come naturally to any biochemist because we're used to dealing with single molecules rather than live animals. It was a matter of getting that idea across to all the Merck people: That was something of a challenge, initially, because they were experts in other things, mostly pharmacology and chemistry. I thought we had the world's best chemists, but they were really held back by the biology. Therefore, focusing on the HMG-CoA reductase was a test for me and a test for the whole laboratory, and a demonstration that the approach was good. It went on from there to the 5-α-reductase for control of prostate size, to new drugs for antibiotics, to new drugs for hypertension. Vasotec® came out of that approach. The angiotensin receptor antagonist came out of that approach. The Prilosec® came from that approach, for hydrochloric acid control. It was one drug after another.

Of course, people love to win, and once it was clear that you could win using this approach, it was just magical at Merck. Merck research at that time was a magical place because we had such great people who loved what they were doing. We could get almost anything done. I remember

that I was close to the end of my time at Merck and was asked whether I thought HIV was going to be treatable. I said, "Absolutely. You'll figure out the enzymes that are involved in that virus, and we'll do what we've done in bacteria and what we've done in disease. Of course it's controllable." That was overly optimistic because it took longer than I anticipated, but the first protease inhibitors followed.

It became obvious that this was a good approach not only for Merck, but for other companies. By the way, I did not discover this approach. People like Jimmy Black focused on the specific proteins: the H2 receptor blockers and the β-blockers. These were all conceptually the same thing. What I did was institutionalize it for drug discovery at Merck, and that's what caused it to spread in the industry.

Andy Marks: Under your watch, Merck developed and provided a treatment for river blindness that stands as an example of corporate morality in its highest form. Was this a difficult sell to the Merck board and your colleagues?

Roy Vagelos: The discovery of ivermectin, shortly after I went to Merck, did not follow my idea of how drugs would be discovered. It was discovered using an animal model. A rodent was the model of a parasitic disease. They put three gastrointestinal parasites into the gut of a mouse, and then they fed fermentation broth to the mouse.

This was a classical approach; it had worked in the past. To my surprise, a fermentation broth was discovered that contained a substance called avermectin, which was isolated by the great isolation chemists at Merck, led by Georg Albers-Schönberg. Avermectin, in toxicology studies, could be improved by reduction of a double bond that converted avermectin to ivermectin. At that point it was the most potent drug for killing parasites by maybe two orders of magnitude over earlier chemicals.

This was a fabulous drug. It was tested on gastrointestinal parasites in cattle, horses, pigs, and sheep, and ultimately heartworm in dogs. It became a great product for animals. But it was not active against hookworms or tapeworms. It was not pursued for human use until one of our clinical physicians, Mohammed Aziz, came and told me about the disease of river blindness, which is caused by a parasite called *Onchocerca volvulus*.

That parasite exits as an adult in a microfilarial form. The microfilaria live in the skin; the disease is transmitted by the bite of a black fly. Flies bite a person, who has these microscopic worms in the skin. Within the fly, the parasite becomes an adult—it essentially metamorphoses, so when the fly bites another human it injects a form of the parasite that can become an adult.

At the site of the bite, the worms become adults. Males are about 8 inches long, females about 14 inches long. They live in lumps in the skin, and they make millions of microfilaria that crawl through the skin and cause terrible itching, so these people are constantly itching. The microfilaria get into the eyes, causing scarring and blindness.

This disease is called river blindness because the parasite, *Onchocerca volvulus*, and the flies, which are the transmitters, live along the rivers. People want to be near the rivers in order to have more fertile farmland. When they live there, they get bitten by the flies and get onchocerciasis, river blindness.

Mohammed Aziz said, "Shall we try this drug on the disease?" I said, "Why not?" He went to Dakar, Senegal, in the western tip of Africa, and saw these people who had the lumps and were going blind. At that point, there were 18 million people who were going blind via eye infections and over 100 million at risk among the poorest people in the world.

He took a pinch of skin over the hip of these patients and counted the number of microfilaria. There were a dozen or two dozen per pinch. These were people who were totally infested. He gave one tablet of ivermectin to these patients, and then came back in a month, did another pinch, and found that the parasites were all gone. We got very excited about that and called the World Health Organization to come and see these results. They came, and they said, "Something's wrong. It's impossible."

They told us we had screwed up the experiments, and they left. We turned on a huge development program because we knew we couldn't have been wrong. We went back and carried out a program where we gave one tablet to patients who had the infection in their skin and eyes. Then we returned at 1, 3, 6, 9, and 12 months, and there were no parasites after a single tablet.

At the end of 12 months, the disease started to reappear. It was clear that we had a drug that would eliminate this disease when given as one tablet once a year.

Andy Marks: It wasn't going to be a blockbuster, though.

Roy Vagelos: It was not. Our salespeople said, "Of course, we can sell it," and I said, "To whom?" These people were the poorest people in the world. I visited people in Chad, which is in the middle of Africa, and these people lived in mud huts and wore grass skirts. They were really poor. They had never been outside their village.

We were left with these exciting developments. The clinical research was being finished. This was heading toward 1987, and we needed to have it approved by a sophisticated regulatory agency, and we chose France. The US Food and Drug Administration would not take it because they had no river blindness. The French took it because of French Africa and French people living in Paris with river blindness. They took it, and to my surprise—far faster than ever with a commercially important drug—they called and said, "We're going to approve it in two days." At that point, we had been meeting monthly with an executive group to determine how we were going to get the drug to these people.

We had no plan. We had no decision, but there had been a cover story in the Sunday *New York Times* with a picture of patients with river blindness accompanying a story that Merck had this drug. We had to make a very rapid decision. We decided in a two-day period. We had a press conference in Washington, where we announced that Merck would provide the drug free to anyone, anywhere in the world, for as long as it was required.

That was exciting. It was done in a tremendous rush, so much so that I did not talk with the board. I committed the company, and this brought in a flood of high morale within the company and among our stockholders. At the next board meeting, I explained what had happened, and someone said, "Don't you think, Roy, that you should have come to the board?" I said, "I really didn't think of it. It was happening so fast, and we had to make a decision. Is there anyone here who would have made another decision?" I looked around the table, and there was no other decision.

We started in 1987, and last I heard—which was about 2009—Merck was treating something over 90 million patients a year, free, in sub-Saharan Africa, Latin America, and Asia. There are countries where the cycle has been broken. All the large-enough regions had been covered with the drug, so the flies no longer had access to the parasite and the disease was eradicated. The patients can stop taking the drug.

That's the ivermectin story.

Andy Marks: What did you leave on the table when you retired from Merck?

Roy Vagelos: Retiring from Merck to me was like dropping off a cliff. I hated it.

Andy Marks: You were a young man at that time.

Roy Vagelos: I was 65. When you become 65, and you know this when you take the job, you must retire. There's no choice, and there have been no exceptions. There wasn't one then. I had no plans. I had a successor for head of research: Ed [Edward M.] Skolnick, who had been with me since 1981. He was very smart, and I thought he would be fully capable of carrying on the research.

I had someone who was also going to succeed me as head of the company for five years, but at the last moment, for reasons that are personal, he left the company. The company was left without a CEO. They went outside, and hired [Raymond] Gilmartin, who succeeded me. I had no say in that hiring.

I left on the table a research organization that was absolutely first rate and leadership that I thought was first rate. Unfortunately, the person whom I had groomed had left the company.

Andy Marks: Are there any unfinished projects that you wish you could have—?

Roy Vagelos: Unfinished projects all over the place and—

Andy Marks: Any one in particular?

Roy Vagelos: Most of them were well on their way. The fosamax one was done, for osteoporosis. All our major projects were coming along. We had lots of projects that were still under way and were taken over.

Andy Marks: No regrets, then, except that you would have stayed longer.

Roy Vagelos: I would definitely have stayed longer.

Andy Marks: I've got one more question: How do think your scientific career would have been different had you remained in academia instead of moving to the pharma industry?

Roy Vagelos: That's interesting. Had I remained in academia, I assume that I would have continued to be productive and to do interesting things. Of course, there has been an explosion in lipid modification of various things, and intermediates and activators and signaling molecules. There was a great biology that grew from that field and continues to grow.

There was lots of excitement that I would have been in the middle of, given that I'd been in the middle of it for so long. I divided my career almost in halves: 19 years in academia, between the NIH and Washington University, and then 19 years at Merck, between head of research for 10 years and 9 years as head of the company. As head of the company, I never felt that I was disassociated from research. I was extremely close to all the projects and felt that I could talk with the scientists, just less frequently.

Andy Marks: Thank you.

Roy Vagelos: Thank you, Andy. It's been a pleasure.